



## Review article

## Progressing neurobiological strategies against proteostasis failure: Challenges in neurodegeneration



Ayeman Amanullah<sup>a</sup>, Arun Upadhyay<sup>a</sup>, Vibhuti Joshi<sup>a</sup>, Ribhav Mishra<sup>a</sup>, Nihar Ranjan Jana<sup>b</sup>, Amit Mishra<sup>a,\*</sup>

<sup>a</sup> Cellular and Molecular Neurobiology Unit, Indian Institute of Technology Jodhpur, Rajasthan, 342011, India

<sup>b</sup> Cellular and Molecular Neuroscience Laboratory, National Brain Research Centre, Manesar, Gurgaon, 122051, India

## ARTICLE INFO

## ABSTRACT

## Article history:

Received 28 January 2017

Received in revised form 1 June 2017

Accepted 25 August 2017

Available online 1 September 2017

## Keywords:

Proteostasis

Neurodegeneration

Aging

Proteins are ordered useful cellular entities, required for normal health and organism's survival. The proteome is the absolute set of cellular expressed proteins, which regulates a wide range of physiological functions linked with all domains of life. In aging cells or under unfavorable cellular conditions, misfolding of proteins generates common pathological events linked with neurodegenerative diseases and aging. Current advances of proteome studies systematically generates some progress in our knowledge that how misfolding of proteins or their accumulation can contribute to the impairment or depletion of proteome functions. Still, the underlying causes of this unrecoverable loss are not clear that how such unsolved transitions give rise to multifactorial challengeable degenerative pathological

**Abbreviations:** AAA, ATPases associated with diverse cellular activities; 17-AAG, 17-N-allylamino-17-demethoxygeldanamycin; ABC, ATP-binding cassette; ABCE1, ATP binding cassette subfamily E member 1; AD, Alzheimer's disease; AIF, apoptosis inducing factor; Akt, Alpha serine/threonine-protein kinase; ALS, amyotrophic lateral sclerosis; AMFR, Autocrine motility factor receptor; AMPK, AMP-activated protein kinase; Aβ, Amyloid beta; APP, Amyloid precursor protein; AQUA, Absolute quantification; ATG, autophagy related gene; Atg8, Autophagy-related protein 8; ATM, Ataxia-telangiectasia mutated; BAD, Bcl 2 associated death; BAG3, B-cell lymphoma 2-associated athogene 3; Bax, Bcl-2 associated X protein; Bcr-Abl, Breast cancer-Abelson murine leukemia viral oncogene homolog 1; BiP, Binding immunoglobulin protein; CAP, Chaperone assisted proteasomal degradation; cAMP, Cyclic adenosine monophosphate; CASA, Chaperone-assisted selective autophagy; Cbl-b, Casitas B-lineage lymphoma B cells; Cdc, Cell division cycle; Cdc48, cell-division cycle 48; CFTR, Cystic fibrosis transmembrane conductance regulator; CHIP, Carboxyl terminus of Hsc70-interacting protein; CHOP, CCAAT-enhancer-binding protein homologous protein; ClpP, Clp protease proteolytic subunit; CMA, Chaperone mediated autophagy; CpDA, 3',5'-cyclic AMP phosphodiesterase; CRBN, cereblon; Cue1, Coupling of ubiquitin conjugation to ER degradation protein 1; Derlin-1, Degradation in endoplasmic reticulum protein 1; DHA, Docosahexaenoic acid; DIGE, Difference gel electrophoresis; DIP, Database of interacting proteins; DNA-PK, DNA-dependent protein kinase; Doa10, degradation of alpha2-10; DUBs, Deubiquitinating enzymes; eIF2α, Eukaryotic translation initiation factor; ER, Endoplasmic reticulum; ERAD, Endoplasmic reticulum associated degradation; ERKs, Extracellular signal-regulated kinases; ETC, Electron transport chain; FAD, Flavin adenine dinucleotide; FOXO, forkhead Box O; GABA, γ-aminobutyric acid; GPCR, G-protein-coupled receptor; GRP78, Glucose regulated protein 78; GRP94, Glucose-regulated protein 94; Gp78, Glycoprotein 78; HD, Huntington's disease; HDAC6, histone deacetylase 6; hDJ-1, Human DJ-1; HDM2, Human Mdm2; HIV, Human immunodeficiency virus; HeI2, Histone H3 ligase; HEWL, Hen egg white lysozyme; Hrd1, HMG-CoA reductase degradation protein 1; Hsc70, Heat shock cognate 70; HspB8, Heat shock protein B8; Hsp40, Heat shock protein 40; Hsp70, Heat shock protein 70; Hsp90, Heat shock protein 90; Hsp26, Heat shock protein 26; Hsp100, Heat shock protein 100; HSFI, Heat shock transcription factor 1; HSR, heat shock response; HSV-1, Herpes simplex virus-1; HTA2, High temperature requirement protease alpha 2; IGF-1, insulin/insulin growth factor 1; IRE1, Inositol-requiring enzyme 1; IM, Intermembrane; Inpp5a, Inositol polyphosphate-5-phosphatase A; IPOD, Insoluble protein deposit; iTRAQ, Isobaric tag for relative and absolute quantification; JUNQ/INQ, Juxtanuclear quality control compartment LAMP-2A Lysosome-associated membrane protein type 2A; LC3, Light chain 3; LONP, Lon protease homologue; MA, Macroautophagy; MALDI-TOF, Matrix-assisted laser desorption ionization time-of-flight; MAPK, Mitogen-activated protein kinase; Mcl-1, Myeloid cell leukemia 1; MEK, MAPK/ERK kinase; MGRN1, Mahogunin ring finger 1; MIPS, Munich information centre for protein sequences; mRNA, messenger RNA; MS, mass spectrometry; MtB, *Mycobacterium tuberculosis*; mTOR, mammalian target of rapamycin; mtQC, mitochondrial quality control; MAO-B, Monoamine oxidase B; MuRF1, Muscle ring finger 1; MUTHY, mutY Homolog; NAC, Nascent polypeptide-associated complex; NADPH, Nicotinamide adenine dinucleotide phosphate; NBD2, Nucleotide binding domain 2; NDDs, Neurodegenerative diseases; NF-κB, Nuclear factor kappa B; Nox4, NADPH Oxidase 4; NSAIDs, Nonsteroidal anti-inflammatory drug; OA, Oleic acid; OGG1, 8-Oxoguanine DNA Glycosylase; OMM, Outer mitochondrial membrane; PA, Palmitic acid; PARP1, Protein poly (ADP-ribose) polymerase 1; PEDRo, Proteomics experiment data repository; PERK, Protein kinase-like endoplasmic reticulum kinase; PD, Parkinson's disease; PDI, Protein disulfide isomerase; PINK1, PTEN-induced putative kinase 1; PI3K, Phosphatidylinositol-3-kinase; PQC, Protein quality control; Protacs, Proteolysis Targeting Chimeras; QC, Quality control; RAC, Ribosome-associated complex; RES, Resveratrol; RNP, Ribonucleoproteins; RML, Rocky Mountain Laboratory; ROS, Reactive oxygen species; SCF, Skp1-cullins-f-box proteins; Sch9/Akt, serine/threonine-protein kinase; SELDI-MS, Surface-Enhanced Laser Desorption-Ionization Mass Spectrometry; sHSPs, small heat shock proteins; Siah2, Seven in absentia homolog protein 2; SILAC, Stable isotope labeling by amino acids in cell culture; SIRT1, Sirutin 1; SOD1, Superoxide dismutase 1; SUMO, Small ubiquitin like modifiers; TDP43, TAR DNA binding protein 43; TOR, target of rapamycin; TRAF6, TNF receptor associated factor 6; TSC2, Tuberous sclerosis protein 2; TTR, Transthyretin; Ubc1/7, Ubiquitin conjugating enzyme 1/7; UCHL5, Ubiquitin carboxyl-terminal hydrolase isozyme L5; Uev1a, Ubiquitin-conjugating enzyme E2 variant 1A; UPR, Unfolded protein response; UPR<sup>ER</sup> and UPR<sup>mt</sup>, unfolded protein response of endoplasmic reticulum and mitochondria; UPS, Ubiquitin proteasome system; USP, Ubiquitin specific protease; XBP-1, X-box binding protein 1.

\* Corresponding author.

E-mail address: [amit@iitj.ac.in](mailto:amit@iitj.ac.in) (A. Mishra).

conditions in neurodegeneration. In this review, we specifically focus and systematically summarize various molecular mechanisms of proteostasis maintenance, as well as discuss progressing neurobiological strategies, promising natural and pharmacological candidates, which can be useful to counteract the problem of proteopathies. Our article emphasizes an urgent need that now it is important for us to recognize the fundamentals of proteostasis to design a new molecular framework and fruitful strategies to uncover how the proteome defects are associated with aging and neurodegenerative diseases. A enhance understanding of progress link with proteome and neurobiological challenges may provide new basic concepts in the near future, based on pharmacological agents, linked with impaired proteostasis and neurodegenerative diseases.

© 2017 Elsevier Ltd. All rights reserved.

## Contents

1. Introduction .....	3
1.1. How proteostasis is crucial for normal cellular health and fitness? .....	3
1.2. Dense network of cellular proteome and linkage with diseases .....	3
1.3. Systematic approach to understand the issues of proteome balance .....	3
2. Understanding of living genetic balance and variations of cellular proteome .....	4
2.1. Variations of cellular protein quality control mechanisms .....	5
2.2. Protective and adaptive functions of cellular proteome .....	8
2.3. Cellular and molecular interactions determine specificity and fitness of proteome .....	9
3. What is the fast track for mapping synergistic clearance of aberrant proteins? .....	11
3.1. Proteasome linked with ubiquitins generates homeostasis at cellular level .....	11
3.2. Autophagy can do compensatory balance functions under proteasome dysfunctions .....	11
3.2.1. Chaperone Mediated Autophagy (CMA) .....	12
3.2.2. Chaperone-Assisted Selective Autophagy (CASA) .....	12
3.3. ERAD & mitochondrial quality control mechanisms are pivotal for cellular health .....	12
3.4. Protein quality control mechanism of nucleus is crucial for proteostasis .....	13
4. How to solve the problem of bottleneck proteotoxic traffic jams in proteome? .....	13
4.1. Upgrade folding of aberrant proteins regulated by multi complex chaperone machinery .....	14
4.2. Filtration and rare target of UPS is important to flip the blocked switch .....	14
4.3. Defining the useful dynamics of ER proteostasis .....	14
4.4. Homeostasis renewal of autophagy may clear unwanted bulk of proteome .....	15
4.4.1. Macroautophagy .....	15
4.4.2. Microautophagy .....	16
5. How loss of proteostasis affects age-risk factor diseases such As cancer and neurodegeneration? .....	16
5.1. Aberrant proteostasis and cancer .....	16
5.2. Proteostasis imbalance and neurodegenerative diseases .....	16
6. Useful model organisms of neurodegeneration & aging linked with proteostasis imbalance .....	17
6.1. <i>Saccharomyces cerevisiae</i> .....	17
6.2. <i>Caenorhabditis elegans</i> .....	17
6.3. <i>Drosophila melanogaster</i> .....	17
6.4. Mice models .....	17
7. Differential proteostasis regulatory mechanisms of somatic vs. reproductive (Gonads) tissues of model organisms .....	18
8. Natural resources & pharmaceutical molecules can stimulate the maintenance of endangered proteostasis .....	18
8.1. Natural compounds based strategies can regulate proteome dysfunctions .....	18
8.1.1. Vitamins .....	19
8.1.2. Natural isothiocyanates .....	19
8.1.3. Natural phenols, flavanoids and flavonols .....	19
8.1.4. Alkaloids .....	20
8.1.5. Fatty acids and their derivatives .....	20
8.1.6. Bacterial isolates .....	20
8.1.7. Fungal isolates .....	20
8.1.8. Terpenes/Terpenoids .....	20
8.1.9. Other natural agents .....	21
8.2. Pharmacological compounds can improve degradative capacity of proteome .....	21
8.2.1. Anti-inflammatory drugs .....	21
8.2.2. Cancer drugs .....	21
8.2.3. Cardiovascular drugs .....	21
8.2.4. Neurological disorder drugs .....	22
8.2.5. Drugs used in other therapies .....	22
9. Key questions and future perspectives .....	22
Conflict of interest .....	30
Acknowledgement .....	30
References .....	30

## 1. Introduction

Cells harbor millions of different kinds of molecules that accomplish all the necessary functions for its survival. Out of these molecules, proteins are involved in majority of cellular processes ranging from gene regulation to cell growth and differentiation (Qin et al., 2015). The importance of properly functioning protein can be understood from the evidence which suggest that organisms having longer lives consist of much stable or damage resistant proteome (Kaushik and Cuervo, 2015; Treaster et al., 2014). Therefore, cells continuously require properly functioning repertoire of proteins and to meet these requirements, cells synthesize and harbor proteins with utmost care (Frydman, 2001; Ibba and Soll, 1999). Regulation of protein synthesis which includes its proper folding, concentration and localization by cell can be termed as cellular proteostasis (Jackson and Hewitt, 2016). Nascent polypeptide chains come out of the ribosome tunnel, and are taken care by a group of cellular proteins, called molecular chaperones (Ellis, 1987; Kim et al., 2013; Wickner et al., 1999).

Chaperones assist nascent polypeptides to attain their necessary three-dimensional shape, without which they cannot function properly; instead they may turn into an unwanted aggregatory form, which start accumulating inside the cells and may sometimes cause lethal damage (Hartl et al., 2011; Hartl and Hayer-Hartl, 2002). Neurodegenerative diseases (NDDs) are the well known examples of such damage, caused by aggregation of proteins (Dobson, 1999; Gregersen et al., 2006; Ross and Poirier, 2004). Common factors that may enhance the risk of protein aggregation include genomic alterations, intra- as well as extracellular stresses, along with insufficient chaperoning capacities (Ramirez-Alvarado et al., 2010; Selkoe, 2004). However, to avoid and counter such obnoxious and toxic accumulation of proteins, cells have developed multiple ways, which majorly include repair systems at the genomic level, and refolding systems at the protein level (Lindahl and Wood, 1999; Tyedmers et al., 2010). If such attempts fail, cells may take final decision to degrade misfolded proteins and their inclusions inside the cells (Goldberg, 2003; Hochstrasser, 1996).

### 1.1. How proteostasis is crucial for normal cellular health and fitness?

Maintenance of cellular proteostasis is the integral need for cellular health and viability. Several cellular pathways linked with aging and age associated pathologies such as redox state of proteins, translation rate, protein folding and heat shock responses are affected in response to proteostasis alteration (Rongo, 2015; Taylor and Dillin, 2011). Further, this perturbed protein environment or proteostasis may lead to toxicity due to abnormal cell signaling, aberrant protein interactions and cellular membrane disruption (Gidalevitz et al., 2010). Proteostasis in cells is not only restricted to cytosol, but is also present in organelles such as in endoplasmic reticulum (ER) and mitochondria. Quality control mechanism in ER ensures proper folding and release of proteins (Elgaard and Helenius, 2003). In ER, the mechanism of proteostasis is maintained by unfolded protein response (UPR<sup>ER</sup>), which senses and restores the disturbed proteostasis by activating pathways that involve translation inhibition, enhanced folding and degradation (Inagi et al., 2014). Intriguingly, perturbations in the ER proteostasis is observed to be linked with neurodegeneration, cancer, and other disorders such as kidney disease (Hetz and Mollereau, 2014; Inagi et al., 2014; Liu and Ye, 2011).

Similarly, proteostasis is crucial for mitochondria so that it can accomplish various cellular tasks such as ATP production through respiratory chain networks,  $\beta$ -oxidation of fatty acids and maintenance of  $\text{Ca}^{2+}$  ion concentration etc. (Baker et al., 2011).

In mitochondria, a defective proteostasis generates UPR<sup>mt</sup> response similar to ER, which utilizes mitochondrial chaperones and proteases that clear proteotoxic load of mitochondria (Jovaisaitė and Auwerx, 2015). A defective proteostasis in mitochondria can produce detrimental effects in cells such as irregularities in ATP production and increased reactive oxygen species generation that may in turn contribute in different neurological, cancer and hereditary disorders (Haynes and Ron, 2010). Proteostasis also plays a central role in aging, and loss of proteostasis is considered as a common characteristic of aging (Labbadia and Morimoto, 2015). The cellular proteome of an aging cell is constantly challenged with different stress conditions that results in misfolded proteins production. These misfolded proteins with their hydrophobic surfaces exposed are highly prone to aggregation and formation of toxic inclusions in the cell (Taylor and Dillin, 2011). In older cells, the probability of toxic inclusion formation is more, since an older cell have limited expression of various protein quality control machineries to relieve cells from the toxic effects of aggregated proteins (Gidalevitz et al., 2010). Together, finding strategies that can provide us with novel tools or targets to precisely regulate the mechanism of proteostasis can prove to be beneficial from therapeutic point of view.

### 1.2. Dense network of cellular proteome and linkage with diseases

Techniques such as microarrays and yeast two-hybrid screens, have made it possible to efficiently acquire large amount of data that contains valuable information of cellular environment. However, to gain clear understandings of these mechanisms, datasets must be converted into meaningful set of information. Systematic arrangement of the data acquired, into well defined interaction network, made up by universal laws may provide us with new insights in understanding of cellular organization, as well as disease occurrence (Barabasi and Oltvai, 2004). A normal cell can be considered to be composed of a complex web of interaction networks having three basic interacting components i.e. genes, proteins and metabolites (Han, 2008). Being an important component and having diverse array of functions, understanding proteins have always remained a subject of interest to many researchers.

Properly folded functional proteins interact with each other and other metabolic components in a well defined manner, to perform respective assigned physiological functions (Saghafelian and Cravatt, 2005). Considerable studies have been performed in the past to understand the cellular machinery through generation and analysis of protein-protein interaction networks (Li et al., 2016; Rual et al., 2005). The mechanism of proteostasis can itself be considered as an integral part of cellular interaction network, involved in maintenance of a healthy proteome. However, under certain stress conditions or mutations, the state of proteostasis can get perturbed, resulting in a defective proteome network, ultimately generating pathological state (Barabasi et al., 2011). The severity of disease condition can be assumed to be dependent on the number of interactions or the mechanisms, the proteins have been involved in, which have been disturbed (Barabasi et al., 2011; Missiro et al., 2009). As evident from a study, highly connected protein or hub protein if gets deleted results in more lethal outcomes as compared to less connected protein (He and Zhang, 2006).

### 1.3. Systematic approach to understand the issues of proteome balance

The large network of the proteome is always maintained to achieve the utmost functional values of all proteins, present in the cell (Roth and Balch, 2011). This harmony is maintained till

proteome imbalance condition is generated, caused due to improper governing during new proteins synthesis or inefficient degradation of former ones (Harper and Bennett, 2016). In the late nineties, the development of various scientific approaches were initiated, giving a new direction to analyze the proteome involved in the maintenance of healthy cellular *milieu* and changes involved in occurrence of disease (Pennington et al., 1997). Before yeast two-hybrid system, techniques like Co-IP (co-immunoprecipitation), crosslinking and chromatography-based techniques were the typical used to identify protein-protein interactions (Fields and Song, 1989). Later, linking of mass spectrometry (MS) and two-dimensional gel electrophoresis demonstrated a useful alternate for proteome studies in yeasts (Shevchenko et al., 1996).

But because of its limitations, other techniques were developed that showed much better results, such as linking MS with separation techniques, which is commonly known as quantitative analysis of proteome (Gygi et al., 2000). Further, multiple techniques were combined to develop an effective method of quantitative proteome analysis, including isotope tagging of peptides by solid phase (beads) capture, that were further eluted and analyzed with microcapillary liquid chromatography and tandem mass spectrometry (Zhou et al., 2002). Similarly, techniques based on fluorescence-based detection methods, e.g., multiplexed proteomics, became popular due to its added advantage of ease in downstream processing of proteins by mass spectrometry along with conventional organic dyes like coomassie blue and silver staining (Candiano et al., 2004).

Detection of proteins by proteolytic modifications, reporter enzymes, differential gel electrophoresis (DIGE), and isotope coded affinity tagging also added significantly to the efficiency of proteome analysis methods. Matrix-Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) and Surface-Enhanced Laser Desorption-Ionization Mass Spectrometry (SELDI-MS) are the other two special mass spectrometry based methods that have been developed for peptide mapping with higher accuracy; however, there are many challenges that still remain in the use of these two techniques (Patton, 2002). In the last few decades, researchers have tried to analyze the yeast proteome with stable isotope labeling by amino acids in cell culture (SILAC), followed by its computational quantification (Cox et al., 2009; de Godoy et al., 2006). Some systematic approaches were also developed to study large experimental data of proteomics such as Proteomics Experiment Data Repository (PEDRo) schema (Taylor et al., 2003).

Few other systematic approaches, including databases such as The Munich Information Centre for Protein Sequences (MIPS) and Database of Interacting Proteins (DIP) have also been developed to study protein-protein network topology in order to identify the functional roles and localization of different proteins (Yook et al., 2004). Optimization of some older techniques of proteome analysis, e.g., in-gel digestion followed by MALDI-MS or LC-MS/MS; and development of efficient sample preparation methods, like filter aided sample preparation also led to increase the sensitivity of proteome analysis (Shevchenko et al., 2006; Wisniewski et al., 2009). Orbitrap mass detector, shotgun proteomics, absolute quantification (AQUA), isobaric tag for relative and absolute quantification (iTRAQ) and ribosome footprinting are some recent advances in systematic proteome analysis (Vogel and Marcotte, 2012). Even after such technological development in the field of proteome detection and analysis we still need much sophistication in terms of ease and sensitivity. There is an immense need for further optimization and modifications, so that these techniques may aid in gaining deep insights of proteome functions in future along with other applications such as disease diagnosis.

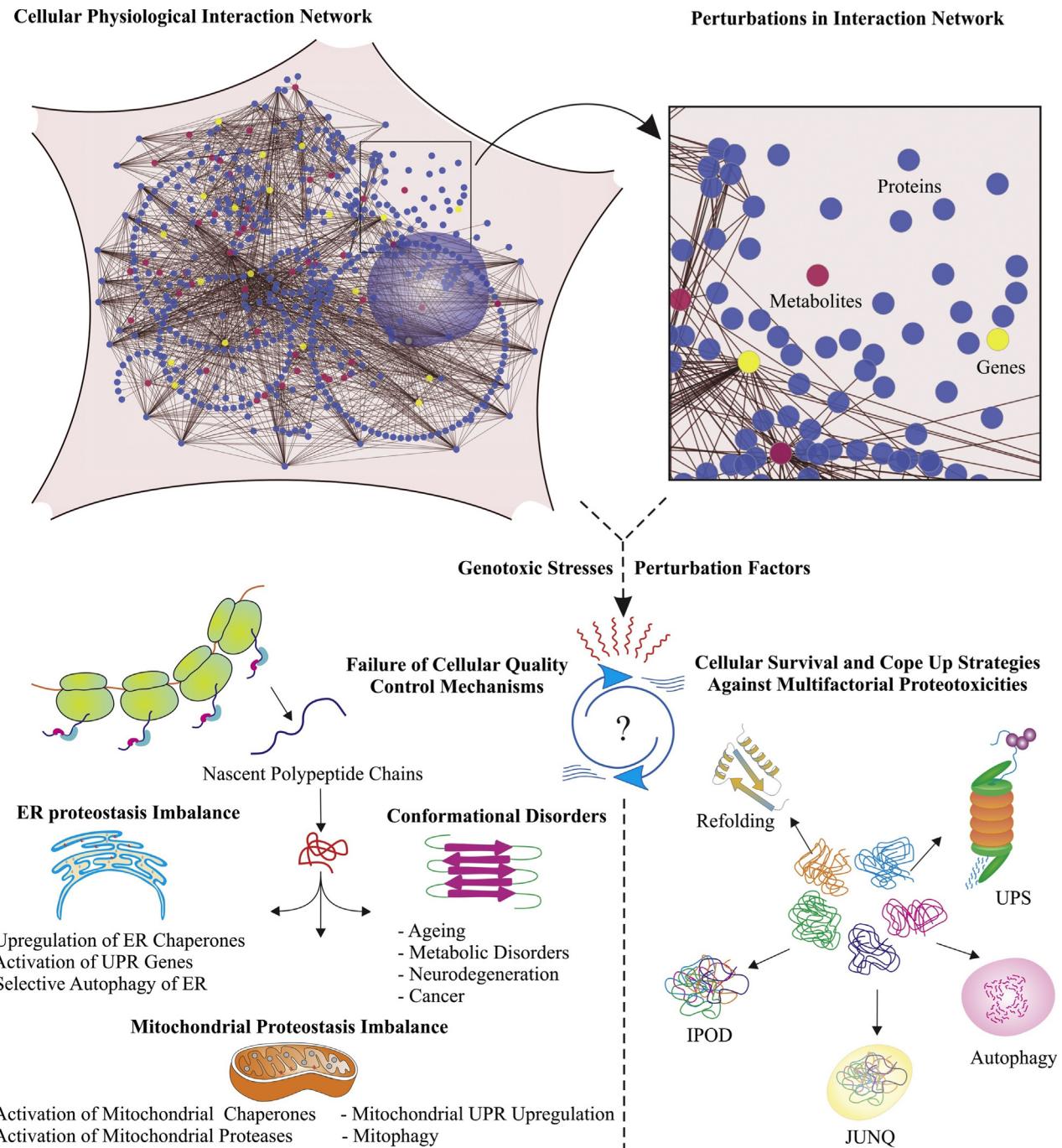
Mounting evidence suggests that proteins execute most of the cellular physiological functions under the continuous monitoring

of cellular protein quality control mechanisms. Cells have evolved with multiple lines of subsystems, which provide them various defense strategies to counter the imbalance and re-establish internal proteostasis. Cellular proteome is composed of large number of proteins interacting networks with each other to achieve diverse functions occurring inside the cells. Impairment of proteostasis affects these networks and may cause disturbances in homeostasis of cellular *milieu*, leading to multifactorial diseased state. To cope up against the effects of such genotoxic disturbances or perturbations, cells maintain aberrant protein homeostasis by rigorously scrutinized PQC processes as shown in Fig. 1.

Furthermore, the proteome analysis paves the basic ways to better understand differentiation of normal proteostasis or healthy state of the cell compare to imbalance or diseases associated with deregulated protein synthesis. Earlier assorted chemical, physical, biological and computational methods have been developed and modified according to the need of time, to study proteome in depth and in an efficient manner to acquire maximum knowledge as depicted in Table 1. However, still there is crucial indigence in the technical advancement of these methods, which may provide new opportunities to understand and predict more real cellular proteome functionality. Next sections of this article elaborate fundamental concepts and relevant landmark findings that specifically describe how cumulative functions of the intracellular PQC mechanisms ensure the maintenance of overall cellular fitness and survival. A better understanding of stress factors effects on proteostasis disturbance can explain possible therapeutic applications. Efficient utilization of various natural compounds and pharmacological agents can specifically target and reduce the defects of proteome linked with the threatening existence of aberrant proteins in dynamic proteome.

## 2. Understanding of living genetic balance and variations of cellular proteome

A healthy cellular system encompasses large number of underlying mechanisms that serve to accomplish various essential functions inside the cell. Every cell is programmed with genetic material called DNA that contains a library of coded instructions in the form of genes. On requirement, the process of transcription extracts the instructions from this library in the form of messenger RNA (mRNA), which is then decoded or translated with the help of ribosomes into proteins (Kozak, 1989). Large number of these proteins work as an integrated system working in well coordinated manner as per the cells requirement to keep it in a healthy or homeostatic state can be referred as cellular proteome of healthy cell (Berggard et al., 2007; Roth and Balch, 2011). Under normal circumstances, in order to achieve healthy and homeostatic state of a cell, proteins have to be properly synthesized, folded and stabilized so that they can do their normal functions in routine cellular metabolism (Gidalevitz et al., 2011; Hartl and Hayer-Hartl, 2009). Cells achieve it with the help of various monitoring or quality control (QC) mechanisms that can be broadly divided into three levels i.e., (i) at DNA level where quality of DNA is checked for any damage or mutations (Lindahl and Wood, 1999) (ii) at translational level or during protein synthesis where errors in protein translation is assessed (Hartl and Hayer-Hartl, 2002) and (iii) after protein translation, where, as per requirement or quality, proteins are targeted for refolding or degradation (Wickner et al., 1999). However, besides the aforementioned scenario, the cells have to face various challenging situations that occur due to different genetic, non-genetic and external environmental factors that may lead cells to diseased state, further discussed in the next section.



**Fig. 1.** Downstream effects of proteome disturbance and proteome analysis approaches. An exemplary representation of an interactome composed of genes, proteins and metabolites. Protein quality control mechanism (PQC) is represented as an integrated sub-network of this interactome involved in providing a healthy proteome, leading to a homeostatic state. On exposure to perturbation factors, cells try to achieve state of proteostasis by employing various protein quality control mechanisms which include refolding, sequestration and degradation. Failure in PQC mechanisms may lead to protein misfolding and can cause proteostasis imbalance of vital cellular organelles such as endoplasmic reticulum and mitochondria.

## 2.1. Variations of cellular protein quality control mechanisms

The state of cellular proteostasis can get perturbed due to insults caused by various stress factors, such as pathogens, mutations, abnormal or misfolded proteins, environmental stresses, improper nutrition and toxic chemicals leading to a diseased state as shown in Fig. 2. The challenges posed by pathogens on proteostasis can be understood with the studies such as in neuronal cells, HSV-1(Herpes simplex virus) virus has been shown to generate neurotoxicity as a result of the increased

amyloid precursor protein (APP) fragmentation (De Chiara et al., 2010). Another study reported the presence of aggregated  $\alpha$ -synuclein in hippocampus, cortex and the brain stem regions of mice on infection with highly pathogenic H5N1 influenza virus (Jang et al., 2009). Similarly, natural chronic bacterial infections and injections in animals may cause amyloid depositions (Miklossy, 2008). Interestingly, a recent study has reported that exoenzymes U and Y of bacteria *Pseudomonas aeruginosa* caused transmissible cellular injury, a characteristic of infectious proteinopathy, as a result of its high molecular weight tau inducing

property (Morrow et al., 2016). Another recent study has shown the presence of fungal infections in brain tissues of Alzheimer's disease patients, a disease characterized by the presence of hyperphosphorylated tau tangles and amyloid deposits (Pisa et al., 2015). Further studies directed towards understanding role of pathogens on proteome functioning may provide us with new insights on their contribution in generating proteinopathies.

Genomic instability is another factor that has been studied for its involvement in causing disturbances in normal protein functioning. Prolonged activation of protein poly (ADP-ribose) polymerase 1 (PARP1) in response to DNA single strand breaks may lead to release of apoptosis inducing factor (AIF), which may cause cell death, a mechanism relevant in diseases like diabetes, arthritis, brain and heart damage (Caldecott, 2008). Malfunctioning and

**Table 1**  
Summary of major advances in multiple approaches developed towards proteome analysis since the discovery of first protein-protein interaction till mapping of human proteome.

Major Advances In The Field Of Proteome Analysis	References
<b>1901-1930</b>	
1922: Identification of first regulatory protein-protein interaction	(Northrop, 1922)
1928: Invention of ultracentrifugation method to determine molecular weight of proteins	(Svedberg and Chirnoaga, 1928)
1930: Apparatus was designed using electrophoresis concept for analysis of proteins	(Tiselius, 1937)
<b>1931-1960</b>	
1941: Antibody was first time labeled with FITC, giving rise to the field of immunofluorescence	(Coons et al., 1941)
1944: Qualitative analysis of proteins by paper-based partition chromatography	(Consden et al., 1944)
1950: Amino acids sequencing method was developed for peptides	(Edman, 1949)
1953: Dinitrophenyl method was applied to identify amino acids sequence of insulin-1	(Sanger and Tuppy, 1951)
1959: X-ray crystallography was utilized to obtain high-resolution structure of a myoglobin	(Kendrew, 1959)
<b>1961-1990</b>	
1962: First bioluminescent protein GFP was extracted and purified from jellyfish <i>Aequorea</i>	(Shimomura et al., 1962)
1967: Development of SDS-PAGE for molecular weight estimation of polypeptide chains	(Shapiro et al., 1967)
1971: Establishment of the Protein Data Bank (PDB) by Brookhaven National Laboratory	(Bernstein et al., 1977)
1975: A method of high-resolution 2D Gel-Electrophoresis was established for proteins	(O'Farrell, 1975)
1975: Unique antibody adsorbent protein A was identified to study antigen- antibody interactions	(Kessler, 1975)
1978: First inclusion of NMR for protein structure determination	(Wüthrich et al., 1978)
1978: Generation of protein-protein interaction modes using computational method	(Wodak and Janin, 1978)
1987: Incorporation of MALDI-TOF in field of protein and polymer analysis	(Tanaka et al., 1988)
1989: Yeast two-hybrid system was developed to detect protein-protein interaction	(Fields and Song, 1989)
<b>1990-Continue</b>	
1993: Mass Spectrophotometry and 2D gel electrophoresis were linked for rapid proteome analysis	(Henzel et al., 1993)
1993: Development of SELDI-TOF-MS method for mass spectrometric analysis of macromolecules	(Hutchens and Yip, 1993)
1999: Identification of protein microarray for gene expression and interaction studies	(Lueking et al., 1999)
2001: TAP-tag method came into existence for protein complex purification	(Puig et al., 2001)
2002: Development of quantitative proteome analysis method μLC-MS/MS	(Zhou et al., 2002)
2002: Increase in accuracy for expression proteomic study using SILAC	(Ong et al., 2002)
2014: A draft map of human proteome prepared on the basis of mass spectrometry	(Kim et al., 2014)

**Table 1.** Summary of major advances in multiple approaches developed towards proteome analysis since the discovery of first protein-protein interaction till mapping of human proteome.

#### References of Table-1

- Bernstein FC, Koetzle TF, Williams GJ, Meyer EF, Jr., Brice MD, Rodgers JR, Kennard O, Shimanouchi T and Tasumi M (1977) The Protein Data Bank: a computer-based archival file for macromolecular structures. *Journal of molecular biology* **112**:535-542.
- Consden R, Gordon AH and Martin A (1944) Qualitative analysis of proteins: a partition chromatographic method using paper. *Biochemical Journal* **38**:224.
- Coons AH, Creech HJ and Jones RN (1941) Immunological Properties of an Antibody Containing a Fluorescent Group. *Proceedings of the Society for Experimental Biology and Medicine* **47**:200-202.
- Edman P (1949) A method for the determination of amino acid sequence in peptides. *Archives of biochemistry* **22**:475.

**Table 1** (Continued)

- Fields S and Song O (1989) A novel genetic system to detect protein-protein interactions. *Nature* **340**:245-246.
- Henzel WJ, Billeci TM, Stults JT, Wong SC, Grimley C and Watanabe C (1993) Identifying proteins from two-dimensional gels by molecular mass searching of peptide fragments in protein sequence databases. *Proceedings of the National Academy of Sciences of the United States of America* **90**:5011-5015.
- Hutchens TW and Yip T-T (1993) New desorption strategies for the mass spectrometric analysis of macromolecules. *Rapid Communications in Mass Spectrometry* **7**:576-580.
- Kendrew J (1959) Structure and function in myoglobin and other proteins, in *Federation proceedings* p 740.
- Kessler SW (1975) Rapid isolation of antigens from cells with a staphylococcal protein A-antibody adsorbent: parameters of the interaction of antibody-antigen complexes with protein A. *Journal of immunology* **115**:1617-1624.
- Kim MS, Pinto SM, Getnet D, Nirujogi RS, Manda SS, Chaerkady R, Madugundu AK, Kelkar DS, Isserlin R, Jain S, Thomas JK, Muthusamy B, Leal-Rojas P, Kumar P, Sahasrabuddhe NA, Balakrishnan L, Advani J, George B, Renuse S, Selvan LD, Patil AH, Nanjappa V, Radhakrishnan A, Prasad S, Subbannayya T, Raju R, Kumar M, Sreenivasamurthy SK, Marimuthu A, Sathe CJ, Chavan S, Datta KK, Subbannayya Y, Sahu A, Yelamanchi SD, Jayaram S, Rajagopalan P, Sharma J, Murthy KR, Syed N, Goel R, Khan AA, Ahmad S, Dey G, Mudgal K, Chatterjee A, Huang TC, Zhong J, Wu X, Shaw PG, Freed D, Zahari MS, Mukherjee KK, Shankar S, Mahadevan A, Lam H, Mitchell CJ, Shankar SK, Satishchandra P, Schroeder JT, Sirdeshmukh R, Maitra A, Leach SD, Drake CG, Halushka MK, Prasad TS, Hruban RH, Kerr CL, Bader GD, Iacobuzio-Donahue CA, Gowda H and Pandey A (2014) A draft map of the human proteome. *Nature* **509**:575-581.
- Lueking A, Horn M, Eickhoff H, Bussow K, Lehrach H and Walter G (1999) Protein microarrays for gene expression and antibody screening. *Analytical biochemistry* **270**:103-111.
- Northrop JH (1922) The Inactivation of Trypsin : II. The Equilibrium between Trypsin and the Inhibiting Substance Formed by Its Action on Proteins. *The Journal of general physiology* **4**:245-260.
- O'Farrell PH (1975) High resolution two-dimensional electrophoresis of proteins. *The Journal of biological chemistry* **250**:4007-4021.
- Ong SE, Blagoev B, Kratchmarova I, Kristensen DB, Steen H, Pandey A and Mann M (2002) Stable isotope labeling by amino acids in cell culture, SILAC, as a simple and accurate approach to expression proteomics. *Molecular & cellular proteomics : MCP* **1**:376-386.
- Puig O, Caspary F, Rigaut G, Rutz B, Bouveret E, Bragado-Nilsson E, Wilim M and Seraphin B (2001) The tandem affinity purification (TAP) method: a general procedure of protein complex purification. *Methods* **24**:218-229.
- Sanger F and Tuppy H (1951) The amino-acid sequence in the phenylalanyl chain of insulin. 1. The identification of lower peptides from partial hydrolysates. *Biochemical Journal* **49**:463-481.
- Shapiro AL, Vinuela E and Maizel JV, Jr. (1967) Molecular weight estimation of polypeptide chains by electrophoresis in SDS-polyacrylamide gels. *Biochemical and biophysical research communications* **28**:815-820.
- Shimomura O, Johnson FH and Saiga Y (1962) Extraction, purification and properties of aequorin, a bioluminescent protein from the luminous hydromedusan, Aequorea. *Journal of cellular and comparative physiology* **59**:223-239.
- Svedberg T and Chirnoaga E (1928) The molecular weight of hemocyanin. *Journal of the American Chemical Society* **50**:1399-1411.
- Tanaka K, Waki H, Ido Y, Akita S, Yoshida Y, Yoshida T and Matsuo T (1988) Protein and polymer analyses up to m/z 100 000 by laser ionization time-of-flight mass spectrometry. *Rapid Communications in Mass Spectrometry* **2**:151-153.
- Tiselius A (1937) A new apparatus for electrophoretic analysis of colloidal mixtures. *Transactions of the Faraday Society* **33**:524-531.
- Wodak SJ and Janin J (1978) Computer analysis of protein-protein interaction. *Journal of molecular biology* **124**:323-342.
- Wüthrich K, Wagner G and Bundi A (1978) NMR Studies of the Molecular Dynamics of Peptides and Proteins, in *Nuclear Magnetic Resonance Spectroscopy in Molecular Biology: Proceedings of the Eleventh Jerusalem Symposium on Quantum Chemistry and Biochemistry Held in Jerusalem, Israël, April 3-7, 1978* (Pullman B ed) pp 201-210, Springer Netherlands, Dordrecht.
- Zhou H, Ranish JA, Watts JD and Aebersold R (2002) Quantitative proteome analysis by solid-phase isotope tagging and mass spectrometry. *Nature biotechnology* **20**:512-515.

deregulation of proteins involved in DNA damage repair, such as ATM, Pol $\beta$ ,  $\beta$ -OGG1, MUTYH and DNA-PK have also been linked with various neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's disease (Merlo et al., 2016). Various other studies that have linked instability in genome and its repair mechanisms in neurodegeneration and aging have been reviewed timely (Jeppesen et al., 2011; Martin, 2008; Rao, 1993). Additionally, a recent study has linked Inpp5a deletion with Purkinje cell degeneration and ataxia (Yang et al., 2015).

In a properly functioning proteome network, presence of correctly folded functional proteins is essential requirement. Abnormal functioning, due to misfolding and aggregation of proteins such as  $\alpha$ -synuclein (Sherer et al., 2002), huntingtin (Marti, 2016), TDP43 (Scotter et al., 2015), prions (Bolton et al., 1982), alphaB-crystallin (Vicart et al., 1998), CFTR (Bobadilla et al., 2002), proinsulin (Izumi et al., 2003), SOD1 (Strong et al., 2005) and tau (Usenovic et al., 2015) have been linked as crucial factors in various disease development mechanisms. Another important factor involved in misfolding and malfunctioning of proteins is oxidative and nitritative stress induced by reactive oxygen and nitrogen species (Cobb and Cole, 2015). Oxidative stress has been linked to elevated monoamine oxidase B (MAO-B) levels and reduced parkin E3 ubiquitin ligase activity (Siddiqui et al., 2012). Similarly, reactive nitrogen species have been shown to disturb parkin functions resulting in the development of Parkinson's disease (Cobb and Cole, 2015). Interestingly, high osmotic pressure mediated reactive oxygen species generation has been observed to induce endoplasmic reticulum (ER) stress, causing apoptosis (Wang et al., 2016). Functionality of proteins has also been observed to be affected by temperature, such as in the case of CFTR mutant (CFTR $\Delta$ F508). Reducing temperature leads to proper processing and delivery of this mutant to plasma membrane like wild type CFTR (Denning et al., 1992).

Electrostatic interactions play an important role in providing stability to proteins. Change in pH may cause destabilization of proteins, as a result of unfavorable interactions due to introduction of positive or negative charges (Anderson et al., 1990). Dietary restrictions has also been considered as an effective strategy to slow down aging and progression of age related diseases (Meydani, 2001). A recent study has reported increased amyloid beta (A $\beta$ ) deposition in response to high fat diet (Lin et al., 2016). Salt, besides being a major factor in causing high blood pressure leading to cardiac complexities, has also been shown to cause efferent arterioles remodeling in mice (Zhao et al., 2016). In another study, high salt fed hypertensive Dahl rats showed reduced cardiac ATP dependent proteasomal catalytic activity, along with elevated levels of oxidized proteins and soluble oligomers (Ferreira et al., 2012). Similarly, exposure to high sucrose levels at early life stages have been shown to cause metabolic disturbances. In this study it has been shown that high sucrose can lead to disruption in ER homeostasis and reduced level of glucose regulated protein (GRP78), an ER chaperone involved in correct protein folding (Pinto et al., 2016).

Apart from these, exposure to various drugs, chemicals and heavy metals have also been observed to cause impaired protein quality control mechanisms and protein aggregation. Commonly used Nonsteroidal anti-inflammatory drug (NSAIDs) like aspirin, diclofenac and ibuprofen have been shown to cause proteasome dysfunction (Amanullah et al., 2017; Dikshit et al., 2006; Upadhyay et al., 2016a). Increased use of insecticides and herbicides has elevated the risks of their exposure and intake by the human body. Rotenone, a broad spectrum insecticide, causes ubiquitin proteasome system (UPS) impairment via upregulation of NADPH oxidase (Pal et al., 2014). Similarly, paraquat has been reported to increase  $\alpha$ -synuclein aggregation, which is involved in causing Parkinson's disease (Manning-Bog et al., 2002).

Metals including aluminum, copper, iron, cobalt and manganese, some of which are also essential for metabolism, have been linked with accelerating  $\alpha$ -synuclein aggregation and fibril formation (Dusek et al., 2015; Uversky et al., 2001). Also, toxic environmental agents like lead (Pb) have been reported to elevate the expression of APP and its amyloidogenic products (Basha et al., 2005). Thus, cellular proteome network has to face a variety of internal and external perturbation factors ranging from genomic instability to improper lifestyle, that pose a constant threat to stability of this network leading to diseased state. Some of these factors such as mutations and aberrant proteins have gained a lot more attention in understanding their roles in disease pathology in relation to proteostasis, as compared to factors such as pathogens and lifestyle. However, recent studies as mentioned above has provided an opportunity to look carefully into these less explored but important factors for their roles in proteostasis and disease mechanisms underlying proteostasis disturbance.

## 2.2. Protective and adaptive functions of cellular proteome

To keep cellular proteome working properly, cells employ various quality control mechanisms at different levels during course of protein synthesis as represented in Fig. 3. At the DNA level alone, there are several repair pathways that constantly work to check and remove errors in DNA. These include direct reversal, homologous recombination, non homologous end joining pathway, base excision repair, nucleotide excision repair and the bypass mechanism (Hakem, 2008; Lindahl and Wood, 1999). Development of various diseases like diabetes, cancer, neurodegenerative disorders, cockayne syndrome, xeroderma pigmentosum and severe combined immunodeficiency have been considered as a consequences of defects in DNA damage repair mechanisms (Blasiak et al., 2004; Hakem, 2008; Maynard et al., 2015). Decreased repair capacity, leading to disturbed proteome balance (Tokarz et al., 2013), provides an evidence of the crucial roles played by DNA repair mechanisms in maintaining cellular fitness.

It is important to prevent formation and accumulation of abnormal proteins at the initial stage of protein synthesis, the co-translational QC mechanisms act at the ribosomal sites, where proteins are synthesized and guide newly synthesized polypeptide chains into properly folded functional proteins (Hartl and Hayer-Hartl, 2002). The co-translational QC mechanism is equipped with two complexes; nascent polypeptide-associated complex (NAC) and ribosome-associated complex (RAC) which are involved in protecting nascent polypeptide chains from unwanted interactions and stabilize them (Amm et al., 2014; Hartl and Hayer-Hartl, 2002). Occasionally, transcriptional errors may lead to formation of defective mRNAs, like non-stop mRNA, that may result in ribosomal stalling. Cells overcome such situations with help of surveillance mechanism that includes Dom34/Pelota-Hbs1 and ATP binding cassette subfamily E member 1 (ABCE1) which senses stalled ribosome and disassemble ribosome into its subunits causing mRNA to dissociate, leading to its degradation (Inada, 2016; Pisarev et al., 2010; Shoemaker and Green, 2011).

Further, E3 ubiquitin ligase like Listerin ubiquitinates the defective nascent polypeptide chain that may lead to proteasomal degradation (Shao et al., 2013). Other E3 ubiquitin ligases like Histone E3 ligase (Hel2) and Not4 have also been suggested to be involved in co-translational quality control (Duttler et al., 2013; Panasenko, 2014). Thus, quality control mechanism at the ribosome level plays a crucial role in preventing aberrant translation leading to aggregation and proteotoxicity. However, more studies are still needed to uncover underlying hidden mechanisms to gain further understanding of this crucial process.

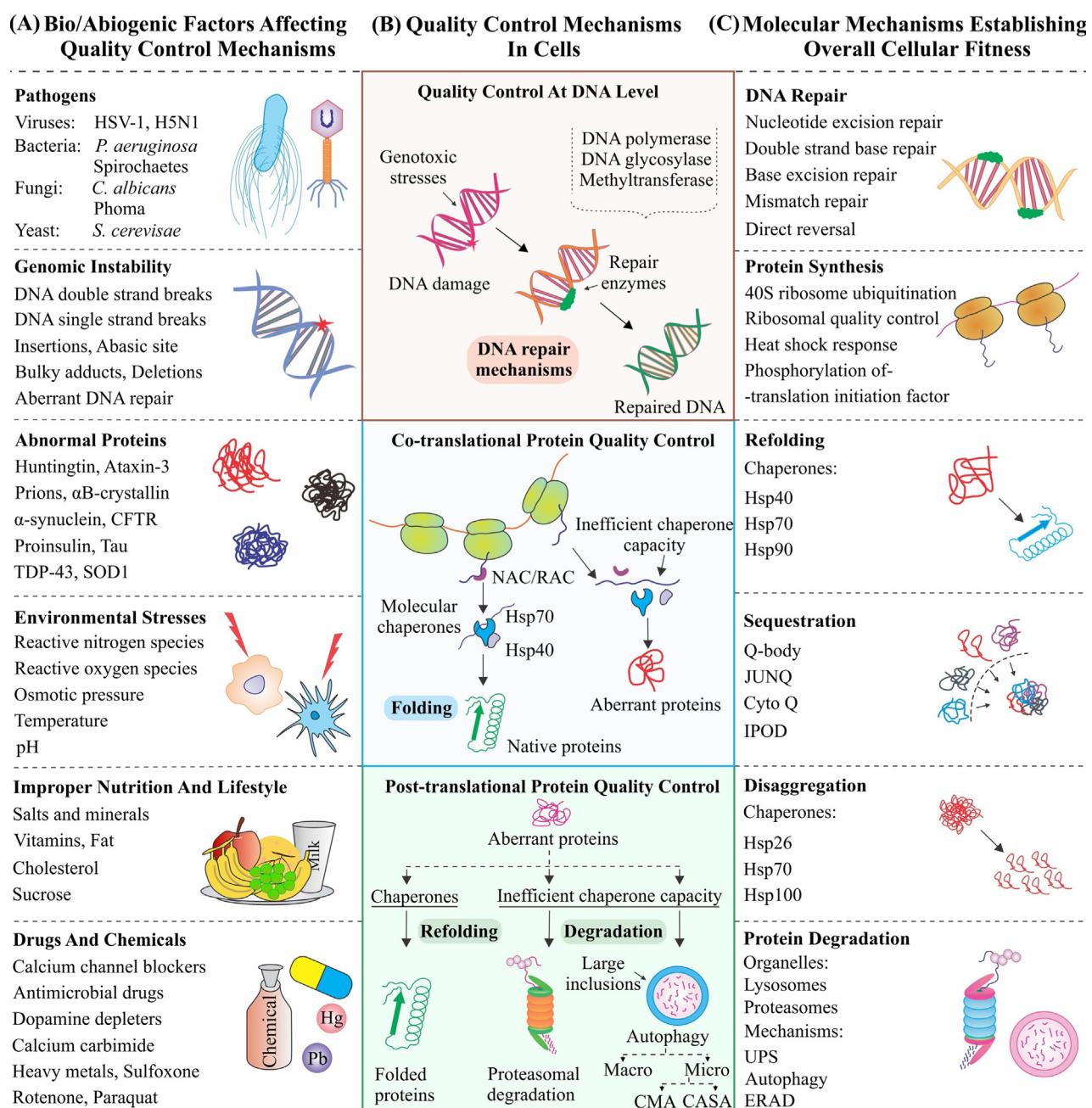
The quality control mechanisms present at transcriptional and translational levels protect cells regularly from the formation of

misfolded proteins. However, mutations, stress conditions and failures at transcription and translational levels may result in formation of misfolded proteins and toxic protein aggregates (Amm et al., 2014). To counter such situations, a cell is equipped with another set of QC system termed as post-translational protein quality control. Here, misfolded proteins are recognized by protein folding machineries called as chaperones that tries to refold them into functional forms or target them to protein degrading pathways such as ubiquitin proteasome system and autophagy (Ciechanover and Kwon, 2015; Wickner et al., 1999). These mechanisms will be further discussed in other section of the review. Together, to establish a properly working and tightly regulated proteome network, comprising huge number of proteins, which keep on varying as per requirement, the cell has to be

equipped with an efficient quality control mechanism. The elasticity these quality control mechanisms exhibit by getting precisely activated in response to a particular requirement in constantly changing dynamics of cellular environment, makes it a quite interesting and attractive system to gain further insights.

### 2.3. Cellular and molecular interactions determine specificity and fitness of proteome

A cell spends considerable energy for its proteome fitness (Maklakov and Immler, 2016). Appearance of a non-functional or misfolded protein may interfere and lead to disturbance in this protein network, which is normalized with help of integrated system of energy utilizing proteostasis network that repair or

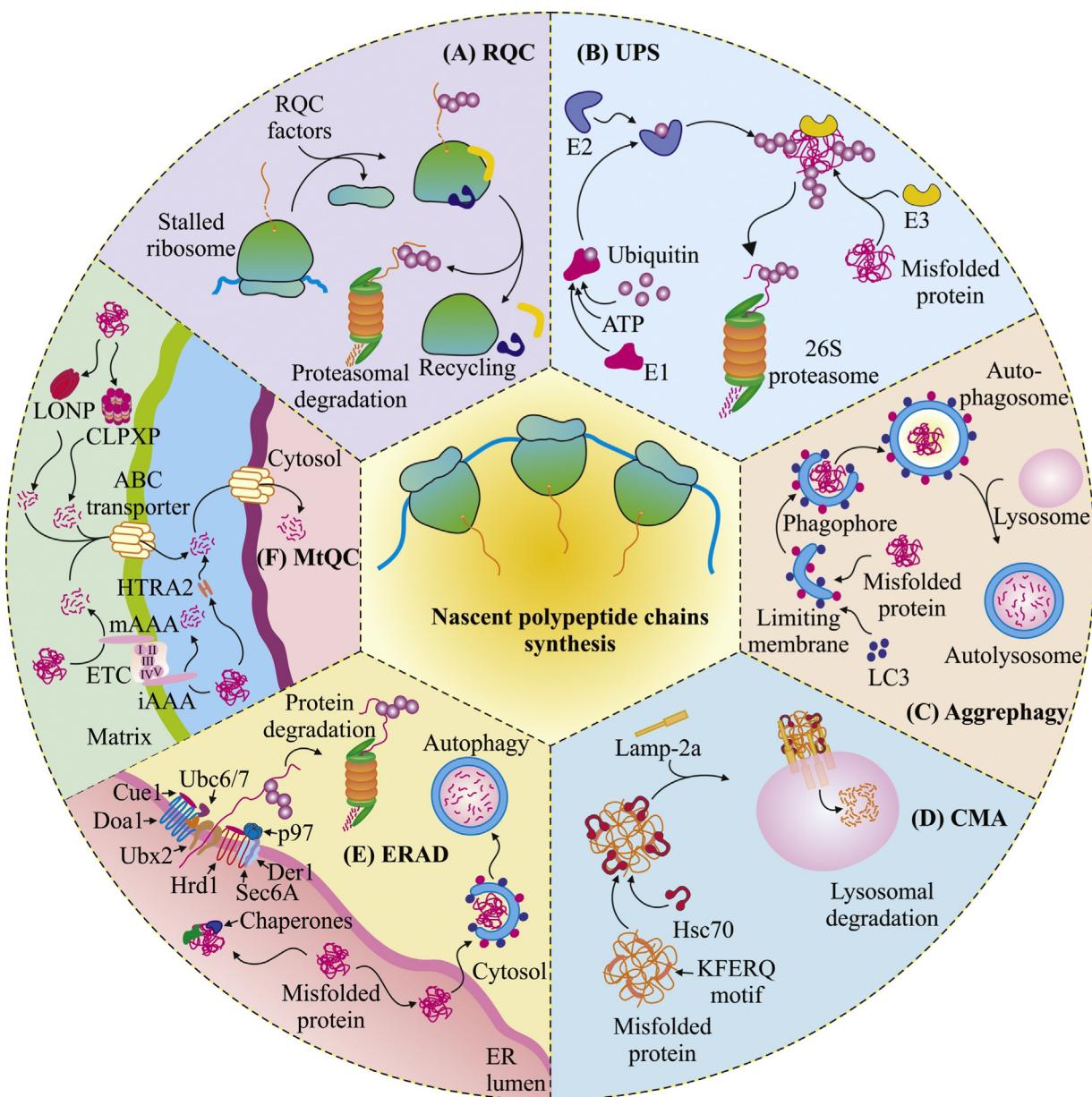


**Fig. 2.** Overview of perturbation factors and cellular defense mechanisms. (A) Endogenous and exogenous factors that may disturb cellular proteostasis further leading to diseased state and cytotoxicity (B) Different levels of cellular protein quality control mechanisms involved in achieving cellular proteostasis (C) Molecular machineries acting at different levels as per requirement to establish cellular fitness essential for cell survival.

remove such proteins that requires energy (Diaz-Villanueva et al., 2015; Gidalevitz et al., 2011). The presence of DNA repair mechanisms mentioned previously for genome errors gives an idea that cells try to limit the formation of such misfolded proteins right from the initial stage of protein synthesis, thereby reducing energy wastage in translating such proteins (Drummond and Wilke, 2009; Maquat, 1995). Still, if transcription occurs cells inhibit translation of protein by phosphorylation of eukaryotic translation initiation factor (eIF2alpha) and possibly 40S ribosomal ubiquitination which can be considered as an energy conserving support system (Higgins et al., 2015; Koumenis et al., 2002). Another process that a cell utilizes is refolding, that uses chaperones which helps cell to reduce loss in energy spent on replacing an aberrant protein with a newly synthesized

polypeptide chain. Chaperones such as Hdj1, Hsp70 and Hsp90 have been shown to be involved in this refolding process (Freeman and Morimoto, 1996). In case if denatured or misfolded proteins form aggregates, chaperones like Hsp26, Hsp70 and Hsp100 helps in there disaggregation to make them available for refolding (Cashikar et al., 2005; Liberek et al., 2008).

However, if the chaperone system is not able to refold misfolded proteins, they are then sent for degradation with the help of mechanisms that involve proteasome and lysosome (Ciechanover, 1994; Ravikumar et al., 2002). Under conditions when the degrading machinery faces sudden load of accumulating substrates, cells try to sequester those misfolded proteins into compartments such as Q-bodies, juxtanuclear quality control compartment (JUNQ/INQ), insoluble protein deposit (IPOD), and



**Fig. 3.** Schematic representation of various strategies to protect nascent polypeptide chains against misfolding. (A) Ribosome-associated complex (RAC) and nascent polypeptide-associated complex (NAC) monitors efficient dispersal of newly synthesized polypeptide chains. (B) Ubiquitin proteasome system performs intracellular protein degradation, using a very specific approach via assistance of E3 ubiquitin ligases. (C) Unwanted bulks of cellular protein aggresomes are cleared by process of aggraphagy. (D) Chaperone-mediated autophagy recognizes specific motif containing substrates and degrades them through lysosomal pathway. (E) There exists a separate set of ER chaperones and ER associated QC E3 ubiquitin ligases, which identify and ubiquitinate respectively, ER resident incorrectly folded proteins to translocate them to the cytosol, where proteasomal degradation of such ERAD substrates take place. (F) Mitochondria are another cellular subsystem, which separately possess its own quality control system, i.e. mitochondrial quality control (MtQC). Diverse mitochondrial proteases in mitochondrial matrix, IMM, and OMM contribute majorly in MtQC.

Cyto-Q (Escusa-Toret et al., 2013; Kaganovich et al., 2008; Miller et al., 2015). By applying such strategy, cells also protect their homeostatic state from interference by these misfolded proteins, as exposed hydrophobic regions of these misfolded proteins may become a site of unwanted interactions for normal functioning proteins (Fink, 1998). Hence, by recycling and adapting efficient pathways, cells try to maximize its available energy and resources in maintaining proteome. The organization and working of the PQC network with its reach from a single protein to the complete proteome gives an idea of how various cellular protein quality control mechanisms in cells aid to achieve state of proteostasis.

### 3. What is the fast track for mapping synergistic clearance of aberrant proteins?

Proteins are the major macromolecules inside the cells. It has been explained how cells perform all the major functions with the help of a healthy and functional pool of proteins (Balchin et al., 2016). Under deleterious stress-like conditions, these normal proteins tend to accumulate into highly toxic aberrant forms, which result in occurrence of various diseases (Tyedmers et al., 2010). To avoid such abnormal situations, cells need a system which can continuously monitor such unwanted changes and perform specific clearance of toxic proteinaceous bodies from the cytoplasm (Bukau et al., 2006). Therefore, cells have developed some specialized mechanisms, which aid cells to accomplish the task of maintenance of a healthy cellular proteome; and these systems are collectively referred as protein quality control systems (Hartl, 2016). Protein quality control at the ribosome is one such mechanism, which during translation monitors and checks thoroughly to ensure that any aberrant protein is not being dispersed in the cell (Pechmann et al., 2013). The efforts to avoid misfolding start from the time when nascent polypeptides emerge out from the ribosome exit tunnel. There are several groups of proteins, which form specialized protein complexes like Ribosome-Associated Complex (RAC) and Nascent-Polypeptide-Associated Complexes (NAC), in order to co-translationally safeguard nascent chains from the *de novo* protein misfolding events (Hartl et al., 2011; Preissler and Deuerling, 2012).

Several other cytosolic chaperone complexes also perform the further proofreading of cellular proteins to ensure that newly synthesized polypeptides achieve their native three-dimensional structures (Duttler et al., 2013; Pechmann et al., 2013). These chaperone complexes not only guard nascent polypeptides while folding, but under stressed conditions, they may also switch their roles to degrade any aberrantly misfolded proteins with the help of coordinated actions of other cellular degradation systems (Hartl et al., 2011). Ubiquitin proteasome system (UPS) and autophagy are two broad systems which continuously clear the cellular *milieu* from aggregated proteins (Kroemer et al., 2010; Varshavsky, 2012). Cellular organelles have developed their own strategies and mechanisms to locally monitor any stress-like situation and re-establish the cellular proteostasis balance. Endoplasmic reticulum associated degradation (ERAD) and mitochondrial quality control (mtQC) are major examples of such subsystems (Wolff et al., 2014).

#### 3.1. Proteasome linked with ubiquitins generates homeostasis at cellular level

Cellular proteins are synthesized by ribosomes, whereas their maturation takes place at the endoplasmic reticulum (ER) membranes, to later get transported over their respective cellular locations (Braakman and Bulleid, 2011). Proteins have certain half-lives, which are the major determinants for their cellular presence, activities and functions (Eden et al., 2011; Plotkin, 2011). To ensure the best possible regulation over their functions, cells have chosen

well-regulated specific degradation machinery, which tags proteins, to be degraded, very specifically, through a small ubiquitin molecule, and directs them to a large barrel-shaped multi-protein proteolysis unit called proteasome (Hershko and Ciechanover, 1982; Hough et al., 1987). The cascade of reactions is catalyzed by three different kinds of enzymes: E1 ubiquitin activating, E2 ubiquitin conjugating and E3 ubiquitin ligase enzymes. E1 activates small ubiquitin molecules in an ATP-dependent manner, which is later conjugated to E2 enzymes. Thereafter, E3 ubiquitin ligases attach these ubiquitin molecules to the substrates proteins (Hershko and Ciechanover, 1982, 1992). There are other enzyme classes, known as, E4 and deubiquitylating enzymes (DUBs), which also play important roles in maintaining the homeostasis of the cell. E4 enzymes lengthen the ubiquitin chain, whereas DUBs release free ubiquitin molecules once the substrate protein enters the proteasome (Koegl et al., 1999; Reyes-Turcu et al., 2009). The specificity of the system is generated by a large number of E3 ubiquitin ligases, which target their specific substrates, for proteasomal degradation (Finley, 2009).

In the past, another mechanism of proteasomal degradation of non-native cellular proteins has been proposed, i.e., chaperone assisted proteasomal degradation (CAP) (Meacham et al., 2001; Patterson and Höfeld, 2008). In CAP, ubiquitinated proteinaceous inclusions are identified by chaperones Hsc70 and are delivered to proteasome for their degradation (Arndt et al., 2007; Kettern et al., 2010). Co-chaperones Hsp40 and CHIP play important roles in the functional regulation of chaperone-assisted degradation mechanisms (Joshi et al., 2016; Shiber and Ravid, 2014). The proteins, which are degraded by CAP, are involved in multiple crucial cellular pathways, ranging from signaling to apoptosis; therefore, its own regulation by co-chaperones is also equally important, in order to accomplish its cellular tasks (Kettern et al., 2010). The limitation of proteasome system lies in its incapability to degrade bulky mass of protein aggregates, or insoluble inclusions present inside neuronal cells, as reported in a number of neurodegenerative diseases (Bence et al., 2001; Bennett et al., 2005; Venkatraman et al., 2004).

#### 3.2. Autophagy can do compensatory balance functions under proteasome dysfunctions

To overcome the limitations of the proteasome, cells encompass a dynamic recycling system, termed as 'autophagy', which not only removes bulky masses from the cytoplasm, including old or damaged cell organelles and insoluble protein inclusions, but also produces energy, and provide new building blocks for further renovation inside the cells (Mizushima and Komatsu, 2011; Ravikumar et al., 2010). Although the importance of lysosomal lysis of intracellular substances is known for around hundred years, yet the essence of this organelle for proteostasis has been established recently. Cytoplasmic protein inclusion bodies are delivered to lysosomes by similar ubiquitin like modifications, as happens in UPS degradation, and is digested thoroughly by a set of lysosomal enzymes (Cuervo, 2008; Klionsky, 2007). As cellular proteostasis could be defined in simpler terms as a fine balance between biosynthesis and turnover, it is now believed that insufficiency of this system with increasing age could be a major cause of many diseases including cancer and neurodegeneration (He and Klionsky, 2009).

Although, the autophagy system is a bulk degradation pathway, still its own regulation at transcriptional and translational levels is very important for many physiological pathways running inside the cell. Involvement of a number of genes in its regulation over the induction and the magnitude of autophagy is indicative of its regulatory importance. Several attempts to modulate the system, in order to maintain its balanced state, are under investigation (Feng et al., 2015; Ohsumi, 2014). In general terms, autophagy

refers to macroautophagy (MA), which involves a bulk degradation process of a whole cytosolic region, by the formation of autophagosome, followed by fusion with lysosomes and in turn its digestion (Mizushima et al., 2008). But, some specialized and selective forms of lysosomal degradation of proteins also exist inside the cells which are: chaperone mediated autophagy (CMA), and chaperone-assisted selective autophagy (CASA).

### 3.2.1. Chaperone Mediated Autophagy (CMA)

Similar to E3 ubiquitin ligases, chaperones are also involved in the recognition of aberrant cytosolic proteins, which are not acted upon by UPS, for their clearance from the cell (Feder and Hofmann, 1999). Chaperones also redirect a large number of substrates for lysosomal degradation (Kettern et al., 2010). One characteristic feature of such proteins which are targeted by chaperones for autophagic degradation is the presence of a pentapeptide motif 'KFERQ', without which their recognition is abolished (Cuervo, 2011; Dice et al., 1986). This degradation mechanism does not require the formation of vesicle; instead the substrate is picked from crowded cytosol, by Hsc70 chaperones and attached to the outer lysosomal membrane, through the cytosolic tail of lysosome-associated membrane protein type 2A (LAMP-2A) (Cuervo, 2010). After binding, substrate unfolds its three-dimensional structure and gets internalized into the lysosome in a linear form, where degradatory enzymes cleave them with the help of lysosomal chaperones (Kaushik and Cuervo, 2012a). The rate limiting step of this system is the substrate binding with the transiently multi-merized LAMP-2A, which are later disassembled by membrane bound Hsc70 molecules (Arias and Cuervo, 2011). The effects of CMA dysfunction in various neurodegenerative diseases have been investigated in past; which is indicative of its active involvement in clearance of misfolded proteins (Cuervo and Wong, 2014).

### 3.2.2. Chaperone-Assisted Selective Autophagy (CASA)

CASA is another mechanism of selective autophagy of protein aggregates, which is orchestrated by chaperones Hsc70 along with few associated co-chaperones (Arndt et al., 2010; Upadhyay et al., 2016b). Hsc70 and HspB8 bind to target cargo protein, which is later ubiquitinated by CHIP, a co-chaperone, whereas B-cell lymphoma 2 (BCI2)-associated athanogene 3 (BAG3), another co-chaperone mediates this association (Kaushik and Cuervo, 2012b). Upon ubiquitination, this cargo becomes identifiable to an adapter protein p62, which, through its interaction with phagophore protein light chain 3 (LC3), mediates formation of autophagosome (Gamerdinger et al., 2009; Pankiv et al., 2007). Bulky aggregates of huntingtin and SOD1 are targeted for degradation through this autophagy pathway. Unlike CMA, where Hsc70 is dissociated before engulfment, CASA consumes chaperones, through which cargo transport is mediated (Kaushik and Cuervo, 2012b).

### 3.3. ERAD & mitochondrial quality control mechanisms are pivotal for cellular health

Protein synthesis takes place on ribosomes, present at the membranes of rough endoplasmic reticulum (ER) and the nascent polypeptides are cotranslationally transferred through translocon complexes, into the lumen of the ER (Ellgaard et al., 1999). Most of the proteins undergo proofreading, put up by ER itself, before being forwarded to secretory pathways (Wang and Hebert, 2003). ER lumen contains a high proportion of glycan-dependent chaperones, folding sensors and enzymes (Gething and Sambrook, 1992). Ion concentrations and redox conditions are also very different from cytosol. This provides a suitable *milieu* to covalently modify new polypeptide chains, which is also essential for their proper folding (Ellgaard and Helenius, 2003). Synthesis and maturation

processes of native polypeptide chains sometimes results in generation of misfolded or incorrectly folded proteins, which unlike normal proteins, are retained inside the ER. Chaperones and folding enzymes like BiP, protein disulfide isomerase (PDI), calnexin, calreticulin, and GRP94, etc., provide the retention capacity to ER (Ellgaard et al., 1999). These obnoxious ER-retained proteins are prone towards aggregation, and hence need a proper clearance from ERAD, as well as cytoplasm (Klausner and Sitia, 1990; Lippincott-Schwartz et al., 1988).

For selective degradation of ER retained proteins, few E3 ubiquitin ligase complexes are present on ER membranes (Hirsch et al., 2009). Hrd1-Derlin is one such well-known E3 ubiquitin ligase complex, present in yeasts as well as human, which along with its associated proteins, is found to be involved in selective ubiquitination and translocation of misfolded proteins to cytosol through Sec61 translocation system (Bays et al., 2001; Wiertz et al., 1996). Yeast Cdc48 or mammalian AAA-ATPase p97 proteins play crucial roles in these retrotranslocation steps (Romisch, 2006). Sel1 or Ubx2 proteins are also required to link Cdc48 complex with the Hrd1-Derlin or Doa1 E3 ubiquitin ligase complexes (Neuber et al., 2005; Schubert and Buchberger, 2005). Ubc1 and Ubc7 are E2 ligases that are recruited to membrane bound E3 ubiquitin ligase complexes with the help of another protein Cue1 (coupling of ubiquitin conjugation to ER degradation 1) to selectively ubiquitinate ER substrates (Biederer et al., 1997; Hirsch et al., 2009). Another E3 ubiquitin ligase identified in yeast ERAD system is Doa10, which has been less explored. Similar to Hrd1, it also has Ubc6 and Ubc7 as E2 partners (Kreft et al., 2006). Transmembrane protein autocrine motility factor receptor (AMFR) is also an E3 ubiquitin ligase, which has been characterized with ERAD for ubiquitinating misfolded proteins (Fang et al., 2001). It is believed that ER lumen itself does not contain proteasome or other UPS components. The misfolded proteins, once ubiquitylated are retrotranslocated to cytoplasm; and then targeted to proteasome for their degradation (Christianson and Ye, 2014).

Mitochondria is another subcellular system, homeostasis of which is very critical for overall cellular health (Tatsuta and Langer, 2008). Aging could also be associated with decrease in mitochondrial health and proteostasis, which may later lead to many age-related diseases (Lopez-Otin et al., 2013). Cellular proteostasis systems continuously monitor mitochondrial health, and if found any dysfunctional mitochondria, it is engulfed by lysosomal vesicles, which subsequently removes mitochondria from cytosol by a process, known as mitophagy (Youle and Narendra, 2011). Recent advances have shown that Parkinson's related genes kinase PTEN-induced putative kinase protein 1 (PINK1) and parkin play major roles in mitophagy. PINK1, an outer mitochondrial membrane (OMM) kinase detects any damage in mitochondria with some yet to be elucidated mechanism, followed by phosphorylation of cytosolic parkin, a well known E3 ubiquitin ligase (Scarffe et al., 2014). Parkin translocates to mitochondria, where it ubiquitinates mitochondrial substrates in Lys-63 manner and delivers the damaged mitochondria to autophagosomes for their clearance (Narendra et al., 2010). A broader term, mitochondrial quality control (mtQC), is used to describe various aspects and mechanisms involved in maintaining functional health of the cellular power house (Rugarli and Langer, 2012). Functions of mtQC range from controlling production of reactive oxygen species to degradation of proteinaceous inclusions inside mitochondria (Baker and Haynes, 2011). To meet all these requirements, mitochondria have a set of proteases, which are involved in regulated maturation of mitochondrial proteins (with the help of chaperones), as well as their proteolysis, if required (Hamon et al., 2015; Voos and Rottgers, 2002).

ATPases associated with diverse cellular activities (AAA) are major proteases involved in mtQC (Langer et al., 2001).

Intermembrane space and matrix AAA (iAAA and mAAA) proteases, Lon protease homologue (LONP), Clp protease proteolytic subunit (CLPP) are ATP dependent proteases which assemble themselves to form multimeric complexes having proteolytic compartments (Quiros et al., 2015; Rugarli and Langer, 2012). Damaged electron transport chain (ETC) components are also removed by these AAA proteases. LONP and CLPP are serine proteases which specifically identify and degrade misfolded proteins of the matrix (Quiros et al., 2015). HTRA2 enzyme has also been identified with important proteolytic roles in maintaining mitochondrial homeostasis. A trimer formed by HTRA2 in mitochondrial intermembrane (IM) space where it chiefly regulate many misfolded proteins (Clausen et al., 2011). ATP23, a metalloproteases is found in intermembrane space and helps iAAA in maintenance of ETC component proteins (Osman et al., 2007). ATP-binding cassette (ABC) transporters on mitochondrial membranes release broken small peptides from mitochondria matrix to IM space and then they are delivered to cytosol, where further degradation takes place to release free amino acids (Young et al., 2001). Under stress conditions, or when damaged proteins are accumulated inside the mitochondria, it may confer another combating response to provide protection from stress-like conditions (Haynes and Ron, 2010). Such a coordinated response is known as mitochondrial unfolded protein response (UPR), which mount signals to the nucleus to synthesize new proteases and chaperones which can take over the load of unfolded proteins accumulated inside the mitochondria (Zhao et al., 2002).

### 3.4. Protein quality control mechanism of nucleus is crucial for proteostasis

In order to properly regulate the expression of genetic material, the state of proteostasis inside nucleus becomes an obvious requisite for a cell. Although, as compared to cytoplasm and endoplasmic reticulum the understanding of proteostasis mechanism in nucleus is lacking (Jones and Gardner, 2016). According to current understanding, mostly nuclear proteins are synthesized and imported from cytoplasm through nuclear pores, which is expandable and aqueous in nature (Gallagher et al., 2014). The aqueous nature of nuclear pore provides a path to import nuclear proteins in a fully folded conformation, reducing the burden of nucleus to fold these proteins. Still, the need of restructuring cannot be excluded for some large molecules due to constriction occurred while passing through these pores (Alberts et al., 2002). So far, different studies have provided clues of involvement of chaperone machinery, ubiquitin proteasome system and autophagy in maintaining nuclear proteostasis. Chaperones such as Hsp26 (Willsie and Clegg, 2002), Hsp70 (Chughtai et al., 2001), and Hsp90 (Tapia and Morano, 2010) have been found to relocate in nucleus in response to stress which might be a protective response. Interestingly, chaperones or co-chaperones like Hsp70 and Hsp40 have been found to colocalize with aggregates or inclusions formed by TDP43 and polyglutamine expansions of huntingtin and ataxin proteins (Gallagher et al., 2014; Udan-Johns et al., 2014), which might have protective roles.

The involvement of ubiquitin proteasome system in removing aberrant proteins from nucleus was initially observed in *Saccharomyces cerevisiae* (Gardner et al., 2005). They identified nuclear E3 ubiquitin ligase, San1p along with E2s Cdc34p and Ubc1p, that ubiquitinates misfolded nuclear protein and targets for proteasomal degradation. Further report also indicated that this E3 ubiquitin ligase with the help of a cytosolic chaperone Hsp70 (Ssa1p), recognizes and interacts with nucleotide binding domain 2 (NBD2) domain of Ste6p (an ERAD substrate) leading to its proteasomal degradation (Guerrero et al., 2013). This study can be considered as an example of the crosstalk that exists between

nuclear and cytoplasmic protein quality control components in a cell. Another E3 ubiquitin ligase, Mahogunin ring finger 1 (MGRN1) was recently shown to redistribute in nucleus from cytoplasm as a result of proteasome impairment in aging neurons, aiding in protective response against proteotoxic stress (Benvegnù et al., 2017). Previously, we have reported MGRN1 nuclear presence with Huntingtin protein (Chhangani et al., 2014). Similarly, it has also been observed that Degradation of alpha2-10 (Doa10), an ER situated E3 ubiquitin ligase also localizes to inner nuclear membrane and takes part in nuclear protein quality control (Boban et al., 2014).

A form of autophagy, termed as nucleophagy also aids in maintaining integrity of nucleus by digesting unwanted nuclear regions or material (Mijaljica and Devenish, 2013). The role of autophagy in maintaining nuclear homeostasis was also confirmed from the study by Park et al. (Park et al., 2009) that showed nuclear components in autophagosomes and increase in nuclear abnormalities on inhibition of autophagy. Additionally, the autophagy protein light chain 3/Autophagy-related protein 8 (LC3/Atg8) has been recently shown to have nuclear presence. This study also observed the role of LC3 in restricting tumorigenesis through senescence induction by degrading nuclear lamina protein lamin B1 in response to oncogenic insults (Dou et al., 2015). Thus, the above mentioned studies provide considerable evidence that like ER and mitochondria, proteostasis mechanism is also present for nucleus that work along with cytoplasmic proteostasis components in maintaining a stable nuclear protein environment. The association of different neurodegenerative diseases including Huntington's disease and spinal cerebellar ataxias with nuclear protein aggregates or inclusions (Gallagher et al., 2014) shows critical role played by nuclear proteostasis mechanism in maintaining homeostasis at organism level. Despite these studies further research is still required to unravel signaling mechanisms involved in sensing nuclear proteostasis. It would be interesting to further elucidate how crosstalk between different proteostasis pathways both inside and outside nucleus works. Also, finding downstream effects of nuclear protein aggregates or inclusions along with their affects on other vital nuclear processes will be crucial to gain insights of link between nuclear proteostasis and disease occurrence.

### 4. How to solve the problem of bottleneck proteotoxic traffic jams in proteome?

As described in the previous sections, there are multiple pathways that work for balancing the cellular proteostasis network, by eliminating the load of toxic proteins from the cell (Tyedmers et al., 2010). At many instances, these quality control pathways get interrupted by various cellular or environmental factors and lead to multiple disease conditions, like neurodegenerative disorders, cancer and aging (Cook et al., 2012; Kabashi and Durham, 2006). Hence, the question arises, how to induce the clearance capacity of cellular quality control system to compensate the loss of physiological functionality. Basic principle of evolution suggests that nature selects the fittest factor and same fundamental applies from organism level up to the basic unit of life i.e. cell. Whenever the condition of aberrant proteins accumulation occurs because of flaws in clearance of these proteins from cell, the first body defense system which includes molecular chaperones, heat shock proteins, UPR, integrated stress responses, and adaptive protein degradation mechanisms play a key role in cellular survival (Schneider and Bertolotti, 2015). Apart from the efforts made by components of cellular quality control mechanism, sometimes it is important to provide few external stimulus to maintain the intracellular proteome balance (Harper and Bennett, 2016). Upcoming sub-sections provide the detailed description about

the cellular pathways and their molecular partners, which are directly related to the maintenance of functional proteome. Fig. 4 is a systematic representation of possible components of cellular quality control mechanism that have the ability to remove aberrant proteins from cell, which can be used for therapeutic purpose.

#### 4.1. Upgrade folding of aberrant proteins regulated by multi complex chaperone machinery

To deal with the disaster of proteotoxic load of aberrant proteins, chaperones or heat shock proteins are the first point, which are responsible for folding of nascent polypeptide chains into properly folded functional proteins (Wang et al., 2013). Work on modulation of heat shock proteins has started with the regulation of heat shock transcription factor 1 (HSF1) (Anckar and Sistonen, 2011). There are numerous chemicals like MG132 and natural compounds including celastrol etc., which regulate the HSF1 activity in multiple manners, have a high potential to be used as therapeutic agents for diseases linked with the intracellular misfolded protein accumulation and aging (Westerheide and Morimoto, 2005). Regulating transcription factor like HSF1 affects transcription of all heat shock proteins simultaneously; however, specificity in target selection is generated by altering the Hsp70 ATPase activity such as to regulate tau degradation in tauopathies (Jinwal et al., 2009). Recently, apotozole was also discovered as small molecule which binds specifically to Hsp70 and inhibits its ATPase activity, and leads to induction of apoptosis in cancer cells (Berman et al., 2015).

A new 4,5-diaryloxazole adenosine triphosphate-binding site inhibitor, NVP-AUY922, of another specific heat shock protein Hsp90 has been exploited to induce apoptosis and give beneficial outcomes in oral squamous cells cancer (Okui et al., 2011). Other strategy developed to reduce the proteotoxicity was, use of pharmacological chaperones such as nicotine,  $\gamma$ -aminobutyric acid (GABA) etc. that modulate the activities of lysosomal enzymes, ion channels, G-protein-coupled receptor (GPCR) to stabilize the target protein and increase folded protein population inside the cells in disease conditions like epilepsy, cystic fibrosis and many more (Wang et al., 2014). The same effect was also observed in pharmacological retromer chaperones and others such as galactose for neurological diseases including Alzheimer's and non neurological diseases like lysosomal storage and endosomal disorders (Berman et al., 2015; Parenti et al., 2015). Chaperones based methods or chaperones mediated autophagy have also been used as a better alternate of enzyme replacement therapy for neurodegenerative, lysosomal and other diseases, such as treatment of cystic fibrosis by molecular stabilizers like glycerol (Suzuki, 2014; Xilouri and Stefanis, 2015). More efforts need to be done in future before using pharmacological chaperones for treatment purposes to provide specificity and to obtain maximum outcomes.

#### 4.2. Filtration and rare target of UPS is important to flip the blocked switch

Ubiquitin proteasome system efficiently functions to recognize specifically aberrant proteins for their elimination and maintain a cellular proteostatic balance between synthesis and degradation of proteins. The exploration of different components of UPS protein cascade for therapeutic purposes involves E1 activating enzyme inhibition by natural compounds including panepophenanthrin and himeic acid obtained from mushroom and mould respectively, whereas E2 conjugating enzyme UbcH10 has been inhibited by RNA interference for treating cancer cells (Berlingieri et al., 2007; Eldridge and O'Brien, 2010). But both these strategies showed less

impact, as E1 and E2 enzymes have a global degradatory function over UPS inside the cell; hence can affect the whole system. Another class of proteins involved in the UPS, deubiquitinase (DUBs), were also targeted to fight cancer by chemical compound like b-AP15, which inhibits DUBs; USP14 and UCHL5, which are directly associated with proteasome and hence shows some possibilities for drug development (D'Arcy et al., 2011; D'Arcy and Linder, 2012).

E3 ubiquitin ligases that are known for providing specificity to this system in the selection of aberrant proteins have been modulated, activated or inhibited according to need of diseases and pharmacology to treat that particular disease (Edelmann et al., 2011). Nutlin-3a act as competitive inhibitor of HDM2, which was further found to be inhibited by HLI98 and RITA (Issaeva et al., 2004; Vassilev et al., 2004; Yang et al., 2005). Other examples of E3 ubiquitin ligase inhibition are SCF<sup>skp2</sup> by CpdA, cereblon by thalidomide, MuRF1 by P013222 etc., which show some positive effect in neurodegeneration and cancer (Chen et al., 2008; Eddins et al., 2011; Ito et al., 2010). The inhibition of the proteolytic machinery of the UPS, 20S proteasome is not a new thought, as it was observed that its inhibition, by small molecules induces apoptosis in cancer cells (Voorhees and Orlowski, 2006). The most studied chemical example of this mechanism is bortezomib, a well known proteasome inhibitor proved to be beneficiary in both animal models and patients suffering with multiple myeloma (Hideshima et al., 2005). Other than bortezomib, carfilzomib, MLN9708, CEP-18770 and few others are proteasome inhibitors under phase-I or phase-II clinical trials (Crawford et al., 2011). Exploitation of UPS system for drug development is increasing leaps and bounds, and have reached up to conjugation of protein with ubiquitin molecules (Bedford et al., 2011; Huang and Dixit, 2016). But still a huge gap between research and drug development need to be filled in upcoming years.

#### 4.3. Defining the useful dynamics of ER proteostasis

Various steps in protein quality control system not only help in maintenance of proteome balance inside the cells, but they also play a significant role in the generation of proteome equilibrium in all the cellular compartments (Wolff et al., 2014). Most of the ER resident proteins are translocated there at the time of translation and folding, therefore to maintain the ER proteostasis, it is essential that ER chaperones function properly to avoid an ER stress linked conditions (Wang and Kaufman, 2016). Chaperones and E3 ubiquitin ligases residing inside ER, such as HRD1, are induced by ER stress, and this property of induction makes both these molecules target for neurodegenerative diseases like Alzheimer's and Parkinson's (Kostova et al., 2007; Nomura et al., 2016). Gp78, the ERAD E3 ubiquitin ligase has also been explored for reducing ER stress (Chen et al., 2014). There is a long list of natural compounds like vitexin, which increase chaperone Hsp90 during ER stress and studied for drug development (Liu et al., 2016). Few researchers suggested that antioxidant pathway modulation is one of the solutions for ER stress, e.g., a lipid soluble antioxidant butylated hydroxyanisole has been found to reduce ER stress under *in vitro* conditions (Malhotra et al., 2008). ER itself have an UPR system to fight against a load of unfolded proteins and activation of UPR by MG132, radicicol and 17-AAG (17-N-allylamino-17-demethoxygeldanamycin) etc. are under preclinical trials for cancer treatment (Hetz et al., 2013). ERAD pathway specifically work for QC of ER proteins, which makes it a good therapeutic target for treatment of ER stress mediated pathologies (Kim et al., 2008). Some protein targets found, do not only function to control ER protein homeostasis, but also do similar function for Golgi complex (Wlodkowic et al., 2009).

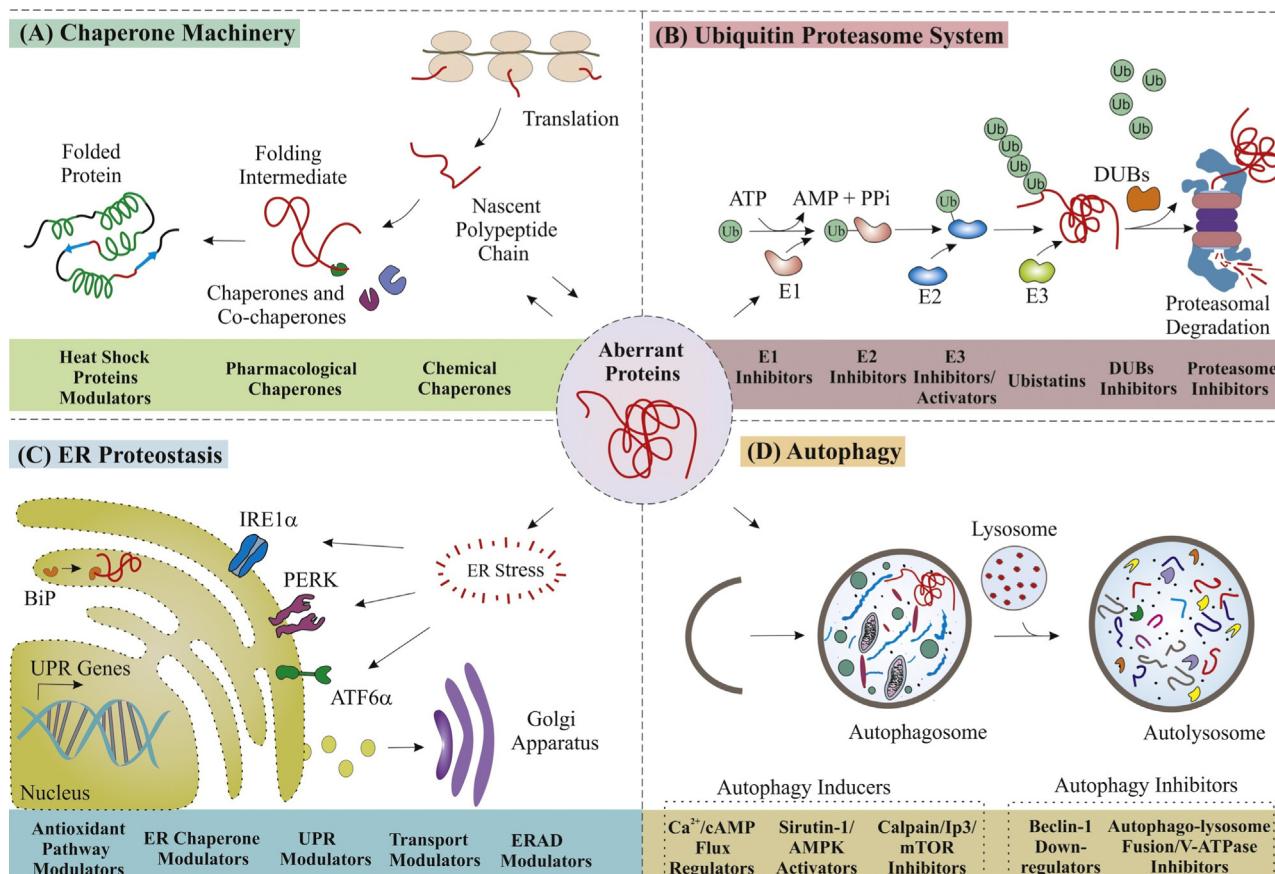
#### 4.4. Homeostasis renewal of autophagy may clear unwanted bulk of proteome

In cellular conditions, where other proteostasis mechanisms get ineffective or inefficient, the catastrophic event of the cell known as autophagy, takes charge of bulk removal of unwanted proteins from cells to keep proteome balanced (White, 2012; Williams et al., 2006). The whole process is carried out at two different levels: the smaller one microautophagy and massive one macroautophagy; both of these pathways could be selective or non-selective in bulk removal (Glick et al., 2010). The feature that shows the difference between these two processes are autophagosome formation in macroautophagy and vacuole invagination in microautophagy (Feng et al., 2014). Modulation of various signaling molecules of autophagy pathway, such as  $\text{Ca}^{2+}/\text{cAMP}$  flux regulation by verapamil, AMPK activation by metformin or reduction by clonidine and rilmenidine, help in fast recovery of cells from aberrant proteins and various diseases (Puri and Chandra, 2014). Targeting proteins involved in autophagy like mTOR inhibited by rapamycin in cell and animal models of neurodegenerative diseases and use of autophagy inducers such as trehalose, resveratrol etc. gives new hopes in therapeutic implications for aging and multiple neurological disorders (Tan et al., 2014; Vidal et al., 2014). In lymphoproliferative disorders, targeting autophagy components with drugs, like chloroquine causes p53-mediated cell death (Pujals et al., 2015). Some others like sorafenib reached up to

phase II clinical trials (Guidetti et al., 2012). PI3K and mTOR inhibitors including CAL-101, ridaforolimus, respectively, were also used to regulate autophagy and control disease conditions (Pierdominici et al., 2014). Beclin-1, which is involved in the autophagy stimulating mechanism, is downregulated to treat breast cancer, which gives new hopes in the direction of drug development (Rubinsztein et al., 2007).

##### 4.4.1. Macroautophagy

As discussed in the above section, formation of autophagosome, a vacuole with double membrane around the cytoplasmic bulk of aberrant proteins, which eventually merge with lysosome, represent macroautophagy (Feng et al., 2014; Mehrpour et al., 2010; Yang and Klionsky, 2010). It is mainly considered as a cellular bulk clearance pathway of the cell, but also plays a cytoprotective role in some conditions like starvation or nutrient deprivation, and removes unwanted load of cytoplasmic misfolded proteins (Mizushima et al., 2008; Moreau et al., 2010; Yang and Klionsky, 2010). The loss of autophagy genes like Atg7 in neurons cause neurodegeneration and acute condition lead to death, hence focusing autophagy is important for developing therapeutics against neurodegenerative diseases (Komatsu et al., 2006). Recently, some RNA and their complexes with ribonucleoproteins (RNPs) were also found as a part of phagophore for lysosomal degradation (Fujiwara et al., 2013). Similar studies suggest that RNA and RNPs serve as a regulator of macroautophagy and hence



**Fig. 4.** Diagrammatic representation of target mechanisms for faster clearance of multifactorial proteotoxic load generated by aberrant protein for therapeutic implication. Various components that have been utilized and identified in four key molecular mechanisms, i.e. chaperone machinery, ubiquitin proteasome system, endoplasmic reticulum stress response and autophagy, involved in proteostasis maintenance are represented as therapeutic targets. Panels below each mechanism mentions those targets i.e. (A) Induction or inhibition of heat shock proteins and synthesis or screening of molecules that can work as chaperones (pharmacological and chemical chaperones). (B) Activation or inhibition of different components of UPS including E1, E2, E3, ubistatins, DUBs and proteasome. (C) Modulation of ER stress response by modulating antioxidant pathway, ER chaperones, UPR and ERAD and (D) Various upstream and downstream signaling molecules involved in autophagy, regulated by natural or synthetic molecules have shown beneficial outcomes to counter diseases, like cancer and neurodegeneration and hence need to be explored more for therapeutic purposes.

can be targeted in future for therapeutic implications (Frankel et al., 2016). Xenophagy, a special kind of selective autophagy where intracellular pathogens like *Mycobacterium tuberculosis* are targeted, is a novel method against infections caused by antibiotic resistance bacteria (Kimmey and Stallings, 2016). The involvement of autophagy in various neurodegenerative, immune disorders and cancers is already well described; however, studies also elaborate its involvement in various oral diseases (Mizushima et al., 2008; Tan et al., 2016). Understanding the complete mechanism of macroautophagy and associated pathological conditions may give a new direction in modulation of this pathway for the establishment of healthy cellular environment.

#### 4.4.2. Microautophagy

In case of microautophagy there is direct engulfment of cytosolic components as compared to multistep process for recruitment in macroautophagy (Li et al., 2012). Microautophagy could be non selective or selective microautophagy (Kissova et al., 2007; Kraft et al., 2009). This form of autophagy is normally observed in mammals, which includes engulfment of cytosolic mass of misfolded proteins and can be divided into multiple stages, i.e., invagination of lysosomal membrane and formation of autophagic tubes, vesicle formation, vesicle expansion, vesicle scission, vesicle degradation and recycling (Kunz et al., 2004; Sahu et al., 2011). The selective microautophagy found in yeasts targets aberrant proteins of organelles viz. peroxisomes (micropexophagy), nucleus (piecemeal microautophagy) and mitochondria (micromitophagy) for quality control of cell (Farre and Subramani, 2004; Krick et al., 2009; Lemasters, 2014). A recent study has reported the functional importance of endosomal microautophagy in controlling neurotransmission by regulating synaptic protein turnover (Uytterhoeven et al., 2015).

The mechanism of microautophagy has also been involved in maintaining organelle shape, in this mechanism a large tubular invagination is formed by vacuoles membrane that gives rise to vesicle bud and this inverse budding is similar to microautophagocytosis (Muller et al., 2000). Therefore, involvement of autophagy in such type of house keeping functions makes this process one of the centre to study different pathologies (Todde et al., 2009). Autophagy could be induced by nutrient limitation or by carbon and nitrogen starvation. Rapamycin, which inhibit TOR signaling pathway is one of the known inducer of piecemeal autophagy (Roberts et al., 2003). Other than rapamycin, many FDA approved drugs like clonidine, lithium etc. and nutritional supplements such as caffeine were studied as an inducers of autophagy (Levine et al., 2015). But still, there is a need to search more efficient autophagy inducers to obtain therapeutic importance of this process. Further, increased understanding of microautophagy induction and its regulating mechanisms from drug discovery perspective can prove to be beneficial for cancer, neurodegenerative disorders and aging.

### 5. How loss of proteostasis affects age-risk factor diseases such As cancer and neurodegeneration?

Accumulating studies have demonstrated impaired proteostasis as one of the key features of aging (Ben-Zvi et al., 2009; Lopez-Otin et al., 2013). Different mechanisms involved in maintaining proteostasis like chaperones machinery and proteolytic systems have been analyzed to gain an understanding of their role in aging. Reduction in chaperone synthesis, decrease in HSF DNA binding capacity, damaged chaperones and overloaded chaperones are various factors that contribute to age associated impairment in chaperone machinery (Soti and Csermely, 2007). Similarly, alterations in components of ubiquitin proteasome system viz. ubiquitin, E2 conjugating enzyme, E3 ubiquitin ligases

and proteasome have been observed with aging (Tsakiri and Trougakos, 2015). Proteasome is the most extensively studied component of UPS with respect to aging. Decreased proteasome activity, reduced proteasome subunit expression, proteasome disassembly and proteasome inactivation due to clogging by protein aggregates are common features of aging (Ferrington et al., 2005; Saez and Vilchez, 2014). Moreover, a mutation in E1 activating enzyme of UPS resulted in the development of aging-like phenotypes in *Drosophila* (Liu and Pfleger, 2013). However, further studies targeted towards understanding role of E1, E2, E3, and ubiquitin in aging are needed to unravel hidden aging associated pathways affected due to a disturbance in UPS. Like UPS, disruption in autophagy has also been reported with aging (He et al., 2013). Proteins such as autophagy related gene (ATG), sirtuin 1 and beclin which are involved in autophagy induction, have been observed to be down regulated with aging (Lipinski et al., 2010; Rubinsztein et al., 2011). The numerous connections that have been discussed above between different components of proteostasis mechanisms and aging provides enough support to target these mechanisms for finding therapeutic solutions of various age-related problems.

#### 5.1. Aberrant proteostasis and cancer

Disturbance in proteostasis caused by various stress conditions such as genomic instability, hypoxia, mutations, nutrient deprivation, tumor suppressor protein aggregation and redox imbalance are emerging as critical factors that have implications in cancer development and progression (Ano Bom et al., 2012; Urra et al., 2016). To overcome proteotoxic load caused by the proteostasis imbalance, cancer cells enhance its proteostasis maintenance capacity by up-regulating chaperone and proteolytic machinery (Deshaiyes, 2014; Zorzi and Bonvini, 2011). In leukemic cells increased expression of proteasomes have been observed (Kumatori et al., 1990). Another component of UPS, the E3 ubiquitin ligases like Mdm2 and SCF complex have also been found to be amplified in different types of cancers (Chen et al., 1998; Zhang and Wang, 2000). Similarly, both in tumor and malignant cancers chaperone machinery may help cancer cells to overcome proteostasis imbalance induced apoptotic signaling (Urra et al., 2016; Whitesell and Lindquist, 2005). Recently, it was found that CHIP E3 ubiquitin ligase targets DNA damage-induced apoptosis suppressor (DDIAS) for proteasomal degradations, having therapeutic implications in cancer treatment (Won et al., 2017). Interestingly, the elevated levels of chaperones Hsp90, Hsp70 and Hsp27 have also been shown as a contributing factor in causing resistance to various cancer therapies (Gabai et al., 1995; Heinrich et al., 2016; Whitesell et al., 2014). In addition to UPS and the chaperone machinery, the role of autophagy has also been extensively studied in cancer and metastasis (Mathew et al., 2007; Mowers et al., 2017; White, 2015). However, the involvement of autophagy in tumorigenesis is complex. Autophagy has been found to be tumor suppressing at initial stages of tumor formation while in established tumors it promotes cell survival, thus act as a tumor promoting mechanism (Choi, 2012). This dual behavior of autophagy can be taken as an example of how at different stages of cancer the environment of cancer cell changes. Therefore, research focusing on understanding the role of proteostasis in various stages of cancer development is required so that efficiency of currently available anticancer strategies could be improved.

#### 5.2. Proteostasis imbalance and neurodegenerative diseases

An indication of disruption in proteostasis is the presence of protein inclusions containing misfolded protein aggregates; a clinical feature widely observed in several NDDs (neurodegenerative diseases) (Yerbury et al., 2016). It is obvious that being major

processes involved in clearance of misfolded or aberrant proteins, the chaperone machinery, and proteolytic mechanisms have a key role to play in neurodegenerative diseases progression. Accordingly, different studies have reported a disturbance in expression levels and function of various constituents of proteostasis network such as chaperones, ubiquitin and proteasome in different neurodegenerative diseases (Ben Yehuda et al., 2017; McNaught et al., 2003; Yoo et al., 2001). Also, accumulating studies have provided evidence that show a loss in function of different components of proteostasis network as a causal factor of NDDs (Deng et al., 2011; Kitada et al., 1998).

Interestingly, besides removing damaged proteins in neurons, proteostasis mechanisms such as UPS also takes part in neuronal development, presynaptic functions, and postsynaptic plasticity aiding in proper functioning of the nervous system (Yi and Ehlers, 2007). Thus any alterations in proteostasis mechanisms may also affect these processes leading to aberrant nervous system operations. It has been observed that mice lacking a maternal copy of E3 ubiquitin ligase UBE3A/E6-AP shows Angelman syndrome-like characteristics i.e. motor dysfunction, seizures and learning deficit (Jiang et al., 1998). Thus the outcome of dysfunction in proteostasis is not just limited to neuronal toxicity, but it also disturbs the overall functionality of the nervous system. Therefore, studies designed to understand wider consequences of proteostasis imbalance are required. Such studies may prove to be clinically useful as it would help in understanding the mechanisms underlying disease progression in addition to disease occurrence.

## 6. Useful model organisms of neurodegeneration & aging linked with proteostasis imbalance

Proteostasis imbalance caused by any external or internal factor may result in the occurrence of aging symptoms and associated complex diseases in lower as well as higher organisms (Labbadia and Morimoto, 2014; Taylor and Dillin, 2011). Multiple lines of evidence in the literature are available of various model organisms that have been studied to explore consequences of disturbance in the state of protein homeostasis in terms of its relation to aging and various life-threatening diseases (Cohen et al., 2009; Kikis et al., 2010; Kirstein-Miles and Morimoto, 2010).

### 6.1. *Saccharomyces cerevisiae*

As the fundamental proteostasis mechanism is conserved, different eukaryotic organisms have been utilized to study the effect of proteostasis collapse in neurodegenerative diseases (Balch et al., 2008). In this regard, models of yeast *Saccharomyces cerevisiae* have proven to be quite useful (Khurana and Lindquist, 2010; Piper, 2006). Studies using yeast models showed that aggregate formation by amyloidogenic proteins (S100A8 and S100A9) is non-toxic in nature but still is able to generate the disturbance in protein homeostasis inside cells (Eremenko et al., 2013; Kryndushkin et al., 2012). The role of proteostasis disturbance in various neurodegenerative disorders like Parkinson's, Alzheimer's, Prion's disease and few others have also been studied utilizing different yeast models (Khurana and Lindquist, 2010; Miller-Fleming et al., 2008; Yerbury et al., 2016). In addition, yeast models have also been helpful in gaining a better understanding of impaired proteostasis mechanisms in diseases involving protein misfolding and aggregation (Hipp et al., 2014). Similarly, yeast models have also been developed to find linkage between early aging onsets as a result of proteostasis misbalance, which might be overcome by overexpression of sirtuin 2 (Sir2) or inhibition of target of rapamycin (TOR), serine/threonine-protein kinase (Sch9/Akt) proteins or caloric restriction in cells (Kaeberlein et al., 2007).

### 6.2. *Caenorhabditis elegans*

*Caenorhabditis elegans* is another extensively studied model organism that has been utilized to observe changes in response to collapse in proteostasis. Using *C. elegans*, it has been proposed that proteostasis disturbance is an initial event in organism's aging (Ben-Zvi et al., 2009). Similarly, disturbed protein homeostasis due to increase in insolubility and aggregation of proteins influencing lifespan has been found, becoming a critical factor for aging associated changes in *C. elegans*. This may be delayed or stopped by reducing insulin/IGF-1 signaling resulting in life span extension of the organism (David et al., 2010). Additionally, genes such as hsf-1 and daf-16 were found to play a critical role in lifespan determination using *C. elegans* model (Rodriguez et al., 2013). Furthermore, it was observed that chaperone subnetwork provide protection to cellular proteostasis in *C. elegans* and animal cells models studied for complex diseases and aging (Brehme et al., 2014). Altogether, *C. elegans* models expressing aggregation-prone misfolded proteins in various tissue types have aided considerably in exploring protein aggregation associated changes in cells as well as help small molecules for therapeutic solutions of aggregation associated diseases (Holmberg and Nollen, 2013; Kikis, 2016; Nussbaum-Krammer and Morimoto, 2014).

### 6.3. *Drosophila melanogaster*

Like *C. elegans*, multiple human neurodegenerative diseases like Parkinson's, Alzheimer's, polyglutamine diseases have been studied in *Drosophila melanogaster* fly models (Bilen and Bonini, 2005; Bonini and Fortini, 2003). These models may provide a deep knowledge of fundamental aspects, cellular and molecular pathogenic events of various proteinopathies and their possible modifiers for therapeutic advancement (Poidevin et al., 2015; Rincon-Limas et al., 2012). In *Drosophila* model of Parkinson's disease, it was observed that exogenous expression of Hsp70 chaperone reduces the toxicity generated by aggregation of  $\alpha$ -synuclein (Auluck et al., 2002). A recent interesting study in *Drosophila* has uncovered the role of fork-head box O (FOXO) and its target 4E-binding protein (BP) in proteostasis, muscle aging, and lifespan extension. In this study, it was also found that FOXO/4E-BP helps in delaying age-related protein accumulation through reduction of insulin release and clears damaged proteins to some extent by autophagy/lysosome system (Demontis and Perrimon, 2010). Further research on deep understanding of this signaling process revealed that FOXO transcription factor function as a key regulator of protein quality control in *Drosophila* and play a critical role in reducing the risk of neurodegenerative diseases and aging (Webb and Brunet, 2014). It was also reported that increased expression of glucose transporter Glut1 reduces A $\beta$  toxicity by reducing the GRP78 level and inducing unfolded protein response in *Drosophila* model of Alzheimer's disease (Niccoli et al., 2016).

### 6.4. Mice models

The understanding of protein aggregation in multiple diseases like Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) has increased multiple folds with the development of mice models (Janus and Welzl, 2010; Ross and Poirier, 2004; Trancikova et al., 2011). Mice models of various age-associated proteotoxicities suggest the role of insulin/insulin growth factor (IGF-1) signaling in the early onset of aging and show future possibilities for use of this information in the development of therapeutic strategies for Alzheimer's disease (Cohen et al., 2009). A study involving unique mice model expressing heat shock factor 1 (HSF1), a key regulator of transcription of heat shock proteins, reported enhanced

proteostasis and protection from neurodegenerative diseases (Pierce et al., 2010). Mutant mouse model of UPS and autophagy components showed an interplay between UPS and autophagy mechanism that maintains proteostasis. Failure of which leads to numerous neurodegenerative diseases and use of natural or chemical activator as well as inhibitors may help in re-establishment of this homeostasis condition inside the cell (Calamini et al., 2012; Tanaka and Matsuda, 2014). One of the examples is Huntington disease (HD) mice model where UBE3A deficiency results in reduced lifespan of these mice with accelerated occurrence of complex disease phenotypes (Cummings et al., 1999; Maheshwari et al., 2014). Another similar example of reduced life span was observed in HSF1 knockout mice inoculated with Rocky Mountain Laboratory (RML) prions (Steele et al., 2008). A number of knockout mice models were developed to study mitochondrial as well as cellular homeostasis in association with aging and complex diseases (Gumeni and Trougakos, 2016). Additionally, it has been also observed that overexpression of autophagy associated gene Atg5 extends the life span of model mice, which suggest the role of these quality control pathways and their components in maintaining homeostasis (Pyo et al., 2013).

## 7. Differential proteostasis regulatory mechanisms of somatic vs. reproductive (Gonads) tissues of model organisms

As mentioned previously, an imbalanced state of cellular proteome has been observed as a hallmark of a large array of neurodegenerative diseases and aging. It has been concluded through different studies that longevity-promoting pathways have a positive effect on proteostasis mechanisms (Cohen et al., 2006; Khodakarami et al., 2015). So far, different models organisms have been developed that have helped us to better understand the differential regulation of proteostasis and neurodegeneration associated pathways in various tissues of these organisms (Jucker, 2010; Nussbaum-Krammer and Morimoto, 2014). A study conducted in *Drosophila melanogaster* found that gonads of aging flies had high proteasome activity and relatively stable proteome as compared to aged somatic tissues. This age associated enhancement in reproductive tissue proteostasis mechanism seems to be a protective adaptation of *Drosophila*, so that any detriment is not passed on to offspring (Fredriksson et al., 2012; Tsakiri et al., 2013). The crosstalk between somatic and reproductive tissue proteostasis mechanism can be understood further from studies that have reported, increased proteasome activity and autophagy in *C. elegans* lacking germ line tissues (Lapierre et al., 2011; Vilchez et al., 2012). The shift in focus of maintenance from somatic tissues to reproductive tissues has been considered as a critical factor involved in aging associated deterioration (Kirkwood and Austad, 2000; Lemaitre et al., 2015). Interestingly, studies in *Drosophila* and *C. elegans* models have shown increased lifespan on elimination of germ cells (Flatt et al., 2008; Hsin and Kenyon, 1999; Yamawaki et al., 2008).

However, there have been reports that provide different aspect of relationship between reproductive tissues and organism aging. It has been reported that on removal of germ line female *Drosophila* had reduced longevity (Barnes et al., 2006). Likewise, it has been shown that female Mediterranean fruit flies (*Ceratitis capitata*) having higher reproductive potential had longer lifespan probability (Muller et al., 2001). Further, sex steroids such as estradiol, testosterone and progesterone are considered to be neuroprotective in nature, and has been linked to various neurodegenerative disorders (Azcoitia et al., 2003). Additionally, higher deposition of APP and lower degradation of accumulated proteins has been observed in aging females, which could be due to differential regulation in sex hormone secretion (Callahan et al., 2001; Hirata-Fukae et al., 2008; Wang et al., 2003). Also, in Huntington's disease

mouse models derived from R6 donor, which are characterized by the presence of expanded polyglutamine aggregates of huntingtin protein, have significant changes in their gonads. The mice gonads had either reduced functionality or became completely vestigial with diminished mating capabilities (Mangiarini et al., 1996). Recently, in Parkinson's disease patients, presence of aggregates of phosphorylated α-synuclein in reproductive tissues was observed, that may have impeding effect on normal gonad functioning (Garrido et al., 2017). Altogether, the above studies bring us to the conclusion that mechanisms of proteostasis and its disturbance plays a crucial role in the complex signaling and functioning of somatic and reproductive tissues. Further research may help in better understanding of mechanisms and finding novel therapeutic targets for diseases associated with aging and neurodegeneration.

## 8. Natural resources & pharmaceutical molecules can stimulate the maintenance of endangered proteostasis

Folding and degrading mechanisms including trafficking pathways constitutes significant part of proteostasis network (Skliroou et al., 2015). Molecules isolated from natural resources have been shown to produce beneficial outcomes such as anti-aging effects (Argyropoulou et al., 2013). These naturally obtained molecules can also be used in cancer pathology as they shows less side effects and improved treatment for chemo-resistant tumors (Reddy et al., 2003; Tan et al., 2011). Celastrol and sulphoraphane obtained from natural sources affects proteostasis network by modulating heat shock response having therapeutic implications in neurodegenerative diseases and cancer (Sarkar et al., 2012; Trott et al., 2008). Different classes of natural molecules, such as vitamins (Schaeffer et al., 2014), isothiocyanates (Powolny et al., 2011), flavonoids (Jinwal et al., 2009), alkaloids (Tsukamoto et al., 2010), and fatty acids (O'Rourke et al., 2013) have been reported to regulate proteostasis mechanisms showing potential in cancer and protein conformation disorders treatment. Natural compounds with their roles in the induction or inhibition of autophagy have also been studied, they control autophagic pathways by different mechanisms, and can cause apoptosis in cancerous cells (Ding et al., 2014). Interestingly, these molecules are also found to have an impact on the other protein degradatory pathway, i.e., UPS, such as by inhibition of proteasomal activity (Tsukamoto and Yokosawa, 2010).

Apart from the naturally obtained proteostatic regulators, various synthetic chemical compounds utilized and developed for different applications have also been largely studied and screened for their roles in proteostasis modulation. Pharmaceutical drug such as aspirin (NSAID) has been shown to affect proteostasis through inhibition of proteolytic degradatory activity of the proteasome (Dikshit et al., 2006). Furthermore, another NSAID ibuprofen downregulates the expression of Hsp70 chaperone enhancing antitumor activity of cisplatin (Endo et al., 2014). Drugs designed to target proteasome as a strategy to develop antitumor agents has been approved for treatment of multiple myeloma (Kane et al., 2003). To reduce the undesirable side effects such as protein aggregation in non cancerous cells other targets in ubiquitin proteasome system are also being investigated (Buckley and Crews, 2014). Similarly, several other medications have also been reported to affect proteostasis which will be discussed in detail in further sub-sections

### 8.1. Natural compounds based strategies can regulate proteome dysfunctions

Several molecules derived from natural sources have been studied for their potential applications in therapeutics of proteostasis impaired conditions. However, the effectiveness of these

molecules at clinical level is needed to be established (Bent, 2008). For conversion of these naturally derived molecules into a disease specific medications, a deep investigation of the affected molecular mechanisms is required. Despite limitations in terms of understanding due to their chemical complexities (Dias et al., 2012), use of natural products in traditional medications over generations provides a strong evidence of their potential in therapeutic applications. Availability of advanced chemical approaches and computational techniques have regained interest of researchers in identifying new and potentiating efficacy of existing available natural molecules (Rodrigues et al., 2016). A small description of recent studies exploring beneficial roles of natural products as proteostatic regulators is given below.

### 8.1.1. Vitamins

Vitamins are vital components of various biological processes occurring in the cell. They have been reported to modulate various mechanisms involved in proteostasis (Cao et al., 2009; Hoyer-Hansen et al., 2010). A recent study has shown Vitamin K3 as an inhibitor of Siah2 ubiquitin ligase leading to blocking of melanoma tumorigenesis which may be due to attenuation of hypoxia and MAPK signaling (Shah et al., 2009). It has been observed in past that vitamin D<sub>3</sub> increases the levels of its nuclear vitamin D<sub>3</sub> receptor molecules by inhibiting its proteasome mediated degradation (Li, 1999). Role of vitamin D<sub>3</sub> in autophagy regulation has also been studied extensively (Wu and Sun, 2011). Similarly, members of vitamin E family like delta- tocopherol and alpha-tocotrienol have been shown to regulate proteasome activity and elevated levels of p27<sup>Kip1</sup> and p53 (Munteanu et al., 2007). Mechanism elucidating role of vitamins in providing protein stability and activity has also been postulated such as in case of riboflavin (Henriques et al., 2008). Riboflavin therapy has been proved to be beneficial in patients with altered level of flavin adenine dinucleotide (FAD) (Vergani et al., 1999), which in turn has pharmacological chaperone like effects on mitochondrial electron transfer flavoprotein enzyme (Henriques et al., 2008).

Beneficial aspects of vitamins involving proteostasis mechanisms has also been explored in metal induced toxicity. Widespread environmental heavy metal cadmium induced cytotoxicity due to ER stress and unfolded protein response can be attenuated by ascorbic acid treatment (Ji et al., 2012). Recently, role of vitamin k3 in inhibition of amyloid fiber aggregation in hen egg white lysozyme (HEWL) and A<sub>β</sub>-42 peptide was reported (Alam et al., 2016). Despite evidences of therapeutic potential vitamins possess there are also limitations at various levels which pose challenges to use them for clinical purpose. As in case of vitamin D<sub>3</sub> short half life and rapid catabolism limits its availability at the target site (Ramalho et al., 2015). Similarly, reduced stability due to oxidation caused by presence of excess oxygen in cell culture environment and lack of adequate animal models are barrier in investigating possible role of ascorbic acid in disease treatment (Michels and Frei, 2013). However, use of advanced approaches like nanotechnology to increase bioavailability (Ramalho et al., 2015) and genetically modified animals (Maeda et al., 2000) for specific studies has helped in providing a step further to counter such problems and making vitamins clinically usable natural product.

### 8.1.2. Natural isothiocyanates

Natural isothiocyanates produced by hydrolysis of glucosinolates via myrosinase enzyme in cruciferous vegetables have been reported to have useful properties that can be utilized in treatment of cancer, cardiovascular diseases, neurodegeneration, diabetes and as an antibacterial agent (Dufour et al., 2015; Fimognari et al., 2012). They contain N=C=S functional group, which gives them ability to act as an electrophile and react with nucleophilic moiety in protein and hence causing their modification (Fimognari et al.,

2012). Isothiocyanates, such as benzyl and phenyl isothiocyanates inhibit deubiquitinating enzyme (DUBs) USP9x and UCH37, which protect degradation of anti-apoptotic proteins Mcl-1 and oncogenic fusion protein Bcr-Abl (Lawson et al., 2015). Sulforaphane, a well studied isothiocyanate, protects cells from hydrogen peroxide induced oxidative stress by enhancing expression level of proteasomal catalytic subunit and its peptidase activity in neuroblastoma cells (Kwak et al., 2007). Sulforaphane was also found to inhibit heat shock proteins such as Hsp70, Hsp90 and transcription factor HSF1, and upregulated expression level of apoptotic proteins such as Bad and Bax (Sarkar et al., 2012).

Synergistically with arsenic trioxide sulforaphane increases apoptotic induction in multiple myeloma cells, as shown by increase in cleavage of caspase-3, caspase-4, reactive oxygen species (ROS) production, depletion of glutathione, Hsp90 expression and PERK activation in UPR pathway of ER stress (Doudican et al., 2012). Effect of phenethyl isothiocyanate on autophagy has also been reported as a result of suppression of phosphorylation of Akt, mTOR and triggers Atg5-dependent autophagic and apoptotic cell death in prostate cancer cell line (Bommareddy et al., 2009; Zhang et al., 2014). Sulforaphane also modulates proteolytic degradatory machinery of autophagy, by inducing the levels of LC3-II and increasing ROS production in pancreatic cells (Naumann et al., 2011). These studies on different isothiocyanates provide a view of influence of isothiocyanates on various proteostatic pathways. Further research is also needed to provide sufficient evidences on establishing beneficial role of isothiocyanates for a particular disease, such as sulforaphane (a known antiproliferative agent) has also been shown to promote cell proliferation in human mesenchymal stem cells (Bao et al., 2014). Thus further studies leading to proper optimization and in depth characterization of these useful natural products can provide us with novel ways to counter various pathologies.

### 8.1.3. Natural phenols, flavonoids and flavonols

Naturally occurring alkyl phenol such as ginkgolic acid extracted from the leaves of *Ginkgo biloba L*, directly binds to E1 ubiquitin activating enzyme which disrupts formation of E1-SUMO complex, a critical modulator of cellular proteostasis (Fukuda et al., 2009). Polyphenol rich propolis extracts regulates the activation of transcription factor nuclear factor kappa B (NF-κB) by inhibiting the autoubiquitination of TNF receptor associated factor 6 (TRAF6), hence can control the transcription of important anti-inflammatory cytokines, which shows inflammatory properties (Wang et al., 2015). Moreover, previous studies also provides an evidence of role of polyphenolic compound such as curcumin in inhibiting proteolytic activity of proteasome and cellular deubiquitinating activity leading to dysregulation in UPS (Jana et al., 2004; Si et al., 2007). Isolated caffeic acid, a plant polyphenol shows protective effect in cells from the toxicity induced by fluoride through modulation of Nox4, p38alpha, MAPK and restoring levels of heat shock proteins Hsp60, and Hsp27 (Kanagaraj et al., 2015).

Another plant phenol resveratrol (RES) has also been investigated for its functional importance in ER proteostasis. Resveratrol was found to induce UPR response by elevating levels of GRP78 and CHOP resulting in proliferation inhibition of myelogenous leukemia cells (Liu et al., 2010). Resveratrol and hydroxytyrosol (a phenol isolated from olive) can induce SIRT1 signaling mediated autophagy, having protective effects in pathologies of hepatic steatosis and osteoarthritis (Cetrullo et al., 2016; Zhang et al., 2015). Flavonoids extracted from herb *Orostachys japonicus* have an inhibitory effect on calcium dependent enzyme, calpain, and thus may play regulatory roles in autophagy and related turnover rate of proteins having significance in diseases such as Alzheimer's and cataract (Je Ma et al., 2009). Despite actively studied for their roles in various proteostatic pathways, understanding bioavailability

and bioefficacy of these molecules will support in further investigation of their health benefits (Manach et al., 2005). As indicated in study by (Lotito et al., 2011) that flavonoids gets metabolized into derivatives that may produce different effects from the parent one. Similarly another study in past has shown flavonols induced chromosomal aberrations in Chinese hamster ovary cells (Carver et al., 1983) which could be a deleterious side effect in considering them for drug designing.

#### 8.1.4. Alkaloids

Alkaloids are another class of naturally occurring nitrogen containing bioactive compounds that are present in diverse range of distinctive structures produced by plants, marine species, fungi etc. (Qiu et al., 2014). Alkaloids like spongiacidin C, purified from marine sponges have shown to inhibit de-ubiquitinating enzyme USP7 activity with high potency, affecting cellular proteostasis (Tsukamoto, 2016). Lissoclinidine B a pyridoacridine alkaloid from *Lissoclinum cf. badium* can stabilize the level of p53 by inhibiting Hdm2 E3 ubiquitin ligase activity, which can be used to develop anti-cancer therapy (Clement et al., 2008). The protective functions of berberine, an isoquinoline alkaloid, isolated from Chinese herb *Rhizoma coptidis* on intestinal epithelial cells is illustrated by its ability to decrease GRP78 expression and the splicing of xbp-1 mRNA, ameliorating ER stress *in vitro* (Hao et al., 2011). Similarly, another alkaloid kifunensine can restore activity of destabilized lysosomal enzymes prone to degradation by inhibition of ERAD (Wang et al., 2011). Another well studied alkaloid capsaicin, have property to induce autophagy by AMPK mediated SIRT1 activation (Lee et al., 2015).

Alkaloid based drugs like paclitaxel and vinblastine have been used in cancer therapy showing the potential of alkaloids in pharmaceutical applications (Amirkia and Heinrich, 2014). However, alkaloid like tylocrebrine were terminated in Phase I studies due to side effects like CNS toxicity which can be overcome by introducing modifications that reduces its capability to cross blood brain barrier (Chemler, 2009). Further studies targeted to understand the structure and regions that are actually pharmaceutically relevant and thereby designing mimetics of these valuable molecules will prove to be extremely beneficial for diseases like cancer and neurodegeneration that have limited treatment options.

#### 8.1.5. Fatty acids and their derivatives

Fatty acids modulate cellular proteostasis through different mechanisms. Lower levels of polyunsaturated fatty acid, docosahexaenoic acid (DHA) in brain and serum of Alzheimer's patient and reduction in amyloid burden on DHA intake shows importance of fatty acids in proteostasis maintenance (Lim et al., 2005). 4-phenylbutyrate a fatty acid derivative modulates the trafficking of CFTR mutant protein, by modifying the expression level Hsp70 chaperone (Suaad et al., 2011). Similarly, oleic acid (OA), an unsaturated fatty acid decreases protein level of ER chaperone, GRP78, which confers higher insulin resistance in hepatocytes, a mechanism important in type-2 diabetes development (Yamagishi et al., 2012). OA, further have critical functions in regulating ER proteostasis, as it can suppress UPR induced apoptosis by palmitate in INS-1E  $\beta$ -cells (Sommerweiss et al., 2013). Palmitic acid (PA), a saturated fatty acid, has also shown ability to modulate autophagy by regulating levels of different amino acids (Enot et al., 2015). These studies have shown that fatty acids like docosahexaenoic acid, OA and their derivatives like 4-phenylbutyrate have important roles to play in proteostasis maintenance and thus may be useful in diseases like diabetes type-2, Alzheimer's and cystic fibrosis therapeutics.

#### 8.1.6. Bacterial isolates

Hoiamide D, a peptide based p53/MDM2 interaction inhibitor isolated from a Papua New Guinea marine cyanobacteria *Symploca* sp., is an useful therapeutic option in treatment of cancer (Malloy et al., 2012). Using same cyanobacteria *Symploca* sp., another molecule named largazole was isolated which inhibits activation of E1 ubiquitin activating enzyme and consequently leads to reduction in ubiquitination and an increase in level of p27 in the cells (Ungermannova et al., 2012). Bacterial metabolite like Geldanamycin, isolated from *Streptomyces hygroscopicus* increases association of ER chaperone BiP with nascent proteins (Lawson et al., 1998). Rapamycin, another isolate from *Streptomyces hygroscopicus* is a macrolide compound that have shown ability to reduce cardiac hypertrophy by inducing autophagy and decreasing the levels of important autophagic regulator beclin-1 by MEK/ERK signaling pathway (Gu et al., 2016). Well known autophagy inhibitor like baflomycin A1, a macrolide antibiotic isolated from *Streptomyces* sp. is an inhibitor of lysosomal acidification and protein degradation (Yoshimori et al., 1991). These above studies demonstrate that bacterial isolates provide a vast source of molecules that can be used for various therapeutic purpose. Further studies targeted towards understanding properties and specificity of these molecules will add significantly in direction of developing drug targeting mechanisms involved in proteostatic pathway.

#### 8.1.7. Fungal isolates

Since the discovery of penicillin from fungus *Penicillium notatum* by Fleming, researchers have identified various new fungal isolates, some of which exert their effects by modulating proteostasis mechanisms. Molecules such as panepophenanthrin isolated from mushroom and hexylitaconic acid, obtained from marine derived fungus *Arthrinium* sp. modulates ubiquitin proteasome signaling by targeting E1 and E3 enzymes respectively (Sekizawa et al., 2002; Tsukamoto et al., 2006). Versipelostatin, isolated from *Streptomyces versipellis* 4083-SVS6, downregulates ER associated chaperone GRP78, which can be used as strategy in controlling the pathologies of neurodegeneration and cancer (Park et al., 2002). Another recently identified fungal isolate, SD118-xanthocillin X, from *Penicillium commune* has shown to induce autophagy via inhibition of MEK/ERK Pathway (Zhao et al., 2012). Parasitic fungus, *Cordyceps militaris* derived molecule cordycepin (3'-deoxyadenosine), activates AMPK pathway of autophagy and causes reduction in level of mammalian target of rapamycin (mTOR), affecting the activity of Akt and causing autophagy (Wong et al., 2009). Identification of approximately 100,000 species from around 5.1 million estimated fungal species (Blackwell, 2011) and much less commercially cultivable fungi gives an idea of limitations we have in research targeting fungi as source for natural molecules.

#### 8.1.8. Terpenes/Terpenoids

Terpenes are another class of natural molecules involved in organisms defense and interactions have also been shown to have proteostasis modulation properties. Betulinic acid, a pentacyclic triterpenoid and its C-3 position modification can activate or inhibit proteasome respectively (Huang et al., 2007). Similarly, a diterpenoid derivative 15-oxospiramilactone inhibits an UPS deubiquitinase USP30 and thus regulates the ubiquitination of mitofusin, which modulates mitochondrial fusion (Yue et al., 2014). Oridonin, a diterpenoid from *Rabdosia rubescens*, has anti-oncogenic effects; it induces autophagy in HeLa cell line by increasing the protein expression of beclin-1, JNK and MAP-LC3 (Cui et al., 2007). Carnosic acid, a benzenediol diterpene causes degradation of androgen receptor by increasing the ER stress response proteins BiP and CHOP and induces androgen receptor

degradation by the proteolytic machinery of UPS (Petiwala et al., 2016). Being the largest group of natural molecules of various reported structures, functional knowledge of these precious class of molecules is lacking due to limitations in testing at natural settings and their presence as complex mixtures (Gershenson and Dudareva, 2007). However, methods like increasing terpene production by employing molecular biology and genetics tools thereby modulating metabolism are providing helpful solutions for studying these compound for industrial and therapeutic applications (Wu et al., 2006).

#### 8.1.9. Other natural agents

Other than all of the above mentioned naturally derived products there are also other studies that have identified molecules obtained from varied sources the nature provides, which affects proteostasis mechanism. Leucettamols, a sphingoid isolated from marine sponge *Leucetta aff. microrhaphis* inhibits interaction between E2 ubiquitin conjugating enzyme Ubc13 and Uev1A, which can be used to increase the cellular levels of tumor suppressor gene p53 and may be developed in a potential anti-cancer therapy (Tsukamoto et al., 2008). Furthermore, siladenoserinols A-L (a serinol derivative) obtained from tunicate inhibits interaction between p53-Hdm2 (Nakamura et al., 2013). Additionally, Marchantin M, obtained from plant liverwort inhibits chymotrypsin-like and peptidyl-glutamyl peptide-hydrolyzing activities of proteasome, induces ER stress and autophagic death in human prostate cancerous cells (Jiang et al., 2013). Similarly, another plant product allicin, an active ingredient in *Allium sativum* (or commonly known as garlic) induces autophagy in hepatocellular cancer cell line as evident from decreased level of PI3K/mTOR induction in AMPK/TSC2 and Beclin-1 signaling pathways in Hep G2 cells (Chu et al., 2012). Recently, *Acanthostrongylophora ingens* (porifera) obtained manzamine A, an amine derivative, was reported to effectively inhibits proteasome (Tsukamoto, 2016).

#### 8.2. Pharmacological compounds can improve degradative capacity of proteome

Developing new drugs is costly and time consuming process due to limitations in existing procedure of drug development (Dickson and Gagnon, 2004). The cost may reach up to 3 billion dollars with approximately 15 years of time period for a drug to reach in market (Nosengo, 2016). Using natural molecules as lead compounds may add to cost and labor depending on chemical complexity and available knowledge of the same. Scarcity of sources and concerns with intellectual property rights adds difficulty in using natural products at commercial level (Cragg and Newman, 2013; Harvey, 2008). Drug repurposing or repositioning can prove to be an effective alternative both in terms of time and cost. In drug repositioning strategy, known or existing drugs are studied for their effectiveness to treat new indications or diseases, as can be understood by examples of HIV drug plerixafor and antidepressant milnacipran which were later approved for multiple myeloma and fibromyalgia, respectively (Sleigh and Barton, 2010). Recently, fasudil, a vasodilator has been reported to enhance autophagy showing potential to be repositioned for neurodegenerative disorders (Iorio et al., 2010). Further subsections provide some information on existing pharmaceutical drugs that effect important signaling events of proteostasis.

#### 8.2.1. Anti-inflammatory drugs

Anti- inflammatory drug like celecoxib upregulate E3 ubiquitin ligase Casitas in B-lineage lymphoma B cells (Cbl-b), which results in inhibition of Akt activation through rapamycin thereby attenuating gastric cancer cell resistance to rapamycin (Cao et al., 2015). Another example of NSAID induced proteostasis

modulation include aspirin, that inhibits proteasome activity leading to cellular apoptosis (Dikshit et al., 2006). Derivative of salicylic acid, diflunisal acts as pharmacological chaperone, in transthyretin (TTR) amyloidosis, as it stabilizes the tertiary configuration of this protein (Sekijima et al., 2006). Furthermore, anti-inflammatory drug indomethacin has been reported to induce cytoprotective lipophagy in enterocytes (Narabayashi et al., 2014). Thus these few studies provide evidence that anti-inflammatory drugs have role in regulating the proteostasis pathways thus can be used for therapeutic purpose of the same. However, common side effects of anti-inflammatory drugs like ulceration, gastrointestinal bleeding should be kept in mind in designing therapeutic strategies. Also, effects of the original targets of the drug on the disease mechanism must be well investigated.

#### 8.2.2. Cancer drugs

Tyrosine kinase inhibitors such as nilotinib and bosutinib used in leukemia treatment alleviates proteotoxic load in Alzheimer's disease animals by enhancing interaction between parkin and beclin-1 (Lonskaya et al., 2013). Erlotinib another tyrosine kinase inhibitor used to treat non small lung cancer induces autophagy by activation of AMPK pathway and mTOR suppression, a mechanism that could be protective and provides resistance to cancer cell against erlotinib (Li et al., 2013). Similarly, another study reported resistance of cancer cell to anti-cancerous chimeric antibody cetuximab due to activation of autophagy (Li and Fan, 2010). Bortezomib, a well known drug to treat multiple myeloma inhibits proteasome (Kane et al., 2003) causing disturbed proteostasis in cancerous cells. It has also been observed that bortezomib can induce ER stress mediated apoptosis in pancreatic cancer cells (Nawrocki et al., 2005).

As evident from these studies different research work has used several proteostatic modulation strategies to control cancer cell growth. However, usage of anti-cancerous drugs have caused serious side effects, like doxorubicin (Dox) have shown to cause muscle atrophy, as it activates important cellular enzyme calpain in skeletal muscle (Smuder et al., 2011), similarly molecule like cisplatin have been shown to have side-effects like nephrotoxicity, renal failure and cardiotoxicity in cancer patients (Florea and Busselberg, 2011). Therefore, developing anti-cancerous drugs as agents to treat ailments of proteostatic disorders needs a detailed investigation on the chemical properties of these molecules and thought should be put on to reduce their serious side effects.

#### 8.2.3. Cardiovascular drugs

Drugs used in treatment of cardiovascular diseases have potential therapeutic effects in modulating pathways of proteostasis, as drugs like thalidomide, lenalidomide and pomalidomide, binds protein cereblon (CRBN) within the DNA damage binding E3 ubiquitin ligase complex and inhibits CRBN autoubiquitination, leading to reduction in CRBN level and increased p21 level in cancerous cells (Lopez-Girona et al., 2012). Cardioprotective drug, diazoxide, also shows therapeutic effect in metabolic disorder, as it activates K<sub>ATP</sub> channel activity in case of persistent hyperinsulinemic hypoglycemia of infancy, a disease of pancreatic β-cells (Molinari, 2007; Shyng et al., 1998). It can also regulate proteostatic pathway by interacting with Hsp90 and inhibiting cleavage of Bid, a pro-apoptotic protein (Yang et al., 2011). The ability of cardiovascular drug to modulate proteostatic pathway in ER, is used to produce therapeutic effect in disease of ALS, as guanabenz, inhibit the ER chaperone GRP78/Bip, AIF6α and IRE1, which consequently reduces ER stress (Jiang et al., 2014).

Cardiovascular drug, lacidipine can be used in form of a pharmacological chaperone, as it improves folding, trafficking and lysosomal activity of the destabilized glucocerebrosidase via ERAD inhibition in fibroblasts isolated from patients of Gaucher's disease

(Wang and Segatori, 2013). Compounds identified in treating disorders of cardiovascular system are also observed to regulate proteostatic pathway of autophagy, as drugs like minoxidil and clonidine show their therapeutic potential by reducing protein aggregation in a Huntington's disease model by inducing autophagy through the inhibition of  $\text{Ca}^{2+}$  channels, reducing cAMP levels, normalizing enhanced calpain activity and suppressing IP3 (Williams et al., 2008). Fenofibrate, can also cause autophagy in a diabetic mouse cardiac muscles by different mechanism through upregulation of sirutin-1 signaling pathway (Zhang et al., 2016). Above mentioned studies have shown promising evidence of some cardiovascular drugs to be used for therapeutic purpose in proteostasis associated pathologies.

#### 8.2.4. Neurological disorder drugs

Antidepressant drug, clomipramine was reported to inhibit E3 ubiquitin ligase ITCH autoubiquitination which leads to ITCH functional inhibition and autophagy reduction in cancer cells (Rossi et al., 2014). Anti-depressants drugs of various types (serotonin selective, norepinephrine selective, and nonselective reuptake inhibitors, monoamine oxidase inhibitor) treating neurological disorders are shown to increase ubiquitylation and degradation by proteasomal pathway of  $\beta$ -arrestin 2 (Golan et al., 2010). Ubiquitin specific proteases have shown activity against proliferation of non-small cell cancerous cells by acting synergistically with cisplatin (Chen et al., 2011). A $\beta$ -specific  $\beta$ -sheet breaker peptide H102 has shown pharmacological activity to reverse the misfolding and aggregation of A $\beta$  which can be used to treat neurodegeneration caused by aggregation of A $\beta$  in Alzheimer's disease (Bessis and Breton-Gorius, 1965). Neurological drug, valproic acid used to treat epilepsy increases mRNA levels of Hsp70 in rat cortical neurons (Marinova et al., 2009).

The antioxidant edaravone protects against ER stress in autoimmune rats by causing an inhibitory effect on ER chaperone GRP78, which is a putative marker of ER stress (Shimazaki et al., 2010). Lithium, a mood enhancer, alters the proteostasis of ER in galactose fed cells, by modifying the XBP, XBPS levels and UPR signaling pathway in ER stress mechanism, they can also suppress the release of apoptosis associated proteins and inhibit neuronal apoptosis via down-regulating autophagy through reducing the calpain activation in neonatal rat different brain regions (Li et al., 2010; Nagy et al., 2013). In SH-SY5Y cells, zonisamide, at low doses upregulate ER E3 ubiquitin ligase HRD1, which may ameliorate ER stress conditions and ultimately results in decreased neuronal cell death in Parkinson's disease (Omura et al., 2012). Together, drugs used to treat various neurological disorders can be further investigated for neurodegenerative diseases like Alzheimer's and Parkinson's which currently have very limited treatment options.

#### 8.2.5. Drugs used in other therapies

Molecules utilized in treatment of diseases other than proteostatic disorder, have shown further ability to affect proteostatic pathways, N-acetylglucosamine thiazoline enzyme activity regulator of  $\beta$ -hexosaminidase A is currently being developed as pharmacological chaperone to treat disease of lysosomal storage disorder, where it restores the defective enzyme's functional activity (Tropak and Mahuran, 2007). Ritonavir and Metformin, used in treating pathological disorders of HIV and type-2 diabetes, respectively are also used with bortezomib for inducing ER stress (via UPR pathway) and suppressing GRP78-mediated autophagy, to increase the apoptotic function of bortezomib in cancerous cells (Jagannathan et al., 2015; Kraus et al., 2008). Antidiarrheal medication, such as loperamide, causes autophagy in alveolar cells of a mouse animal model infected with *Mycobacterium tuberculosis* (Mtb) by inducing

localization of autophagic protein LC3 with Mtb (Fleming et al., 2011; Juarez et al., 2016).

Antibiotics are normally used to treat microorganisms infections, but they have also shown ability to modulate proteostasis, like azithromycin inhibits autophagy by preventing lysosomal acidification (Renna et al., 2011), whereas, another antibiotic tigecycline induces autophagy with activation of AMPK pathway and inhibition of downstream effectors mTOR and p70S6K (Tang et al., 2014). The scientific research work on compound, metformin, have shown that this molecule can cause re-establish autophagy in various disorders, via restoring disturbed AMPK signaling using different pathways of mTOR activation (Ravindran et al., 2016; Song et al., 2014). Table 2 summarizes various targets that have been identified to modulate protein quality control mechanisms and studies that have been done to screen natural and pharmaceutical molecules that have properties to act on those targets.

Identifying and characterizing compounds derived from either natural resources or from synthetic origin for utilizing in modulating major pathways and machinery of proteostasis i.e. UPS, autophagy, chaperone machinery requires a detailed investigation of the molecule with respect to its bio-availability, pharmacokinetics, pharmacodynamics, chemistry, side-effects and also its clinical suitability. Thus finding specific modulators of the proteostasis, is still a challenge and in this context steps are already being taken as can be understood from example of protacs. Proteolysis targeting chimeras (protacs) are ternary complex, which contains an E3 ubiquitin ligase, linked to another ligand for protein to be targeted for degradation. The E3 ubiquitin ligase, causes polyubiquitination of ligand binned protein, leading to their degradation (Buckley and Crews, 2014). Thus using such chimeric molecules developed by advanced molecular biology and chemical techniques could alleviate problems of specificity.

### 9. Key questions and future perspectives

Despite significant progress in our current understanding that maintenance of functional proteome, or proteostasis is essential to delay aging like processes. But many lines of evidence now suggest that failure of proteostasis may also lead to neurodegeneration. Inefficient clearance of old or aberrant proteins bulk, produced by various genotoxic stresses, declines the capacity of PQC mechanism and suppresses neuroprotective stress-response pathways. However, it is not clear that what other set of genes and their end product proteins are involved in proteostasis regulation of the cells? It could be possible that the induced expressions of these genes under proteome imbalance conditions, may act as a compensatory mechanism to maintain proteostasis. But, still we are too far to understand how these remunerative signaling pathways arise to provide cytoprotection against proteo-pathogenic conditions? Another important question is to observe whether these selective gene expression profiles based cytoprotective molecular mechanisms are same or differ in various neurodegenerative diseases.

It is also important to improve the understanding of those pathways, which are crucial for sustained maintenance of functional and healthy proteome. Another question that remains to be answered is that could therapeutically activation based on natural or multipharmacological agents stimulate the activities of remunerative signaling pathways to prevent proteostasis defects? On the basis of previous findings, it is clear that still a better and detailed understanding of functional characteristics of proteostasis is required, which may ultimately allow us to harness this complex process for the therapeutic purpose. Uncovering the sustainable molecular pathways needful for proteostasis continuance

**Table 2**

Modulators affecting protein quality control mechanisms obtained from various natural and pharmacological sources. Natural and pharmaceutical molecules have been studied for their effects on different protein quality control mechanisms to be used for diverse therapeutic applications.

Mechanisms	Natural Sources								Pharmacological Drugs						
Targets That Are Affected Underlying Protein Quality Control Mechanisms	Vitamins	Saccharides	Natural Isothiocyanate	Natural Phenols Flavonoids/Flavonols	Alkaloids	Fatty acid/Derivatives	Bacterial Isolates	Fungal Isolates	Terpenes/Terpenoids	Other natural agents	Anti-Inflammatory drugs	Cancer drugs	Cardiovascular disease drugs	Neurological disorders drugs	Drugs used in other disease therapy
Ubiquitin Proteasome System				[1]	[2]		[3]	[4]							
E1															
E2						[5]									
E3	[8]	[9]		[10]	[11]		[12]	[13]	[14]	[15]	[16]	[17]	[18]	[19]	
Ubiquitin	[21]	[22]		[23]		[24]				[25]				[26]	
Proteasome	[27]	[28]	[29]	[30]	[31]	[5]	[32]	[33]	[34]	[6]	[35]	[33]	[33]		
DUB enzymes				[36]	[37]	[6]			[38]	[6]				[39]	
Chaperone Machinery															
Pharmacological Chaperone	[40]	[41]			[42]					[43]	[44]	[45]	[45]	[46]	
Chemical Chaperone						[48]		[45]		[48]				[48]	
Heat Shock Protein	[49]	[47]	[50]	[51]	[52]	[53]	[54]	[55]	[56]	[56]	[57]	[58]	[59]	[60]	
ER Proteostasis															
ER Chaperone	[62]	[47]	[63]	[64]	[65]	[66]	[67]	[68]	[69]	[70]	[71]	[72]	[73]	[74]	
UPR	[62]	[76]	[77]	[64]	[78]	[79]	[67]	[80]	[69]	[81]	[82]	[83]	[73]	[84]	
Transport mechanism					[78]						[86]	[87]			
ERAD	[88]	[89]		[90]	[91]	[92]	[91]		[69]	[93]		[94]	[95]	[96]	
Autophagy															
Ca <sup>2+</sup> Flux	[97]				[98]						[99]	[100]	[100]		
cAMP Flux				[101]			[102]			[103]		[99]	[104]		
Sirtuin	[105]		[106]	[107]	[108]	[109]	[110]	[111]	[112]	[113]		[114]	[115]	[116]	
AMPK	[117]	[118]	[106]	[119]	[120]	[121]	[122]	[123]	[124]	[125]	[126]	[127]	[128]	[129]	
Calpain	[131]		[132]	[133]		[134]		[135]	[136]		[137]	[99]	[138]	[139]	
IP3					[140]							[99]	[128]		
mTOR	[97]	[141]	[142]	[135]	[143]	[128]	[130]	[144]	[135]	[135]	[145]	[127]	[100]	[146]	
Beclin-1	[148]	[149]	[150]	[151]	[152]	[121]	[153]	[144]	[135]	[125]	[154]	[155]	[156]	[157]	
V-ATPase							[130]							[158]	
Autophagy-Lysosome fusion	[159]				[130]		[130]		[160]	[161]		[162]	[130]		

**Table 2. Modulators of protein quality control mechanisms screened from various natural and pharmacological sources**

**References of Table 2.**

- 1 Fukuda, I. et al. Ginkgolic Acid Inhibits Protein SUMOylation by Blocking Formation of the E1-SUMO Intermediate. *Chemistry & Biology* **16**, 133–140, doi:10.1016/j.chembiol.2009.01.009 (2009).
- 2 Yamanokuchi, R. et al. Hyrtioreticulins A-E, indole alkaloids inhibiting the ubiquitin-activating enzyme, from the marine sponge Hyrtios reticulatus. *Bioorganic & medicinal chemistry* **20**, 4437–4442, doi:10.1016/j.bmc.2012.05.044 (2012).
- 3 Ungerhoff, D. et al. Largazole and Its Derivatives Selectively Inhibit Ubiquitin Activating Enzyme (E1). *PLoS one* **7**, e29208, doi:10.1371/journal.pone.0029208 (2012).
- 4 Sekizawa, R. et al. Panepophenanthrin, from a Mushroom Strain, a Novel Inhibitor of the Ubiquitin-Activating Enzyme. *J. Nat. Prod.* **65**, 1491–1493, doi:10.1021/np020098q (2002).
- 5 Whitehouse, A., Khal, J. & Tisdale, M. J. Induction of protein catabolism in myotubes by 15 (S)-hydroxyeicosatetraenoic acid through increased expression of the ubiquitin–proteasome pathway. *British journal of cancer* **89**, 737–745 (2003).
- 6 Tsukamoto, S. Search for Inhibitors of the Ubiquitin-Proteasome System from Natural Sources for Cancer Therapy. *Chemical and Pharmaceutical Bulletin* **64**, 112–118, doi:10.1248/cpb.c15-00768 (2016).

**Table 2** (Continued)

- 7 McGuire, V. A. et al. Dimethyl fumarate blocks pro-inflammatory cytokine production via inhibition of TLR induced M1 and K63 ubiquitin chain formation. *Scientific Reports* **6**, 31159, doi:10.1038/srep31159 (2016).
- 8 Shah, M. et al. Inhibition of Siah2 ubiquitin ligase by vitamin K3 (menadione) attenuates hypoxia and MAPK signaling and blocks melanoma tumorigenesis. *Pigment Cell & Melanoma Research* **22**, 799-808, doi:10.1111/j.1755-148x.2009.00628.x (2009).
- 9 Ju, Y. Glucosamine, a naturally occurring amino monosaccharide, inhibits A549 and H446 cell proliferation by blocking G1/S transition. *Molecular Medicine Reports*, doi:10.3892/mmr.2013.1584 (2013).
- 10 Jung, Y., Xu, W., Kim, H., Ha, N. & Neckers, L. Curcumin-induced degradation of ErbB2: A role for the E3 ubiquitin ligase CHIP and the Michael reaction acceptor activity of curcumin. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* **1773**, 383-390, doi:10.1016/j.bbamcr.2006.11.004 (2007).
- 11 Clement, J. A. et al. Discovery of new pyridoacridine alkaloids from *Lissoclinum cf. badium* that inhibit the ubiquitin ligase activity of Hdm2 and stabilize p53. *Bioorganic & Medicinal Chemistry* **16**, 10022-10028, doi:10.1016/j.bmc.2008.10.024 (2008).
- 12 Malloy, K. L. et al. Hoiamide D, a marine cyanobacteria-derived inhibitor of p53/MDM2 interaction. *Bioorganic & Medicinal Chemistry Letters* **22**, 683-688, doi:10.1016/j.bmcl.2011.10.054 (2012).
- 13 Tsukamoto, S., Yoshida, T., Hosono, H., Ohta, T. & Yokosawa, H. Hexylitaconic acid: a new inhibitor of p53-HDM2 interaction isolated from a marine-derived fungus, *Arthrionium* sp. *Bioorg Med Chem Lett* **16**, 69-71, doi:10.1016/j.bmcl.2005.09.052 (2006).
- 14 Gopal, Y. N. V., Chanchorn, E. & Van Dyke, M. W. Parthenolide promotes the ubiquitination of MDM2 and activates p53 cellular functions. *Molecular Cancer Therapeutics* **8**, 552-562, doi:10.1158/1535-7163.mct-08-0661 (2009).
- 15 Nakamura, Y. et al. Siladenoserinols A-L: new sulfonated serinol derivatives from a tunicate as inhibitors of p53-Hdm2 interaction. *Org Lett* **15**, 322-325, doi:10.1021/o13032363 (2013).
- 16 Cao, Y. et al. Celecoxib sensitizes gastric cancer to rapamycin via inhibition of the Cbl-b-regulated PI3K/Akt pathway. *Tumor Biol.* **36**, 5607-5615, doi:10.1007/s13277-015-3232-6 (2015).
- 17 Lonskaya, I., Hebron, M. L., Desforges, N. M., Franjie, A. & Moussa, C. E. H. Tyrosine kinase inhibition increases functional parkin-Beclin-1 interaction and enhances amyloid clearance and cognitive performance. *EMBO Molecular Medicine* **5**, 1247-1262, doi:10.1002/emmm.201302771 (2013).
- 18 Lopez-Girona, A. et al. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia* **26**, 2326-2335, doi:10.1038/leu.2012.119 (2012).
- 19 Rossi, M. et al. High throughput screening for inhibitors of the HECT ubiquitin E3 ligase ITCH identifies antidepressant drugs as regulators of autophagy. *Cell Death Dis* **5**, e1203, doi:10.1038/cddis.2014.113 (2014).
- 20 Burger, A. M., Amemiya, Y. & Seth, A. K. Disulfiram inhibits the ubiquitin E3 ligase activity of the novel breast cancer associated gene BCA2 and the growth of BCA2 expressing breast cancer cell lines. *Cancer research* **66**, 1296-1296 (2006).
- 21 Li, X. Y. 1,25-Dihydroxyvitamin D<sub>3</sub> Increases Nuclear Vitamin D<sub>3</sub> Receptors by Blocking Ubiquitin/Proteasome-Mediated Degradation in Human Skin. *Molecular Endocrinology* **13**, 1686-1694, doi:10.1210/me.13.10.1686 (1999).
- 22 Dong, L. & Xu, C. W. Carbohydrates Induce Mono-ubiquitination of H2B in Yeast. *Journal of Biological Chemistry* **279**, 1577-1580, doi:10.1074/jbc.c300505200 (2003).
- 23 Wang, K. et al. Polyphenol-rich propolis extracts from China and Brazil exert anti-inflammatory effects by modulating ubiquitination of TRAF6 during the activation of NF-κB. *Journal of Functional Foods* **19, Part A**, 464-478, doi:<http://dx.doi.org/10.1016/j.jff.2015.09.009> (2015).
- 24 Ando, H. et al. Fatty Acids Regulate Pigmentation via Proteasomal Degradation of Tyrosinase: A NEW ASPECT OF UBIQUITIN-PROTEASOME FUNCTION. *Journal of Biological Chemistry* **279**, 15427-15433, doi:10.1074/jbc.m313701200 (2004).
- 25 Verma, R. Ubistatins Inhibit Proteasome-Dependent Degradation by Binding the Ubiquitin Chain. *Science* **306**, 117-120, doi:10.1126/science.1100946 (2004).
- 26 Golan, M., Schreiber, G. & Avissar, S. Antidepressants Increase -Arrestin2 Ubiquitylation and Degradation by the Proteasomal Pathway in C6 Rat Glioma Cells. *Journal of Pharmacology and Experimental Therapeutics* **332**, 970-976, doi:10.1124/jpet.109.160218 (2009).
- 27 Munteanu, A., Ricciarelli, R., Massone, S. & Zingg, J.-M. Modulation of Proteasome Activity by Vitamin E in THP-1 Monocytes. *IUBMB Life* **59**, 771-780, doi:10.1080/15216540701697420 (2007).
- 28 Liu, B.-Q. et al. Glucosamine induces cell death via proteasome inhibition in human ALVA41 prostate cancer cell. *Experimental and Molecular Medicine* **43**, 487, doi:10.3858/emm.2011.43.9.055 (2011).
- 29 Kwak, M. K., Cho, J. M., Huang, B., Shin, S. & Kensler, T. W. Role of increased expression of the proteasome in the protective effects of sulforaphane against hydrogen peroxide-mediated cytotoxicity in murine neuroblastoma cells. *Free Radic Biol Med* **43**, 809-817, doi:10.1016/j.freeradbiomed.2007.05.029 (2007).
- 30 Katsiki, M., Chondrogianni, N., Chinou, I., Rivett, A. J. & Gonos, E. S. The olive constituent oleuropein exhibits proteasome stimulatory properties in vitro and confers life span extension of human embryonic fibroblasts. *Rejuvenation research* **10**, 157-172, doi:10.1089/rej.2006.0513 (2007).
- 31 Maity, R., Sharma, J. & Jana, N. R. Capsaicin induces apoptosis through ubiquitin-proteasome system dysfunction. *J Cell Biochem* **109**, 933-942, doi:10.1002/jcb.22469 (2010).

**Table 2** (Continued)

- 32 Gulder, T. A. & Moore, B. S. Salinosporamide natural products: Potent 20 S proteasome inhibitors as promising cancer chemotherapeutics. *Angew Chem Int Ed Engl* **49**, 9346-9367, doi:10.1002/anie.201000728 (2010).
- 33 M. Gaczynska, B. S. P. & P.A. Osmulski, B. S. P. Inhibitor at the Gates, Inhibitor in the Chamber: Allosteric and Competitive Inhibitors of the Proteasome as Prospective Drugs. *Current Medicinal Chemistry-Immunology, Endocrine & Metabolic Agents* **2**, 279-301, doi:10.2174/1568013023358807 (2002).
- 34 Huang, L., Ho, P. & Chen, C. H. Activation and inhibition of the proteasome by betulinic acid and its derivatives. *FEBS Lett* **581**, 4955-4959, doi:10.1016/j.febslet.2007.09.031 (2007).
- 35 Dikshit, P., Chatterjee, M., Goswami, A., Mishra, A. & Jana, N. R. Aspirin Induces Apoptosis through the Inhibition of Proteasome Function. *Journal of Biological Chemistry* **281**, 29228-29235, doi:10.1074/jbc.m602629200 (2006).
- 36 Lawson, A. P. et al. Naturally Occurring Isothiocyanates Exert Anticancer Effects by Inhibiting Deubiquitinating Enzymes. *Cancer Research* **75**, 5130-5142, doi:10.1158/0008-5472.can-15-1544 (2015).
- 37 Si, X. et al. Dysregulation of the Ubiquitin-Proteasome System by Curcumin Suppresses Coxsackievirus B3 Replication. *Journal of Virology* **81**, 3142-3150, doi:10.1128/jvi.02028-06 (2007).
- 38 Yue, W. et al. A small natural molecule promotes mitochondrial fusion through inhibition of the deubiquitinase USP30. *Cell Research* **24**, 482-496, doi:10.1038/cr.2014.20 (2014).
- 39 Chen, J. et al. Selective and Cell-Active Inhibitors of the USP1/ UAF1 Deubiquitinase Complex Reverse Cisplatin Resistance in Non-small Cell Lung Cancer Cells. *Chemistry & Biology* **18**, 1390-1400, doi:10.1016/j.chembiol.2011.08.014 (2011).
- 40 Henriques, B. J., Rodrigues, J. V., Olsen, R. K., Bross, P. & Gomes, C. M. Role of Flavinylation in a Mild Variant of Multiple Acyl-CoA Dehydrogenation Deficiency: A MOLECULAR RATIONALE FOR THE EFFECTS OF RIBOFLAVIN SUPPLEMENTATION. *Journal of Biological Chemistry* **284**, 4222-4229, doi:10.1074/jbc.m805719200 (2008).
- 41 Lieberman, R. L., D'aquino, J. A., Ringe, D. & Petsko, G. A. Effects of pH and Iminosugar Pharmacological Chaperones on Lysosomal Glycosidase Structure and Stability. *Biochemistry* **48**, 4816-4827, doi:10.1021/bi9002265 (2009).
- 42 Kuryatov, A., Luo, J., Cooper, J. & Lindstrom, J. Nicotine acts as a pharmacological chaperone to up-regulate human alpha4beta2 acetylcholine receptors. *Molecular pharmacology* **68**, 1839-1851, doi:10.1124/mol.105.012419 (2005).
- 43 Santos-Sierra, S. et al. Novel pharmacological chaperones that correct phenylketonuria in mice. *Human Molecular Genetics* **21**, 1877-1887, doi:10.1093/hmg/dds001 (2012).
- 44 Galant, N. J. et al. Substoichiometric inhibition of transthyretin misfolding by immune-targeting sparsely populated misfolding intermediates: a potential diagnostic and therapeutic for TTR amyloidoses. *Sci. Rep.* **6**, 25080, doi:10.1038/srep25080 (2016).
- 45 Molinari, M. N-glycan structure dictates extension of protein folding or onset of disposal. *Nature Chemical Biology* **3**, 313-320, doi:10.1038/nchembio880 (2007).
- 46 Tropak, M. B. & Mahuran, D. Lending a helping hand, screening chemical libraries for compounds that enhance beta-hexosaminidase A activity in GM2 gangliosidosis cells. *FEBS Journal* **274**, 4951-4961, doi:10.1111/j.1742-4658.2007.06040.x (2007).
- 47 Tanji, K. et al. Trehalose intake induces chaperone molecules along with autophagy in a mouse model of Lewy body disease. *Biochemical and biophysical research communications* **465**, 746-752, doi:10.1016/j.bbrc.2015.08.076 (2015).
- 48 Sauer, T., Patel, M., Chan, C.-C. & Tuo, J. Unfolding the therapeutic potential of chemical chaperones for age-related macular degeneration. *Expert Review of Ophthalmology* **3**, 29-42, doi:10.1586/17469899.3.1.29 (2008).
- 49 Wu, C., Wang, J., Xu, W., Zhang, W. & Mai, K. Dietary ascorbic acid modulates the expression profile of stress protein genes in hepatopancreas of adult Pacific abalone *Haliotis discus hannai* Ino. *Fish & Shellfish Immunology* **41**, 120-125, doi:10.1016/j.fsi.2014.08.026 (2014).
- 50 Sarkar, R., Mukherjee, S., Biswas, J. & Roy, M. Sulphoraphane, a naturally occurring isothiocyanate induces apoptosis in breast cancer cells by targeting heat shock proteins. *Biochemical and biophysical research communications* **427**, 80-85, doi:10.1016/j.bbrc.2012.09.006 (2012).
- 51 Kanagaraj, V. V., Panneerselvam, L., Govindarajan, V., Ameeramja, J. & Perumal, E. Caffeic acid, a phyto polyphenol mitigates fluoride induced hepatotoxicity in rats: A possible mechanism. *BioFactors* **41**, 90-100, doi:10.1002/biof.1203 (2015).
- 52 Small, B. A., Lu, Y., Hsu, A. K., Gross, G. J. & Gross, E. R. Morphine Reduces Myocardial Infarct Size via Heat Shock Protein 90 in Rodents. *BioMed Research International* **2015**, 1-8, doi:10.1155/2015/129612 (2015).
- 53 Suaud, L. et al. 4-Phenylbutyrate Stimulates Hsp70 Expression through the Elp2 Component of Elongator and STAT-3 in Cystic Fibrosis Epithelial Cells. *Journal of Biological Chemistry* **286**, 45083-45092, doi:10.1074/jbc.m111.293282 (2011).
- 54 Buckley, D. L. & Crews, C. M. Small-Molecule Control of Intracellular Protein Levels through Modulation of the Ubiquitin Proteasome System. *Angewandte Chemie International Edition* **53**, 2312-2330, doi:10.1002/anie.201307761 (2014).
- 55 Sklirou, A. D. et al. Hexapeptide-11 is a novel modulator of the proteostasis network in human diploid fibroblasts. *Redox Biology* **5**, 205-215, doi:10.1016/j.redox.2015.04.010 (2015).

**Table 2** (Continued)

- 56 Zhao, Q. et al. Natural products triptolide, celastrol, and withaferin A inhibit the chaperone activity of peroxiredoxin I. *Chem. Sci.* **6**, 4124-4130, doi:10.1039/c5sc00633c (2015).
- 57 Cronjé, M. J. & Bornman, L. Salicylic Acid Influences Hsp70/Hsc70 Expression in *Lycopersicon esculentum*: Dose- and Time-Dependent Induction or Potentiation. *Biochemical and biophysical research communications* **265**, 422-427, doi:10.1006/bbrc.1999.1692 (1999).
- 58 Shah, S. P. et al. Bortezomib-induced heat shock response protects multiple myeloma cells and is activated by heat shock factor 1 serine 326 phosphorylation. *Oncotarget*, doi:10.18632/oncotarget.10847 (2016).
- 59 Yang, F. et al. Heat shock protein 90 mediates anti-apoptotic effect of diazoxide by preventing the cleavage of Bid in hypothermic preservation rat hearts. *The Journal of Heart and Lung Transplantation*, doi:10.1016/j.healun.2011.04.001 (2011).
- 60 Marinova, Z. et al. Valproic acid induces functional heat-shock protein 70 via Class I histone deacetylase inhibition in cortical neurons: a potential role of Sp1 acetylation. *Journal of Neurochemistry* **111**, 976-987, doi:10.1111/j.1471-4159.2009.06385.x (2009).
- 61 Neznanov, N. et al. Anti-malaria drug blocks proteotoxic stress response: Anti-cancer implications. *Cell cycle* **8**, 3960-3970, doi:10.4161/cc.8.23.10179 (2009).
- 62 Ji, Y.-L. et al. Ascorbic acid protects against cadmium-induced endoplasmic reticulum stress and germ cell apoptosis in testes. *Reproductive Toxicology* **34**, 357-363, doi:10.1016/j.reprotox.2012.04.011 (2012).
- 63 Li, Y.-p. et al. Sulforaphane prevents rat cardiomyocytes from hypoxia/reoxygenation injury in vitro via activating SIRT1 and subsequently inhibiting ER stress. *Acta Pharmacologica Sinica* **37**, 344-353, doi:10.1038/aps.2015.130 (2016).
- 64 Liu, B.-Q. et al. Implication of unfolded protein response in resveratrol-induced inhibition of K562 cell proliferation. *Biochemical and Biophysical Research Communications* **391**, 778-782, doi:10.1016/j.bbrc.2009.11.137 (2010).
- 65 Hao, X. et al. Berberine Ameliorates Pro-inflammatory Cytokine-Induced Endoplasmic Reticulum Stress in Human Intestinal Epithelial Cells In Vitro. *Inflammation* **35**, 841-849, doi:10.1007/s10753-011-9385-6 (2011).
- 66 Yamagishi, N., Ueda, T., Mori, A., Saito, Y. & Hatayama, T. Decreased expression of endoplasmic reticulum chaperone GRP78 in liver of diabetic mice. *Biochemical and Biophysical Research Communications* **417**, 364-370, doi:10.1016/j.bbrc.2011.11.118 (2012).
- 67 Lawson, B., Brewer, J. W. & Hendershot, L. M. Geldanamycin, an hsp90/GRP94-binding drug, induces increased transcription of endoplasmic reticulum (ER) chaperones via the ER stress pathway. *J. Cell. Physiol.* **174**, 170-179, doi:10.1002/(sici)1097-4652(199802)174:2<170::aid-jcp4>3.3.co;2-a (1998).
- 68 Choo, S. J. et al. Deoxyverrucosidin, a novel GRP78/BiP down-regulator, produced by *Penicillium* sp. *The Journal of antibiotics* **58**, 210-213, doi:10.1038/ja.2005.26 (2005).
- 69 Petiwala, S. M. et al. Carnosic acid promotes degradation of the androgen receptor and is regulated by the unfolded protein response pathway in vitro and in vivo. *Carcinogenesis* **37**, 827-838, doi:10.1093/carcin/bgw052 (2016).
- 70 Cha, B.-H. et al. The role of taurooursodeoxycholic acid on adipogenesis of human adipose-derived stem cells by modulation of ER stress. *Biomaterials* **35**, 2851-2858, doi:10.1016/j.biomaterials.2013.12.067 (2014).
- 71 Deng, W. G. Aspirin and salicylate bind to immunoglobulin heavy chain binding protein (BiP) and inhibit its ATPase activity in human fibroblasts. *The FASEB Journal* **15**, 2463-2470, doi:10.1096/fj.01-0259com (2001).
- 72 Kim, I.-K. et al. Cyclosporine A and bromocriptine attenuate cell death mediated by intracellular calcium mobilization. *BMB reports* **45**, 482-487 (2012).
- 73 Jiang, H. Q. et al. Guanabenz delays the onset of disease symptoms, extends lifespan, improves motor performance and attenuates motor neuron loss in the SOD1 G93A mouse model of amyotrophic lateral sclerosis. *Neuroscience* **277**, 132-138, doi:10.1016/j.neuroscience.2014.03.047 (2014).
- 74 Shimazaki, H. et al. The antioxidant edaravone attenuates ER-stress-mediated cardiac apoptosis and dysfunction in rats with autoimmune myocarditis. *Free Radical Research* **44**, 1082-1090, doi:10.3109/10715762.2010.499904 (2010).
- 75 Jagannathan, S. et al. Pharmacologic screens reveal metformin that suppresses GRP78-dependent autophagy to enhance the anti-myeloma effect of bortezomib. *Leukemia* **29**, 2184-2191, doi:10.1038/leu.2015.157 (2015).
- 76 Li, S. et al. Lipopolysaccharide Induces Autophagic Cell Death through the PERK-Dependent Branch of the Unfolded Protein Response in Human Alveolar Epithelial A549 Cells. *Cellular Physiology and Biochemistry* **36**, 2403-2417, doi:10.1159/000430202 (2015).
- 77 Doudican, N. A., Wen, S. Y., Mazumder, A. & Orlow, S. J. Sulforaphane synergistically enhances the cytotoxicity of arsenic trioxide in multiple myeloma cells via stress-mediated pathways. *Oncol Rep* **28**, 1851-1858, doi:10.3892/or.2012.1977 (2012).
- 78 Zhang, K. et al. Berberine Induces hERG Channel Deficiency through Trafficking Inhibition. *Cellular Physiology and Biochemistry* **34**, 691-702, doi:10.1159/000363034 (2014).
- 79 Sommerweiss, D., Gorski, T., Richter, S., Garten, A. & Kiess, W. Oleate rescues INS-1E β-cells from palmitate-induced apoptosis by preventing activation of the unfolded protein response. *Biochemical and biophysical research communications* **441**, 770-776, doi:10.1016/j.bbrc.2013.10.130 (2013).
- 80 Fribley, A. M. et al. Complementary Cell-Based High-Throughput Screens Identify Novel Modulators of the Unfolded Protein Response. *Journal of biomolecular screening* **16**, 825-835, doi:10.1177/108705711414893 (2011).

**Table 2** (Continued)

- 81 Groenendyk, J. et al. Inhibition of the Unfolded Protein Response Mechanism Prevents Cardiac Fibrosis. *PLoS one* **11**, e0159682, doi:10.1371/journal.pone.0159682 (2016).
- 82 Tian, S. et al. The interplay between GRP78 expression and Akt activation in human colon cancer cells under celecoxib treatment. *Anti-Cancer Drugs* **26**, 964-973, doi:10.1097/cad.0000000000000273 (2015).
- 83 Mujtaba, T. & Dou, Q. P. Advances in the understanding of mechanisms and therapeutic use of bortezomib. *Discovery medicine* **12**, 471-480 (2011).
- 84 Nagy, T. et al. Lithium Induces ER Stress and N-Glycan Modification in Galactose-Grown Jurkat Cells. *PLoS ONE* **8**, e70410, doi:10.1371/journal.pone.0070410 (2013).
- 85 Kraus, M. et al. Ritonavir induces endoplasmic reticulum stress and sensitizes sarcoma cells toward bortezomib-induced apoptosis. *Molecular Cancer Therapeutics* **7**, 1940-1948, doi:10.1158/1535-7163.mct-07-2375 (2008).
- 86 Yi, P. et al. Sorafenib-Mediated Targeting of the AAA+ ATPase p97/VCP Leads to Disruption of the Secretory Pathway, Endoplasmic Reticulum Stress, and Hepatocellular Cancer Cell Death. *Molecular Cancer Therapeutics* **11**, 2610-2620, doi:10.1158/1535-7163.mct-12-0516 (2012).
- 87 Wang, F. & Segatori, L. Remodeling the Proteostasis Network to Rescue Glucocerebrosidase Variants by Inhibiting ER-Associated Degradation and Enhancing ER Folding. *PLoS ONE* **8**, e61418, doi:10.1371/journal.pone.0061418 (2013).
- 88 Liu, L., Liu, C., Zhong, Y., Apostolou, A. & Fang, S. ER stress response during the differentiation of H9 cells induced by retinoic acid. *Biochemical and biophysical research communications* **417**, 738-743, doi:10.1016/j.bbrc.2011.12.026 (2012).
- 89 Denzel, Martin S. et al. Hexosamine Pathway Metabolites Enhance Protein Quality Control and Prolong Life. *Cell* **156**, 1167-1178, doi:10.1016/j.cell.2014.01.061 (2014).
- 90 Sasazawa, Y. et al. Xanthohumol Impairs Autophagosome Maturation through Direct Inhibition of Valosin-Containing Protein. *ACS Chem Biol.* **7**, 892-900, doi:10.1021/cb200492h (2012).
- 91 Wang, F., Song, W., Brancati, G. & Segatori, L. Inhibition of Endoplasmic Reticulum-associated Degradation Rescues Native Folding in Loss of Function Protein Misfolding Diseases. *Journal of Biological Chemistry* **286**, 43454-43464, doi:10.1074/jbc.m111.274332 (2011).
- 92 Lee, J. N., Zhang, X., Feramisco, J. D., Gong, Y. & Ye, J. Unsaturated Fatty Acids Inhibit Proteasomal Degradation of Insig-1 at a Postubiquitination Step. *Journal of Biological Chemistry* **283**, 33772-33783, doi:10.1074/jbc.m806108200 (2008).
- 93 Jiang, H. et al. Marchantin M: a novel inhibitor of proteasome induces autophagic cell death in prostate cancer cells. *Cell Death and Disease* **4**, e761, doi:10.1038/cddis.2013.285 (2013).
- 94 Jin, H. R. et al. The antitumor natural compound falcarindiol promotes cancer cell death by inducing endoplasmic reticulum stress. *Cell Death and Disease* **3**, e376, doi:10.1038/cddis.2012.122 (2012).
- 95 Liu, D., Liu, Y., Yi, Z. & Dong, H. Simvastatin protects cardiomyocytes from doxorubicin cardiotoxicity by suppressing endoplasmic reticulum stress and activating Akt signaling. *INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL MEDICINE* **9**, 2193-2201 (2016).
- 96 Omura, T. et al. HRD1 Levels Increased by Zonisamide Prevented Cell Death and Caspase-3 Activation Caused by Endoplasmic Reticulum Stress in SH-SY5Y Cells. *Journal of Molecular Neuroscience* **46**, 527-535, doi:10.1007/s12031-011-9638-8 (2011).
- 97 Wu, S. & Sun, J. Vitamin D, vitamin D receptor, and macroautophagy in inflammation and infection. *Discover Med* **11**, 325-335 (2011).
- 98 Liu, A.-J. et al. Evodiamine, a plant alkaloid, induces calcium/JNK-mediated autophagy and calcium/mitochondria-mediated apoptosis in human glioblastoma cells. *Chemico-Biological Interactions* **205**, 20-28, doi:10.1016/j.cbi.2013.06.004 (2013).
- 99 Williams, A. et al. Novel targets for Huntington's disease in an mTOR-independent autophagy pathway. *Nature Chemical Biology* **4**, 295-305, doi:10.1038/nchembio.79 (2008).
- 100 Fleming, A., Noda, T., Yoshimori, T. & Rubinsztein, D. C. Chemical modulators of autophagy as biological probes and potential therapeutics. *Nature Chemical Biology* **7**, 9-17, doi:10.1038/nchembio.500 (2011).
- 101 Zhang, Y. et al. Resveratrol improves hepatic steatosis by inducing autophagy through the cAMP signaling pathway. *Molecular Nutrition & Food Research* **59**, 1443-1457, doi:10.1002/mnfr.201500016 (2015).
- 102 Shahnazari, S., Namolovan, A., Mogridge, J., Kim, P. K. & Brumell, J. H. Bacterial toxins can inhibit host cell autophagy through cAMP generation. *Autophagy* **7**, 957-965, doi:10.4161/auto.7.9.16435 (2011).
- 103 Sass, M., Csikós, G., Kömüves, L. & Kovács, J. Cyclic AMP in the fat body of *Mamestra brassicae* during the last instar and its possible involvement in the cellular autophagocytosis induced by 20-hydroxyecdysone. *General and Comparative Endocrinology* **50**, 116-123, doi:10.1016/0016-6480(83)90248-4 (1983).
- 104 Shchors, K., Massaras, A. & Hanahan, D. Dual Targeting of the Autophagic Regulatory Circuitry in Gliomas with Repurposed Drugs Elicits Cell-Lethal Autophagy and Therapeutic Benefit. *Cancer Cell* **28**, 456-471, doi:10.1016/j.ccr.2015.08.012 (2015).
- 105 Fukui, K. et al. Changes in microtubule-related proteins and autophagy in long-term vitamin E-deficient mice. *Free radical research* **48**, 649-658, doi:10.3109/10715762.2014.898295 (2014).
- 106 Zhang, Z. et al. Sulforaphane prevents the development of cardiomyopathy in type 2 diabetic mice probably by reversing oxidative stress-induced inhibition of LKB1/AMPK pathway. *Journal of Molecular and Cellular Cardiology* **77**, 42-52, doi:10.1016/j.jmcc.2014.09.022 (2014).

**Table 2** (Continued)

- 107 Cetrullo, S., D'Adamo, S., Guidotti, S., Borzi, R. M. & Flamigni, F. Hydroxytyrosol prevents chondrocyte death under oxidative stress by inducing autophagy through sirtuin 1-dependent and -independent mechanisms. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1860**, 1181-1191, doi:10.1016/j.bbagen.2016.03.002 (2016).
- 108 Lee, Y.-H., Chen, H.-Y., Su, L. J. & Chueh, P. J. Sirtuin 1 (SIRT1) Deacetylase Activity and NAD<sup>+</sup>/NADH Ratio Are Imperative for Capsaicin-Mediated Programmed Cell Death. *J. Agric. Food Chem.* **63**, 7361-7370, doi:10.1021/acs.jafc.5b02876 (2015).
- 109 de Kreutzenberg, S. V. et al. Downregulation of the longevity-associated protein sirtuin 1 in insulin resistance and metabolic syndrome: potential biochemical mechanisms. *Diabetes* **59**, 1006-1015, doi:10.2337/db09-1187 (2010).
- 110 Choi, Y.-J. et al. Rapamycin ameliorates chitosan nanoparticle-induced developmental defects of preimplantation embryos in mice. *Oncotarget*, doi:10.18632/oncotarget.10813 (2015).
- 111 Gao, Z. et al. SIRT1 mediates Sphk1/S1P-induced proliferation and migration of endothelial cells. *The International Journal of Biochemistry & Cell Biology* **74**, 152-160, doi:10.1016/j.biocel.2016.02.018 (2016).
- 112 Zeng, R., Chen, Y., Zhao, S. & Cui, G.-h. Autophagy counteracts apoptosis in human multiple myeloma cells exposed to oridonin in vitro via regulating intracellular ROS and SIRT1. *Acta Pharmacologica Sinica* **33**, 91-100, doi:10.1038/aps.2011.143 (2011).
- 113 Wang, Q. et al. In vivo recovery effect of silibinin treatment on streptozotocin-induced diabetic mice is associated with the modulations of sirt-1 expression and autophagy in pancreatic β-cell. *Journal of Asian Natural Products Research* **14**, 413-423, doi:10.1080/10286020.2012.657180 (2012).
- 114 Zhang, J. et al. Fenofibrate increases cardiac autophagy via FGF21/SIRT1 and prevents fibrosis and inflammation in the hearts of Type 1 diabetic mice. *Clinical Science* **130**, 625-641, doi:10.1042/cs20150623 (2016).
- 115 Lee, W.-Y. et al. Repositioning antipsychotic chlorpromazine for treating colorectal cancer by inhibiting sirtuin 1. *Oncotarget* **6**, 27580-27595, doi:10.18632/oncotarget.4768 (2015).
- 116 Song, Y. M. et al. Metformin alleviates hepatosteatosis by restoring SIRT1-mediated autophagy induction via an AMP-activated protein kinase-independent pathway. *Autophagy* **11**, 46-59, doi:10.4161/15548627.2014.984271 (2014).
- 117 Jang, W. et al. 1,25-Dihydroxyvitamin D3 attenuates rotenone-induced neurotoxicity in SH-SY5Y cells through induction of autophagy. *Biochemical and biophysical research communications* **451**, 142-147, doi:10.1016/j.bbrc.2014.07.081 (2014).
- 118 DeBosch, B. J. et al. Trehalose inhibits solute carrier 2A (SLC2A) proteins to induce autophagy and prevent hepatic steatosis. *Science signaling* **9**, ra21-ra21, doi:10.1126/scisignal.aac5472 (2016).
- 119 Huang, W. W. et al. Kaempferol induces autophagy through AMPK and AKT signaling molecules and causes G2/M arrest via downregulation of CDK1/cyclin B in SK-HEP-1 human hepatic cancer cells. *Int J Oncol* **42**, 2069-2077, doi:10.3892/ijo.2013.1909 (2013).
- 120 Law, B. Y. K. et al. Natural small-molecule enhancers of autophagy induce autophagic cell death in apoptosis-defective cells. *Sci. Rep.* **4**, doi:10.1038/srep05510 (2014).
- 121 Niso-Santano, M. et al. Unsaturated fatty acids induce non-canonical autophagy. *The EMBO Journal* **34**, 1025-1041, doi:10.15252/embj.201489363 (2015).
- 122 Campos, T. et al. Rapamycin requires AMPK activity and p27 expression for promoting autophagy-dependent Tsc2-null cell survival. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* **1863**, 1200-1207, doi:10.1016/j.bbamcr.2016.03.009 (2016).
- 123 Wong, Y. Y. et al. Cordycepin Inhibits Protein Synthesis and Cell Adhesion through Effects on Signal Transduction. *Journal of Biological Chemistry* **285**, 2610-2621, doi:10.1074/jbc.m109.071159 (2009).
- 124 Shen, S., Zhang, Y., Zhang, R., Tu, X. & Gong, X. Ursolic acid induces autophagy in U87MG cells via ROS-dependent endoplasmic reticulum stress. *Chemico-Biological Interactions* **218**, 28-41, doi:10.1016/j.cbi.2014.04.017 (2014).
- 125 Chu, Y.-L., Ho, C.-T., Chung, J.-G., Rajasekaran, R. & Sheen, L.-Y. Allicin Induces p53-Mediated Autophagy in Hep G2 Human Liver Cancer Cells. *J. Agric. Food Chem.* **60**, 8363-8371, doi:10.1021/jf301298y (2012).
- 126 Din, F. V. et al. Aspirin inhibits mTOR signaling, activates AMP-activated protein kinase, and induces autophagy in colorectal cancer cells. *Gastroenterology* **142**, 1504-1515 e1503, doi:10.1053/j.gastro.2012.02.050 (2012).
- 127 Li, Y.-y., Lam, S.-k., Mak, J. C.-w., Zheng, C.-y. & Ho, J. C.-m. Erlotinib-induced autophagy in epidermal growth factor receptor mutated non-small cell lung cancer. *Lung Cancer* **81**, 354-361, doi:10.1016/j.lungcan.2013.05.012 (2013).
- 128 Levine, B., Packer, M. & Codogno, P. Development of autophagy inducers in clinical medicine. *Journal of Clinical Investigation* **125**, 14-24, doi:10.1172/jci73938 (2015).
- 129 Mo, Y., Tang, L., Ma, Y. & Wu, S. Pramipexole pretreatment attenuates myocardial ischemia/reperfusion injury through upregulation of autophagy. *Biochemical and biophysical research communications* **473**, 1119-1124, doi:10.1016/j.bbrc.2016.04.026 (2016).
- 130 Yang, Z. J., Chee, C. E., Huang, S. & Sinicrope, F. A. The Role of Autophagy in Cancer: Therapeutic Implications. *Molecular Cancer Therapeutics* **10**, 1533-1541, doi:10.1158/1535-7163.mct-11-0047 (2011).

**Table 2** (Continued)

- 131 Del Bello, B., Toscano, M., Moretti, D. & Maellaro, E. Cisplatin-Induced Apoptosis Inhibits Autophagy, Which  
Acts as a Pro-Survival Mechanism in Human Melanoma Cells. *PLoS one* **8**, e57236,  
doi:10.1371/journal.pone.0057236 (2013).
- 132 Je Ma, C., Jung, W. J., Lee, K. Y., Kim, Y. C. & Sung, S. H. Calpain inhibitory flavonoids isolated from  
Orostachys japonicus. *Journal of Enzyme Inhibition and Medicinal Chemistry* **24**, 676-679,  
doi:10.1080/14756360802328075 (2009).
- 133 Yoon, J.-S. et al. Neferine isolated from Nelumbo nucifera enhances anti-cancer activities in Hep3B cells:  
Molecular mechanisms of cell cycle arrest, ER stress induced apoptosis and anti-angiogenic response.  
*Phytomedicine* **20**, 1013-1022, doi:10.1016/j.phymed.2013.03.024 (2013).
- 134 Harston, R. K. et al. Rapamycin treatment augments both protein ubiquitination and Akt activation in pressure-  
overloaded rat myocardium. *American journal of physiology. Heart and circulatory physiology* **300**, H1696-1706,  
doi:10.1152/ajpheart.00545.2010 (2011).
- 135 Ding, Q. et al. Natural autophagy regulators in cancer therapy: a review. *Phytochemistry Reviews* **14**, 137-154,  
doi:10.1007/s11101-014-9339-3 (2014).
- 136 Suparji, N. S. et al. Geranylated 4-Phenylcoumarins Exhibit Anticancer Effects against Human Prostate Cancer  
Cells through Caspase-Independent Mechanism. *PLoS one* **11**, e0151472, doi:10.1371/journal.pone.0151472  
(2016).
- 137 Smuder, A. J., Kavazis, A. N., Min, K. & Powers, S. K. Exercise protects against doxorubicin-induced oxidative  
stress and proteolysis in skeletal muscle. *Journal of Applied Physiology* **110**, 935-942,  
doi:10.1152/japplphysiol.00677.2010 (2011).
- 138 Crespo-Biel, N., Camins, A., Pallas, M. & Canudas, A. M. Evidence of calpain/cdk5 pathway inhibition by  
lithium in 3-nitropropionic acid toxicity in vivo and in vitro. *Neuropharmacology* **56**, 422-428,  
doi:10.1016/j.neuropharm.2008.09.012 (2009).
- 139 Escalante, A. M. et al. Preventing the autophagic survival response by inhibition of calpain enhances the  
cytotoxic activity of bortezomib in vitro and in vivo. *Cancer chemotherapy and pharmacology* **71**, 1567-1576,  
doi:10.1007/s00280-013-2156-3 (2013).
- 140 Jaimovich, E. et al. Xestospongin B, a competitive inhibitor of IP3-mediated Ca2+signalling in cultured rat  
myotubes, isolated myonuclei, and neuroblastoma (NG108-15) cells. *FEBS Letters* **579**, 2051-2057,  
doi:10.1016/j.febslet.2005.02.053 (2005).
- 141 Ravikumar, B. Raised intracellular glucose concentrations reduce aggregation and cell death caused by mutant  
huntingtin exon 1 by decreasing mTOR phosphorylation and inducing autophagy. *Human Molecular Genetics* **12**,  
985-994, doi:10.1093/hmg/ddg109 (2003).
- 142 Bommareddy, A. et al. Atg5 Regulates Phenethyl Isothiocyanate-Induced Autophagic and Apoptotic Cell Death  
in Human Prostate Cancer Cells. *Cancer Research* **69**, 3704-3712, doi:10.1158/0008-5472.can-08-4344 (2009).
- 143 Wang, N. et al. Berberine induces autophagic cell death and mitochondrial apoptosis in liver cancer cells: The  
cellular mechanism. *Journal of Cellular Biochemistry* **111**, 1426-1436, doi:10.1002/jcb.22869 (2010).
- 144 Zhao, Y. et al. SD118-Xanthocillin X (1), a Novel Marine Agent Extracted from Penicillium commune, Induces  
Autophagy through the Inhibition of the MEK/ERK Pathway. *Marine Drugs* **10**, 1345-1359,  
doi:10.3390/md10061345 (2012).
- 145 Narabayashi, K. et al. Indomethacin suppresses LAMP-2 expression and induces lipophagy and lipoapoptosis  
in rat enterocytes via the ER stress pathway. *Journal of Gastroenterology* **50**, 541-554, doi:10.1007/s00535-014-0995-  
2 (2014).
- 146 Ma, J. et al. Methamphetamine induces autophagy as a pro-survival response against apoptotic endothelial cell  
death through the Kappa opioid receptor. *Cell Death Dis* **5**, e1099, doi:10.1038/cddis.2014.64 (2014).
- 147 Ravindran, S., Kuruvilla, V., Wilbur, K. & Munusamy, S. Nephroprotective Effects of Metformin in Diabetic  
Nephropathy. *Journal of Cellular Physiology*, doi:10.1002/jcp.25598 (2016).
- 148 Wang, Y. et al. Vitamin D induces autophagy of pancreatic  $\beta$ -cells and enhances insulin secretion. *Molecular  
Medicine Reports*, doi:10.3892/mmr.2016.5531 (2016).
- 149 Jiang, L., Jin, Y., Wang, H., Jiang, Y. & Dong, J. Glucosamine protects nucleus pulposus cells and induces  
autophagy via the mTOR-dependent pathway. *Journal of Orthopaedic Research* **32**, 1532-1542,  
doi:10.1002/jor.22699 (2014).
- 150 Fortunato, F. Autophagy and cell death signaling following dietary sulforaphane act independently of each  
other and require oxidative stress in pancreatic cancer. *International Journal of Oncology*,  
doi:10.3892/ijo.2011.1025 (2011).
- 151 Chen, J.-J. et al. Inhibition of autophagy augments the anticancer activity of  $\alpha$ -mangostin in chronic myeloid  
leukemia cells. *Leukemia & lymphoma* **55**, 628-638, doi:10.3109/10428194.2013.802312 (2013).
- 152 Lu, J.-H. et al. Isorhynchophylline, a natural alkaloid, promotes the degradation of alpha-synuclein in neuronal  
cells via inducing autophagy. *Autophagy* **8**, 98-108, doi:10.4161/auto.8.1.18313 (2012).
- 153 Gu, J. et al. Rapamycin Inhibits Cardiac Hypertrophy by Promoting Autophagy via the MEK/ERK/Beclin-1  
Pathway. *Frontiers in Physiology* **7**, doi:10.3389/fphys.2016.00104 (2016).
- 154 Li, X., Lu, Y., Pan, T. & Fan, Z. Roles of autophagy in cetuximab-mediated cancer therapy against EGFR.  
*Autophagy* **6**, 1066-1077, doi:10.4161/auto.6.8.13366 (2010).

**Table 2** (Continued)

- 155 Gao, K. et al. Neuroprotective Effect of Simvastatin via Inducing the Autophagy on Spinal Cord Injury in the Rat Model. *BioMed Research International* **2015**, 1–9, doi:10.1155/2015/260161 (2015).
- 156 Duarte-Silva, S. et al. Lithium Chloride Therapy Fails to Improve Motor Function in a Transgenic Mouse Model of Machado-Joseph Disease. *The Cerebellum* **13**, 713–727, doi:10.1007/s12311-014-0589-9 (2014).
- 157 Sarkaki, A. et al. Metformin improves anxiety-like behaviors through AMPK-dependent regulation of autophagy following transient forebrain ischemia. *Metabolic Brain Disease* **30**, 1139–1150, doi:10.1007/s11011-015-9677-x (2015).
- 158 Tan, Q. et al. Effect of pantoprazole to enhance activity of docetaxel against human tumour xenografts by inhibiting autophagy. *British journal of cancer* **112**, 832–840, doi:10.1038/bjc.2015.17 (2015).
- 159 Rajawat, Y., Hilioti, Z. & Bossis, I. Retinoic Acid Induces Autophagosome Maturation Through Redistribution of the Cation-Independent Mannose-6-Phosphate Receptor. *Antioxidants & Redox Signaling* **14**, 2165–2177, doi:10.1089/ars.2010.3491 (2011).
- 160 Veldhoen, R. A. et al. The chemotherapeutic agent paclitaxel inhibits autophagy through two distinct mechanisms that regulate apoptosis. *Oncogene* **32**, 736–746, doi:10.1038/onc.2012.92 (2012).
- 161 Sudo, R., Sato, F., Azechi, T. & Wachi, H. 7-Ketocholesterol-induced lysosomal dysfunction exacerbates vascular smooth muscle cell calcification via oxidative stress. *Genes to Cells* **20**, 982–991, doi:10.1111/gtc.12301 (2015).
- 162 Nguyen, H. G. et al. Targeting autophagy overcomes Enzalutamide resistance in castration-resistant prostate cancer cells and improves therapeutic response in a xenograft model. *Oncogene* **33**, 4521–4530, doi:10.1038/onc.2014.25 (2014).

underlying the regulation of development to degeneration will certainly help to design new effective molecules against improper intracellular protein aggregation. However, in near future it is also important to plan alternative molecular therapeutic strategies, based on small molecules that enhance the overall capabilities of those supportable protecting pathways, which can prevent aging of neurons and their degeneration.

### Conflict of interest

The authors do not have any actual or potential conflicts of interests to disclose.

### Acknowledgement

This work was supported by Extra Mural Research Funding (Individual Centric): Science and Engineering Research Board (SERB)EMR/2016/000716, Department of Science and Technology, Government of India. AU and VJ were supported by a research fellowship from University Grants Commission, Council for Scientific and Industrial Research, Government of India. The authors would like to thank Mr. Bharat Pareek for his technical assistance and entire lab management during the manuscript formation. We apologize to several authors whose findings could not be involved because of space limit.

### References

- Alam, P., Chaturvedi, S.K., Siddiqi, M.K., Rajpoot, R.K., Ajmal, M.R., Zaman, M., Khan, R.H., 2016. Vitamin k3 inhibits protein aggregation: implication in the treatment of amyloid diseases. *Sci. Rep.* **6**, 26759.
- Alberts, B., Lewis, J.A., et al., 2002. The transport of molecules between the nucleus and the cytosol, Molecular Biology of the Cell. 4th edition Garland Science, New York.
- Amanullah, A., Upadhyay, A., Chhangani, D., Joshi, V., Mishra, R., Yamanaka, K., Mishra, A., 2017. Proteasomal dysfunction induced by diclofenac engenders apoptosis through mitochondrial pathway. *J. Cell. Biochem.* **118** (5), 1014–1027.
- Amirkia, V., Heinrich, M., 2014. Alkaloids as drug leads – a predictive structural and biodiversity-based analysis. *Phytochem. Lett.* **10**, xlvi–lii.
- Amm, I., Sommer, T., Wolf, D.H., 2014. Protein quality control and elimination of protein waste: the role of the ubiquitin-proteasome system. *Biochim. Biophys. Acta* **1843**, 182–196.
- Ankar, J., Sistonen, L., 2011. Regulation of HSF1 function in the heat stress response: implications in aging and disease. *Annu. Rev. Biochem.* **80**, 1089–1115.
- Anderson, D.E., Becktel, W.J., Dahlquist, F.W., 1990. pH-induced denaturation of proteins: a single salt bridge contributes 3–5 kcal/mol to the free energy of folding of T4 lysozyme. *Biochemistry* **29**, 2403–2408.
- Ano Bom, A.P., Rangel, L.P., Costa, D.C., de Oliveira, G.A., Sanches, D., Braga, C.A., Gava, L.M., Ramos, C.H., Cepeda, A.O., Stumbo, A.C., De Moura Gallo, C.V., Cordeiro, Y., Silva, J.L., 2012. Mutant p53 aggregates into prion-like amyloid oligomers and fibrils: implications for cancer. *J. Biol. Chem.* **287**, 28152–28162.
- Argyropoulos, A., Aligiannis, N., Trougakos, I.P., Skaltsounis, A.I., 2013. Natural compounds with anti-ageing activity. *Nat. Prod. Rep.* **30**, 1412–1437.
- Arias, E., Cuervo, A.M., 2011. Chaperone-mediated autophagy in protein quality control. *Curr. Opin. Cell Biol.* **23**, 184–189.
- Arndt, V., Rogon, C., Hohfeld, J., 2007. To be, or not to be?molecular chaperones in protein degradation. *Cell. Mol. Life Sci.* **64**, 2525–2541.
- Arndt, V., Dick, N., Tawo, R., Dreiseidler, M., Wenzel, D., Hesse, M., Furst, D.O., Saftig, P., Saint, R., Fleischmann, B.K., Hoch, M., Hohfeld, J., 2010. Chaperone-assisted selective autophagy is essential for muscle maintenance. *Curr. Biol.* **20**, 143–148.
- Auluck, P.K., Chan, H.E., Trojanowski, J.Q., Lee, V.M.-Y., Bonini, N.M., 2002. Chaperone suppression of  $\alpha$ -synuclein toxicity in a Drosophila model for Parkinson's disease. *Science* **295**, 865–868.
- Azcoitia, I., DonCarlos, L.L., Garcia-Segura, L.M., 2003. Are gonadal steroid hormones involved in disorders of brain aging? *Aging Cell* **2**, 31–37.
- Baker, B.M., Haynes, C.M., 2011. Mitochondrial protein quality control during biogenesis and aging. *Trends Biochem. Sci.* **36**, 254–261.
- Baker, M.J., Tatsuta, T., Langer, T., 2011. Quality control of mitochondrial proteostasis. *Cold Spring Harb. Perspect. Biol.* **3**.
- Balch, W.E., Morimoto, R.I., Dillin, A., Kelly, J.W., 2008. Adapting proteostasis for disease intervention. *Science* **319**, 916–919.
- Balchin, D., Hayer-Hartl, M., Hartl, F.U., 2016. In vivo aspects of protein folding and quality control. *Science* **353**, aac4354.
- Bao, Y., Wang, W., Zhou, Z., Sun, C., 2014. Benefits and risks of the hormetic effects of dietary isothiocyanates on cancer prevention. *PLoS One* **9**, e114764.
- Barabasi, A.L., Oltvai, Z.N., 2004. Network biology: understanding the cell's functional organization. *Nat. Rev. Genet.* **5**, 101–113.
- Barabasi, A.L., Gulbahce, N., Loscalzo, J., 2011. Network medicine: a network-based approach to human disease. *Nat. Rev. Genet.* **12**, 56–68.
- Barnes, A.I., Boone, J.M., Jacobson, J., Partridge, L., Chapman, T., 2006. No extension of lifespan by ablation of germ line in Drosophila. *Proc. Biol. Sci.* **273**, 939–947.
- Basha, M.R., Murali, M., Siddiqi, H.K., Ghosal, K., Siddiqi, O.K., Lashuel, H.A., Ge, Y.W., Lahiri, D.K., Zawia, N.H., 2005. Lead (Pb) exposure and its effect on APP proteolysis and Abeta aggregation. *FASEB J.* **19**, 2083–2084.
- Bays, N.W., Gardner, R.G., Seelig, L.P., Joazeiro, C.A., Hampton, R.Y., 2001. Hrd1p/Der3p is a membrane-anchored ubiquitin ligase required for ER-associated degradation. *Nat. Cell Biol.* **3**, 24–29.

- Bedford, L., Lowe, J., Dick, L.R., Mayer, R.J., Brownell, J.E., 2011. Ubiquitin-like protein conjugation and the ubiquitin-proteasome system as drug targets. *Nat. Rev. Drug Discov.* 10, 29–46.
- Ben Yehuda, A., Risheq, M., Novoplansky, O., Bersuker, K., Kopito, R.R., Goldberg, M., Brandeis, M., 2017. Ubiquitin accumulation on disease associated protein aggregates is correlated with nuclear ubiquitin depletion, histone deubiquitination and impaired DNA damage response. *PLoS One* 12, e0169054.
- Ben-Zvi, A., Miller, E.A., Morimoto, R.I., 2009. Collapse of proteostasis represents an early molecular event in *Caenorhabditis elegans* aging. *Proc. Natl. Acad. Sci. U.S. A.* 106, 14914–14919.
- Bence, N.F., Sampat, R.M., Kopito, R.R., 2001. Impairment of the ubiquitin-proteasome system by protein aggregation. *Science* 292, 1552–1555.
- Bennett, E.J., Bence, N.F., Jayakumar, R., Kopito, R.R., 2005. Global impairment of the ubiquitin-proteasome system by nuclear or cytoplasmic protein aggregates precedes inclusion body formation. *Mol. Cell* 17, 351–365.
- Bent, S., 2008. Herbal medicine in the United States: review of efficacy, safety, and regulation: grand rounds at University of California, San Francisco Medical Center. *J. Gen. Intern. Med.* 23, 854–859.
- Benvegnu, S., Mateo, M.I., Palomer, E., Jurado-Arjona, J., Dotti, C.G., 2017. Aging triggers cytoplasmic depletion and nuclear translocation of the E3 ligase mahogunin: a function for ubiquitin in neuronal survival. *Mol. Cell* 66, 358–372 (e357).
- Berggard, T., Linse, S., James, P., 2007. Methods for the detection and analysis of protein-protein interactions. *Proteomics* 7, 2833–2842.
- Berlingieri, M.T., Pallante, P., Guida, M., Nappi, C., Masciullo, V., Scambia, G., Ferraro, A., Leone, V., Sboner, A., Barbareschi, M., Ferro, A., Troncone, G., Fusco, A., 2007. UbcH10 expression may be a useful tool in the prognosis of ovarian carcinomas. *Oncogene* 26, 2136–2140.
- Berman, D.E., Ringe, D., Pettsko, G.A., Small, S.A., 2015. The use of pharmacological retromer chaperones in Alzheimer's disease and other endosomal-related disorders. *Neurotherapeutics* 12, 12–18.
- Bessis, M., Breton-Gorius, J., 1965. [Microtubules and fibrils in spread-out platelets]. *Nouv. Rev. Fr. Hematol.* 5, 657–662.
- Biederer, T., Volkwein, C., Sommer, T., 1997. Role of Cue1p in ubiquitination and degradation at the ER surface. *Science* 278, 1806–1809.
- Bilen, J., Bonini, N.M., 2005. Drosophila as a model for human neurodegenerative disease. *Annu. Rev. Genet.* 39, 153–171.
- Blackwell, M., 2011. The fungi: 1, 2, 3 . . . 5.1 million species? *Am. J. Bot.* 98, 426–438.
- Blasiak, J., Arabski, M., Krupa, R., Wozniak, K., Zadrożny, M., Kasznicki, J., Zurawska, M., Drzewoski, J., 2004. DNA damage and repair in type 2 diabetes mellitus. *Mutat. Res.* 554, 297–304.
- Bobadilla, J.L., Macek Jr., M., Fine, J.P., Farrell, P.M., 2002. Cystic fibrosis: a worldwide analysis of CFTR mutations?correlation with incidence data and application to screening. *Hum. Mutat.* 19, 575–606.
- Boban, M., Pantazopoulou, M., Schick, A., Ljungdahl, P.O., Foisner, R., 2014. A nuclear ubiquitin-proteasome pathway targets the inner nuclear membrane protein Asi2 for degradation. *J. Cell Sci.* 127, 3603–3613.
- Bolton, D.C., McKinley, M.P., Prusiner, S.B., 1982. Identification of a protein that purifies with the scrapie prion. *Science* 218, 1309–1311.
- Bommareddy, A., Hahm, E.R., Xiao, D., Powolny, A.A., Fisher, A.L., Jiang, Y., Singh, S.V., 2009. Atg5 regulates phenethyl isothiocyanate-induced autophagic and apoptotic cell death in human prostate cancer cells. *Cancer Res.* 69, 3704–3712.
- Bonini, N.M., Fortini, M.E., 2003. Human neurodegenerative disease modeling using Drosophila. *Annu. Rev. Neurosci.* 26, 627–656.
- Braakman, I., Bulleid, N.J., 2011. Protein folding and modification in the mammalian endoplasmic reticulum. *Annu. Rev. Biochem.* 80, 71–99.
- Brehme, M., Voisine, C., Rolland, T., Wachi, S., Soper, J.H., Zhu, Y., Orton, K., Villella, A., Garza, D., Vidal, M., 2014. A chaperome subnetwork safeguards proteostasis in aging and neurodegenerative disease. *Cell Rep.* 9, 1135–1150.
- Buckley, D.L., Crews, C.M., 2014. Small-Molecule control of intracellular protein levels through modulation of the ubiquitin proteasome system. *Angew. Chem. Int. Ed.* 53, 2312–2330.
- Bukau, B., Weissman, J., Horwich, A., 2006. Molecular chaperones and protein quality control. *Cell* 125, 443–451.
- Calamini, B., Silva, M.C., Madoux, F., Hutt, D.M., Khanna, S., Chalfant, M.A., Saldanha, S.A., Hodder, P., Tait, B.D., Garza, D., 2012. Small-molecule proteostasis regulators for protein conformational diseases. *Nat. Chem. Biol.* 8, 185–196.
- Caldecott, K.W., 2008. Single-strand break repair and genetic disease. *Nat Rev Genet.* 9, 619–631.
- Callahan, M.J., Lipinski, W.J., Bian, F., Durham, R.A., Pack, A., Walker, L.C., 2001. Augmented senile plaque load in aged female beta-amyloid precursor protein-transgenic mice. *Am. J. Pathol.* 158, 1173–1177.
- Candiano, G., Bruschi, M., Musante, L., Santucci, L., Ghiggeri, G.M., Carnemolla, B., Orechchia, P., Zardi, L., Righetti, P.G., 2004. Blue silver: a very sensitive colloidal Coomassie G-250 staining for proteome analysis. *Electrophoresis* 25, 1327–1333.
- Cao, L., Chen, R., Xu, J., Lin, Y., Wang, R., Chi, Z., 2009. Vitamin E inhibits activated chaperone-mediated autophagy in rats with status epilepticus. *Neuroscience* 161, 73–77.
- Cao, Y., Qu, J., Li, C., Yang, D., Hou, K., Zheng, H., Liu, Y., Qu, X., 2015. Celecoxib sensitizes gastric cancer to rapamycin via inhibition of the Cbl-b-regulated PI3K/Akt pathway. *Tumor Biol.* 36, 5607–5615.
- Carver, J.H., Carrano, A.V., MacGregor, J.T., 1983. Genetic effects of the flavonols quercetin, kaempferol, and galangin on Chinese hamster ovary cells in vitro. *Mutat. Res./Environ. Mutagen. Relat. Subj.* 113, 45–60.
- Cashikar, A.G., Duennwald, M., Lindquist, S.L., 2005. A chaperone pathway in protein disaggregation. *Hsp26 alters the nature of protein aggregates to facilitate reactivation by Hsp104*. *J. Biol. Chem.* 280, 23869–23875.
- Cetrullo, S., D'Adamo, S., Guidotti, S., Borzi, R.M., Flamigni, F., 2016. Hydroxytyrosol prevents chondrocyte death under oxidative stress by inducing autophagy through sirtuin 1-dependent and –independent mechanisms. *Biochimica et Biophysica Acta (BBA) – Gen. Subj.* 1860, 1181–1191.
- Chemler, S.R., 2009. Phenanthroindolizidines and phenanthroquinolizidines: promising alkaloids for anti-Cancer therapy. *Curr. Bioact. Compd.* 5, 2–19.
- Chen, L.C., Manjeshwar, S., Lu, Y., Moore, D., Ljung, B.M., Kuo, W.L., Dairkee, S.H., Wernick, M., Collins, C., Smith, H.S., 1998. The human homologue for the *Caenorhabditis elegans* cul-4 gene is amplified and overexpressed in primary breast cancers. *Cancer Res.* 58, 3677–3683.
- Chen, Q., Xie, W., Kuhn, D.J., Voorhees, P.M., Lopez-Girona, A., Mendy, D., Corral, L.G., Krenitsky, V.P., Xu, W., Moutouh-de Parseval, L., Webb, D.R., Mercurio, F., Nakayama, K.I., Nakayama, K., Orlowski, R.Z., 2008. Targeting the p27 E3 ligase SCF(Skp2) results in p27- and Skp2-mediated cell-cycle arrest and activation of autophagy. *Blood* 111, 4690–4699.
- Chen, J., Dexheimer Thomas, S., Ai, Y., Liang, Q., Villamil Mark, A., Inglese, J., Maloney David, J., Jadhav, A., Simeonov, A., Zhuang, Z., 2011. Selective and cell-active inhibitors of the USP1/UF1 deubiquitinase complex reverse cisplatin resistance in non-small cell lung cancer cells. *Chem. Biol.* 18, 1390–1400.
- Chen, Z., Ballar, P., Fu, Y., Luo, J., Du, S., Fang, S., 2014. The E3 ubiquitin ligase gp78 protects against ER stress in zebrafish liver. *J. Genet. Genomics* 41, 357–368.
- Chhangani, D., Nukina, N., Kurosawa, M., Amanullah, A., Joshi, V., Upadhyay, A., Mishra, A., 2014. Mahogunin ring finger 1 suppresses misfolded polyglutamine aggregation and cytotoxicity. *Biochim. Biophys. Acta* 1842, 1472–1484.
- Choi, K.S., 2012. Autophagy and cancer. *Exp. Mol. Med.* 44, 109–120.
- Christianson, J.C., Ye, Y., 2014. Cleaning up in the endoplasmic reticulum: ubiquitin in charge. *Nat. Struct. Mol. Biol.* 21, 325–335.
- Chu, Y.-L., Ho, C.-T., Chung, J.-G., Rajasekaran, R., Sheen, L.-Y., 2012. Allicin induces p53-Mediated autophagy in hep G2 human liver cancer cells. *J. Agric. Food Chem.* 60, 8363–8371.
- Chughtai, Z.S., Rassadi, R., Matusiewicz, N., Stochaj, U., 2001. Starvation promotes nuclear accumulation of the hsp70 Ssa4p in yeast cells. *J. Biol. Chem.* 276, 20261–20266.
- Ciechanover, A., Kwon, Y.T., 2015. Degradation of misfolded proteins in neurodegenerative diseases: therapeutic targets and strategies. *Exp. Mol. Med.* 47, e147.
- Ciechanover, A., 1994. The ubiquitin-proteasome proteolytic pathway. *Cell* 79, 13–21.
- Clausen, T., Kaiser, M., Huber, R., Ehrmann, M., 2011. HTRA proteases: regulated proteolysis in protein quality control. *Nat. Rev. Mol. Cell Biol.* 12, 152–162.
- Clement, J.A., Kitagaki, J., Yang, Y., Saucedo, C.J., O'Keefe, B.R., Weissman, A.M., McKee, T.C., McMahon, J.B., 2008. Discovery of new pyridoacridine alkaloids from *Lissoclinum cf. bodium* that inhibit the ubiquitin ligase activity of Hdm2 and stabilize p53. *Bioorgan. Med. Chem.* 16, 10022–10028.
- Cobb, C.A., Cole, M.P., 2015. Oxidative and nitrative stress in neurodegeneration. *Neurobiol. Dis.* 84, 4–21.
- Cohen, E., Bieschke, J., Percivalle, R.M., Kelly, J.W., Dillin, A., 2006. Opposing activities protect against age-onset proteotoxicity. *Science* 313, 1604–1610.
- Cohen, E., Paulsson, J.F., Blinder, P., Burstyn-Cohen, T., Du, D., Estepa, G., Adame, A., Pham, H.M., Holzenberger, M., Kelly, J.W., Masliah, E., Dillin, A., 2009. Reduced IGF-1 signaling delays age-associated proteotoxicity in mice. *Cell* 139, 1157–1169.
- Cook, C., Stetler, C., Petruccielli, L., 2012. Disruption of protein quality control in Parkinson's disease. *Cold Spring Harb Perspect Med* 2, a009423.
- Cox, J., Matic, I., Hilger, M., Nagaraj, N., Selbach, M., Olsen, J.V., Mann, M., 2009. A practical guide to the MaxQuant computational platform for SILAC-based quantitative proteomics. *Nat. Protoc.* 4, 698–705.
- Cragg, G.M., Newman, D.J., 2013. Natural products: a continuing source of novel drug leads. *Biochim. Biophys. Acta* 1830, 3670–3695.
- Crawford, L.J., Walker, B., Irvine, A.E., 2011. Proteasome inhibitors in cancer therapy. *J. Cell Commun. Signal.* 5, 101–110.
- Cuervo, A.M., Wong, E., 2014. Chaperone-mediated autophagy: roles in disease and aging. *Cell Res.* 24, 92–104.
- Cuervo, A.M., 2008. Autophagy and aging: keeping that old broom working. *Trends Genet.* 24, 604–612.
- Cuervo, A.M., 2010. Chaperone-mediated autophagy: selectivity pays off. *Trends Endocrinol. Metab.* 21, 142–150.
- Cuervo, A.M., 2011. Chaperone-mediated autophagy: dice's 'wild' idea about lysosomal selectivity. *Nat. Rev. Mol. Cell Biol.* 12, 535–541.
- Cui, Q., Tashiro, S., Onodera, S., Minami, M., Ikejima, T., 2007. Oridonin induced autophagy in human cervical carcinoma HeLa cells through Ras, JNK, and P38 regulation. *J. Pharmacol. Sci.* 105, 317–325.
- Cummings, C.J., Reinstein, E., Sun, Y., Antalffy, B., Jiang, Y., Ciechanover, A., Orr, H.T., Beaudet, A.L., Zoghbi, H.Y., 1999. Mutation of the E6-AP ubiquitin ligase reduces nuclear inclusion frequency while accelerating polyglutamine-induced pathology in SCA1 mice. *Neuron* 24, 879–892.
- D'Arcy, P., Linder, S., 2012. Proteasome deubiquitinases as novel targets for cancer therapy. *Int. J. Biochem. Cell Biol.* 44, 1729–1738.
- D'Arcy, P., Brnjic, S., Olofsson, M.H., Fryknas, M., Lindsten, K., De Cesare, M., Perego, P., Sadeghi, B., Hassan, M., Larsson, R., Linder, S., 2011. Inhibition of proteasome deubiquitinating activity as a new cancer therapy. *Nat. Med.* 17, 1636–1640.

- David, D.C., Olliainen, N., Trinidad, J.C., Cary, M.P., Burlingame, A.L., Kenyon, C., 2010. Widespread protein aggregation as an inherent part of aging in *C elegans*. *PLoS Biol.* 8, e1000450.
- De Chiara, G., Marocci, M.E., Civitelli, L., Argnani, R., Piacentini, R., Ripoli, C., Manservigi, R., Grassi, C., Garaci, E., Palamara, A.T., 2010. APP processing induced by herpes simplex virus type 1 (HSV-1) yields several APP fragments in human and rat neuronal cells. *PLoS One* 5, e13989.
- Demontis, F., Perrimon, N., 2010. FOXO/4E-BP signaling in Drosophila muscles regulates organism-wide proteostasis during aging. *Cell* 143, 813–825.
- Deng, H.X., Chen, W., Hong, S.T., Boycott, K.M., Gorrie, G.H., Siddique, N., Yang, Y., Fecto, F., Shi, Y., Zhai, H., Jiang, H., Hirano, M., Rampersaud, E., Jansen, G.H., Donkervoort, S., Bigio, E.H., Brooks, B.R., Ajroud, K., Sufit, R.L., Haines, J.L., Mugnaini, E., Pericak-Vance, M.A., Siddique, T., 2011. Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. *Nature* 477, 211–215.
- Denning, G.M., Anderson, M.P., Amara, J.F., Marshall, J., Smith, A.E., Welsh, M.J., 1992. Processing of mutant cystic fibrosis transmembrane conductance regulator is temperature-sensitive. *Nature* 358, 761–764.
- Deshais, R.J., 2014. Proteotoxic crisis, the ubiquitin-proteasome system, and cancer therapy. *BMC Biol.* 12, 94.
- Dias, D.A., Urban, S., Roessner, U., 2012. A historical overview of natural products in drug discovery. *Metabolites* 2, 303–336.
- Diaz-Villanueva, J.F., Diaz-Molina, R., Garcia-Gonzalez, V., 2015. Protein folding and mechanisms of proteostasis. *Int. J. Mol. Sci.* 16, 17193–17230.
- Dice, J.F., Chiang, H.L., Spencer, E.P., Backer, J.M., 1986. Regulation of catabolism of microinjected ribonuclease A: identification of residues 7–11 as the essential pentapeptide. *J. Biol. Chem.* 261, 6853–6859.
- Dickson, M., Gagnon, J.P., 2004. Key factors in the rising cost of new drug discovery and development. *Nat. Rev. Drug Discov.* 3, 417–429.
- Dikshit, P., Chatterjee, M., Goswami, A., Mishra, A., Jana, N.R., 2006. Aspirin induces apoptosis through the inhibition of proteasome function. *J. Biol. Chem.* 281, 29228–29235.
- Ding, Q., Bao, J., Zhao, W., Hu, Y., Lu, J., Chen, X., 2014. Natural autophagy regulators in cancer therapy: a review. *Phytochem. Rev.* 14, 137–154.
- Dobson, C.M., 1999. Protein misfolding, evolution and disease. *Trends Biochem. Sci.* 24, 329–332.
- Dou, Z., Xu, C., Donahue, G., Shimi, T., Pan, J.A., Zhu, J., Ivanov, A., Capell, B.C., Drake, A. M., Shah, P.P., Catanzaro, J.M., Ricketts, M.D., Lamark, T., Adam, S.A., Marmorstein, R., Zong, W.X., Johansen, T., Goldman, R.D., Adams, P.D., Berger, S. L., 2015. Autophagy mediates degradation of nuclear lamina. *Nature* 527, 105–109.
- Doudican, N.A., Wen, S.Y., Mazumder, A., Orlow, S.J., 2012. Sulforaphane synergistically enhances the cytotoxicity of arsenic trioxide in multiple myeloma cells via stress-mediated pathways. *Oncol. Rep.* 28, 1851–1858.
- Drummond, D.A., Wilke, C.O., 2009. The evolutionary consequences of erroneous protein synthesis. *Nat. Rev. Genet.* 10, 715–724.
- Dufour, V., Stahl, M., Baysses, C., 2015. The antibacterial properties of isothiocyanates. *Microbiology* 161, 229–243.
- Dusek, P., Roos, P.M., Litwin, T., Schneider, S.A., Flaten, T.P., Aaseth, J., 2015. The neurotoxicity of iron, copper and manganese in Parkinson's and Wilson's diseases. *J. Trace Elem. Med. Biol.* 31, 193–203.
- Duttler, S., Pechmann, S., Frydman, J., 2013. Principles of cotranslational ubiquitination and quality control at the ribosome. *Mol. Cell* 50, 379–393.
- Eddins, M.J., Marblestone, J.G., Suresh Kumar, K.G., Leach, C.A., Sterner, D.E., Mattern, M.R., Nicholson, B., 2011. Targeting the ubiquitin E3 ligase MuRF1 to inhibit muscle atrophy. *Cell Biochem. Biophys.* 60, 113–118.
- Edelmann, M.J., Nicholson, B., Kessler, B.M., 2011. Pharmacological targets in the ubiquitin system offer new ways of treating cancer, neurodegenerative disorders and infectious diseases. *Expert Rev. Mol. Med.* 13, e35.
- Eden, E., Geva-Zatorsky, N., Issaeva, I., Cohen, A., Dekel, E., Danon, T., Cohen, L., Mayo, A., Alon, U., 2011. Proteome half-life dynamics in living human cells. *Science* 331, 764–768.
- Eldridge, A.G., O'Brien, T., 2010. Therapeutic strategies within the ubiquitin proteasome system. *Cell Death Differ.* 17, 4–13.
- Ellgaard, L., Helenius, A., 2003. Quality control in the endoplasmic reticulum. *Nat. Rev. Mol. Cell Biol.* 4, 181–191.
- Ellgaard, L., Molinari, M., Helenius, A., 1999. Setting the standards: quality control in the secretory pathway. *Science* 286, 1882–1888.
- Ellis, J., 1987. Proteins as molecular chaperones. *Nature* 328, 378–379.
- Endo, H., Yano, M., Okumura, Y., Kido, H., 2014. Ibuprofen enhances the anticancer activity of cisplatin in lung cancer cells by inhibiting the heat shock protein 70. *Cell. Death. Dis.* 5, e1027.
- Enot, D.P., Niso-Santano, M., Durand, S., Chery, A., Pietrocola, F., Vacchelli, E., Madeo, F., Galluzzi, L., Kroemer, G., 2015. Metabolomic analyses reveal that anti-aging metabolites are depleted by palmitate but increased by oleate in vivo. *ABBV Cell Cycle* 14, 2399–2407.
- Eremenko, E., Ben-Zvi, A., Morozova-Roche, L.A., Raveh, D., 2013. Aggregation of human S100A8 and S100A9 amyloidogenic proteins perturbs proteostasis in a yeast model. *PLoS One* 8, e58218.
- Escusa-Toret, S., Vonk, W.I., Frydman, J., 2013. Spatial sequestration of misfolded proteins by a dynamic chaperone pathway enhances cellular fitness during stress. *Nat. Cell Biol.* 15, 1231–1243.
- Fang, S., Ferrone, M., Yang, C., Jensen, J.P., Tiwari, S., Weissman, A.M., 2001. The tumor autocrine motility factor receptor, gp78, is a ubiquitin protein ligase implicated in degradation from the endoplasmic reticulum. *Proc. Natl. Acad. Sci. U. S. A.* 98, 14422–14427.
- Farre, J.C., Subramani, S., 2004. Peroxisome turnover by micropexophagy: an autophagy-related process. *Trends Cell Biol.* 14, 515–523.
- Feder, M.E., Hofmann, G.E., 1999. Heat-shock proteins, molecular chaperones, and the stress response: evolutionary and ecological physiology. *Annu. Rev. Physiol.* 61, 243–282.
- Feng, Y., He, D., Yao, Z., Klionsky, D.J., 2014. The machinery of macroautophagy. *Cell Res.* 24, 24–41.
- Feng, Y., Yao, Z., Klionsky, D.J., 2015. How to control self-digestion: transcriptional, post-transcriptional, and post-translational regulation of autophagy. *Trends Cell Biol.* 25, 354–363.
- Ferreira, J.C., Boer, B.N., Grinberg, M., Brum, P.C., Mochly-Rosen, D., 2012. Protein quality control disruption by PKC $\beta$ II in heart failure; rescue by the selective PKC $\beta$ II inhibitor, betalIV-3. *PLoS One* 7, e33175.
- Ferrington, D.A., Husom, A.D., Thompson, L.V., 2005. Altered proteasome structure, function, and oxidation in aged muscle. *FASEB J.* 19, 644–646.
- Fields, S., Song, O., 1989. A novel genetic system to detect protein-protein interactions. *Nature* 340, 245–246.
- Fimognari, C., Turrini, E., Ferruzzi, L., Lenzi, M., Hrelia, P., 2012. Natural isothiocyanates: genotoxic potential versus chemoprevention. *Mutat. Res.* 750, 107–131.
- Fink, A.L., 1998. Protein aggregation: folding aggregates, inclusion bodies and amyloid. *Fold. Des.* 3, R9–23.
- Finley, D., 2009. Recognition and processing of ubiquitin-protein conjugates by the proteasome. *Annu. Rev. Biochem.* 78, 477–513.
- Flatt, T., Min, K.J., D'Alterio, C., Villa-Cuesta, E., Cumbers, J., Lehmann, R., Jones, D.L., Tata, M., 2008. Drosophila germ-line modulation of insulin signaling and lifespan. *Proc. Natl. Acad. Sci. U. S. A.* 105, 6368–6373.
- Fleming, A., Noda, T., Yoshimori, T., Rubinsztein, D.C., 2011. Chemical modulators of autophagy as biological probes and potential therapeutics. *Nat. Chem. Biol.* 7, 9–17.
- Floreac, A.M., Busselberg, D., 2011. Cisplatin as an anti-tumor drug: cellular mechanisms of activity, drug resistance and induced side effects. *Cancers (Basel)* 3, 1351–1371.
- Frankel, L.B., Lubas, M., Lund, A.H., 2016. Emerging connections between RNA and autophagy. *Autophagy* 1–21.
- Fredriksson, A., Johansson Krogh, E., Hernebring, M., Pettersson, E., Javadi, A., Almstedt, A., Nystrom, T., 2012. Effects of aging and reproduction on protein quality control in soma and gametes of *Drosophila melanogaster*. *Aging Cell* 11, 634–643.
- Freeman, B.C., Morimoto, R.I., 1996. The human cytosolic molecular chaperones hsp90, hsp70 (hsc70) and hdj-1 have distinct roles in recognition of a non-native protein and protein refolding. *EMBO J.* 15, 2969–2979.
- Frydman, J., 2001. Folding of newly translated proteins in vivo: the role of molecular chaperones. *Annu. Rev. Biochem.* 70, 603–647.
- Fujiwara, Y., Furuta, A., Kikuchi, H., Aizawa, S., Hatanoaka, Y., Konya, C., Uchida, K., Yoshimura, A., Tamai, Y., Wada, K., Kubata, T., 2013. Discovery of a novel type of autophagy targeting RNA. *Autophagy* 9, 403–409.
- Fukuda, I., Ito, A., Hirai, G., Nishimura, S., Kawasaki, H., Saitoh, H., Kimura K.-i., Sodeoka, M., Yoshida, M., 2009. Ginkgolic acid inhibits protein SUMOylation by blocking formation of the E1-SUMO intermediate. *Chem. Biol.* 16, 133–140.
- Gabai, V.L., Zamalava, I.V., Mosin, A.F., Makarova, Y.M., Mosina, V.A., Budagova, K.R., Malutina, Y.V., Kabakov, A.E., 1995. Resistance of Ehrlich tumor cells to apoptosis can be due to accumulation of heat shock proteins. *FEBS Lett.* 375, 21–26.
- Gallagher, P.S., Oeser, M.L., Abraham, A.C., Kaganovich, D., Gardner, R.G., 2014. Cellular maintenance of nuclear protein homeostasis. *Cell. Mol. Life Sci.* 71, 1865–1879.
- Gamerding, M., Hajieva, P., Kaya, A.M., Wolfrum, U., Hartl, F.U., Behl, C., 2009. Protein quality control during aging involves recruitment of the macroautophagy pathway by BAG3. *EMBO J.* 28, 889–901.
- Gardner, R.C., Nelson, Z.W., Gottschling, D.E., 2005. Degradation-mediated protein quality control in the nucleus. *Cell* 120, 803–815.
- Garrido, A., Aldecoa, I., Gelpi, E., Tolosa, E., 2017. Aggregation of alpha-synuclein in the gonadal tissue of 2 patients with parkinson disease. *JAMA Neurol.* 74, 606–607.
- Gershenson, J., Dudareva, N., 2007. The function of terpene natural products in the natural world. *Nat. Chem. Biol.* 3, 408–414.
- Gething, M.J., Sambrook, J., 1992. Protein folding in the cell. *Nature* 355, 33–45.
- Gidalevitz, T., Kikis, E.A., Morimoto, R.I., 2010. A cellular perspective on conformational disease: the role of genetic background and proteostasis networks. *Curr. Opin. Struct. Biol.* 20, 23–32.
- Gidalevitz, T., Prahlad, V., Morimoto, R.I., 2011. The stress of protein misfolding: from single cells to multicellular organisms. *Cold Spring Harb. Perspect. Biol.* 3.
- Glick, D., Barth, S., Macleod, K.F., 2010. Autophagy: cellular and molecular mechanisms. *J. Pathol.* 221, 3–12.
- Golan, M., Schreiber, G., Avissar, S., 2010. Antidepressants increase beta-arrestin 2 ubiquitylation and degradation by the proteasomal pathway in C6 rat glioma cells. *J. Pharmacol. Exp. Ther.* 332, 970–976.
- Goldberg, A.L., 2003. Protein degradation and protection against misfolded or damaged proteins. *Nature* 426, 895–899.
- Gregersen, N., Bross, P., Vang, S., Christensen, J.H., 2006. Protein misfolding and human disease. *Annu. Rev. Genomics Hum. Genet.* 7, 103–124.
- Gu, J., Hu, W., Song, Z.P., Chen, Y.G., Zhang, D.D., Wang, C.Q., 2016. Rapamycin inhibits cardiac hypertrophy by promoting autophagy via the MEK/ERK/Beclin-1 pathway. *Front. Physiol.* 7, 104.

- Guerrero, C.J., Weiberth, K.F., Brodsky, J.L., 2013. Hsp70 targets a cytoplasmic quality control substrate to the San1p ubiquitin ligase. *J. Biol. Chem.* 288, 18506–18520.
- Guidetti, A., Carlo-Stella, C., Locatelli, S.I., Malorni, W., Pierdominici, M., Barbati, C., Mortarini, R., Devizzi, L., Matteucci, P., Marchiano, A., Lanocita, R., Farina, L., Dodero, A., Tarella, C., Di Nicola, M., Corradini, P., Anichini, A., Gianni, A.M., 2012. Phase II study of sorafenib in patients with relapsed or refractory lymphoma. *Br. J. Haematol.* 158, 108–119.
- Gumeni, S., Trougakos, I.P., 2016. Cross talk of proteostasis and metastasis in cellular homeodynamics, ageing, and disease. *Oxid. Med. Cell. Longevity* 2016.
- Gygi, S.P., Rist, B., Aebersold, R., 2000. Measuring gene expression by quantitative proteome analysis. *Curr. Opin. Biotechnol.* 11, 396–401.
- Hakem, R., 2008. DNA-damage repair; the good, the bad, and the ugly. *EMBO J.* 27, 589–605.
- Hamon, M.P., Bulteau, A.L., Friguet, B., 2015. Mitochondrial proteases and protein quality control in ageing and longevity. *Ageing Res. Rev.* 23, 56–66.
- Han, J.D., 2008. Understanding biological functions through molecular networks. *Cell Res.* 18, 224–237.
- Hao, X., Yao, A., Gong, J., Zhu, W., Li, N., Li, J., 2011. Berberine ameliorates pro-inflammatory cytokine-induced endoplasmic reticulum stress in human intestinal epithelial cells in vitro. *Inflammation* 35, 841–849.
- Harper, J.W., Bennett, E.J., 2016. Proteome complexity and the forces that drive proteome imbalance. *Nature* 537, 328–338.
- Hartl, F.U., Hayer-Hartl, M., 2002. Molecular chaperones in the cytosol: from nascent chain to folded protein. *Science* 295, 1852–1858.
- Hartl, F.U., Hayer-Hartl, M., 2009. Converging concepts of protein folding in vitro and in vivo. *Nat. Struct. Mol. Biol.* 16, 574–581.
- Hartl, F.U., Bracher, A., Hayer-Hartl, M., 2011. Molecular chaperones in protein folding and proteostasis. *Nature* 475, 324–332.
- Hartl, F.U., 2016. Cellular homeostasis and aging. *Annu. Rev. Biochem.* 85, 1–4.
- Harvey, A.L., 2008. Natural products in drug discovery. *Drug Discov. Today* 13, 894–901.
- Haynes, C.M., Ron, D., 2010. The mitochondrial UPR – protecting organelle protein homeostasis. *J. Cell Sci.* 123, 3849–3855.
- He, C., Klionsky, D.J., 2009. Regulation mechanisms and signaling pathways of autophagy. *Annu. Rev. Genet.* 43, 67–93.
- He, X., Zhang, J., 2006. Why do hubs tend to be essential in protein networks? *PLoS Genet.* 2, e88.
- He, L.Q., Lu, J.H., Yue, Z.Y., 2013. Autophagy in ageing and ageing-associated diseases. *Acta Pharmacol. Sin.* 34, 605–611.
- Heinrich, J.C., Donakonda, S., Haupt, V.J., Lennig, P., Zhang, Y., Schroeder, M., 2016. New HSP27 inhibitors efficiently suppress drug resistance development in cancer cells. *Oncotarget* 7, 68156–68169.
- Henriques, B.J., Rodrigues, J.V., Olsen, R.K., Bross, P., Gomes, C.M., 2008. Role of flavinylation in a mild variant of multiple acyl-CoA dehydrogenation deficiency: a molecular rationale for the effects of riboflavin supplementation. *J. Biol. Chem.* 284, 4222–4229.
- Hershko, A., Ciechanover, A., 1982. Mechanisms of intracellular protein breakdown. *Annu. Rev. Biochem.* 51, 335–364.
- Hershko, A., Ciechanover, A., 1992. The ubiquitin system for protein degradation. *Annu. Rev. Biochem.* 61, 761–807.
- Hetz, C., Mollereau, B., 2014. Disturbance of endoplasmic reticulum proteostasis in neurodegenerative diseases. *Nat. Rev. Neurosci.* 15, 233–249.
- Hetz, C., Chevet, E., Harding, H.P., 2013. Targeting the unfolded protein response in disease. *Nat. Rev. Drug Discov.* 12, 703–719.
- Hidemitsu, T., Bradner, J.E., Wong, J., Chauhan, D., Richardson, P., Schreiber, S.L., Anderson, K.C., 2005. Small-molecule inhibition of proteasome and aggresome function induces synergistic antitumor activity in multiple myeloma. *Proc. Natl. Acad. Sci. U. S. A.* 102, 8567–8572.
- Higgins, R., Gendron, J.M., Rising, L., Mak, R., Webb, K., Kaiser, S.E., Zuzow, N., Riviere, P., Yang, B., Fenech, E., Tang, X., Lindsay, S.A., Christianson, J.C., Hampton, R.Y., Wasserman, S.A., Bennett, E.J., 2015. The unfolded protein response triggers site-Specific regulatory ubiquitylation of 40S ribosomal proteins. *Mol. Cell* 59, 35–49.
- Hipp, M.S., Park, S.H., Hartl, F.U., 2014. Proteostasis impairment in protein-misfolding and –aggregation diseases. *Trends Cell Biol.* 24, 506–514.
- Hirata-Fukae, C., Li, H.F., Hoe, H.S., Gray, A.J., Minami, S.S., Hamada, K., Niikura, T., Hua, F., Tsukagoshi-Nagai, H., Horikoshi-Sakuraba, Y., Mughal, M., Rebeck, G.W., LaFerla, F.M., Mattson, M.P., Iwata, N., Saido, T.C., Klein, W.L., Duff, K.E., Aisen, P.S., Matsuo, Y., 2008. Females exhibit more extensive amyloid, but not tau, pathology in an Alzheimer transgenic model. *Brain Res.* 1216, 92–103.
- Hirsch, C., Gauss, R., Horn, S.C., Neuber, O., Sommer, T., 2009. The ubiquitylation machinery of the endoplasmic reticulum. *Nature* 458, 453–460.
- Hochstrasser, M., 1996. Ubiquitin-dependent protein degradation. *Annu. Rev. Genet.* 30, 405–439.
- Holmberg, M., Nollen, E.A., 2013. Analyzing modifiers of protein aggregation in *C. elegans* by native agarose gel electrophoresis. *Methods Mol. Biol.* 1017, 193–199.
- Hough, R., Pratt, G., Rechsteiner, M., 1987. Purification of two high molecular weight proteases from rabbit reticulocyte lysate. *J. Biol. Chem.* 262, 8303–8313.
- Hoyer-Hansen, M., Nordbrandt, S.P., Jaattela, M., 2010. Autophagy as a basis for the health-promoting effects of vitamin D. *Trends Mol. Med.* 16, 295–302.
- Hsin, H., Kenyon, C., 1999. Signals from the reproductive system regulate the lifespan of *C. elegans*. *Nature* 399, 362–366.
- Huang, X., Dixit, V.M., 2016. Drugging the undruggables: exploring the ubiquitin system for drug development. *Cell Res.* 26, 484–498.
- Huang, L., Ho, P., Chen, C.H., 2007. Activation and inhibition of the proteasome by betulinic acid and its derivatives. *FEBS Lett.* 581, 4955–4959.
- Ibba, M., Soll, D., 1999. Quality control mechanisms during translation. *Science* 286, 1893–1897.
- Inada, T., 2016. The Ribosome as a Platform for mRNA and Nascent Polypeptide Quality Control. *Trends Biochem. Sci.*
- Inagi, R., Ishimoto, Y., Nangaku, M., 2014. Proteostasis in endoplasmic reticulum—new mechanisms in kidney disease. *Nat. Rev. Nephrol.* 10, 369–378.
- Iorio, F., Bosotti, R., Scacheri, E., Belcastro, V., Mithbaokar, P., Ferriero, R., Murino, L., Tagliaferri, R., Brunetti-Pierri, N., Isacchi, A., di Bernardo, D., 2010. Discovery of drug mode of action and drug repositioning from transcriptional responses. *Proc. Natl. Acad. Sci. U. S. A.* 107, 14621–14626.
- Issaeva, N., Bozko, P., Enge, M., Protopopova, M., Verhoef, L.G., Masucci, M., Pramanik, A., Selivanova, G., 2004. Small molecule RITA binds to p53, blocks p53-HDM-2 interaction and activates p53 function in tumors. *Nat. Med.* 10, 1321–1328.
- Ito, T., Ando, H., Suzuki, T., Ogura, T., Hotta, K., Imamura, Y., Yamaguchi, Y., Handa, H., 2010. Identification of a primary target of thalidomide teratogenicity. *Science* 327, 1345–1350.
- Izumi, T., Yokota-Hashimoto, H., Zhao, S., Wang, J., Halban, P.A., Takeuchi, T., 2003. Dominant negative pathogenesis by mutant proinsulin in the Akita diabetic mouse. *Diabetes* 52, 409–416.
- Jackson, M.P., Hewitt, E.W., 2016. Cellular proteostasis: degradation of misfolded proteins by lysosomes. *Essays Biochem.* 60, 173–180.
- Jagannathan, S., Abdel-Malek, M.A.Y., Malek, E., Vad, N., Latif, T., Anderson, K.C., Driscoll, J.J., 2015. Pharmacologic screens reveal metformin that suppresses GRP78-dependent autophagy to enhance the anti-myeloma effect of bortezomib. *Leukemia* 29, 2184–2191.
- Jana, N.R., Dikshit, P., Goswami, A., Nukina, N., 2004. Inhibition of proteasomal function by curcumin induces apoptosis through mitochondrial pathway. *J. Biol. Chem.* 279, 11680–11685.
- Jang, H., Boltz, D., Sturm-Ramirez, K., Shepherd, K.R., Jiao, Y., Webster, R., Smeyne, R.J., 2009. Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. *Proc. Natl. Acad. Sci. U. S. A.* 106, 14063–14068.
- Janus, C., Welzl, H., 2010. Mouse models of neurodegenerative diseases: criteria and general methodology. *Methods Mol. Biol.* 602, 323–345.
- Je Ma, C., Jung, W.J., Lee, K.Y., Kim, Y.C., Sung, S.H., 2009. Calpain inhibitory flavonoids isolated from *Orostachys japonicus*. *J. Enzyme Inhib. Med. Chem.* 24, 676–679.
- Jeppesen, D.K., Bohr, V.A., Stevnsner, T., 2011. DNA repair deficiency in neurodegeneration. *Prog. Neurobiol.* 94, 166–200.
- Ji, Y.-L., Wang, Z., Wang, H., Zhang, C., Zhang, Y., Zhao, M., Chen, Y.-H., Meng, X.-H., Xu, D.-X., 2012. Ascorbic acid protects against cadmium-induced endoplasmic reticulum stress and germ cell apoptosis in testes. *Reprod. Toxicol.* 34, 357–363.
- Jiang, Y.H., Armstrong, D., Albrecht, U., Atkins, C.M., Noebels, J.L., Eichele, G., Sweat, J.D., Beaudet, A.L., 1998. Mutation of the Angelman ubiquitin ligase in mice causes increased cytoplasmic p53 and deficits of contextual learning and long-term potentiation. *Neuron* 21, 799–811.
- Jiang, H., Sun, J., Xu, Q., Liu, Y., Wei, J., Young, C.Y., Yuan, H., Lou, H., 2013. Marchantin M: a novel inhibitor of proteasome induces autophagic cell death in prostate cancer cells. *Cell. Death. Dis.* 4, e761.
- Jiang, H.Q., Ren, M., Jiang, H.Z., Wang, J., Zhang, J., Yin, X., Wang, S.Y., Qi, Y., Wang, X., D., Feng, H.L., 2014. Guanabenz delays the onset of disease symptoms, extends lifespan, improves motor performance and attenuates motor neuron loss in the SOD1 G93A mouse model of amyotrophic lateral sclerosis. *Neuroscience* 277, 132–138.
- Jinwal, U.K., Miyata, Y., Koren, J., Jones, J.R., Trotter, J.H., Chang, L., O'Leary, J., Morgan, D., Lee, D.C., Shultz, C.L., Rousaki, A., Weeber, E.J., Zuiderweg, E.R.P., Gestwicki, J.E., Dickey, C.A., 2009. Chemical manipulation of hsp70 ATPase activity regulates tau stability. *J. Neurosci.* 29, 12079–12088.
- Jones, R.D., Gardner, R.G., 2016. Protein quality control in the nucleus. *Curr. Opin. Cell Biol.* 40, 81–89.
- Joshi, V., Amanullah, A., Upadhyay, A., Mishra, R., Kumar, A., Mishra, A., 2016. A decade of boon or burden: what has the CHIP ever done for cellular protein quality control mechanism implicated in neurodegeneration and aging? *Front. Mol. Neurosci.* 9, 93.
- Jovaisaitis, V., Auwerx, J., 2015. The mitochondrial unfolded protein response—synchronizing genomes. *Curr. Opin. Cell Biol.* 33, 74–81.
- Juarez, E., Carranza, C., Sanchez, G., Gonzalez, M., Chavez, J., Saravia, C., Torres, M., Sada, E., 2016. Loperamide restricts intracellular growth of mycobacterium tuberculosis in lung macrophages. *Am. J. Respir. Cell Mol. Biol.* 55, 837–847.
- Jucker, M., 2010. The benefits and limitations of animal models for translational research in neurodegenerative diseases. *Nat. Med.* 16, 1210–1214.
- Kabashi, E., Durham, H.D., 2006. Failure of protein quality control in amyotrophic lateral sclerosis. *Biochim. Biophys. Acta* 1762, 1038–1050.
- Kaeberlein, M., Burtner, C.R., Kennedy, B.K., 2007. Recent developments in yeast aging. *PLoS Genet.* 3, e84.
- Kaganovich, D., Kopito, R., Frydman, J., 2008. Misfolded proteins partition between two distinct quality control compartments. *Nature* 454, 1088–1095.
- Kanagaraj, V.V., Panneerselvam, L., Govindarajan, V., Ameeranjan, J., Perumal, E., 2015. Caffeic acid, a phyto polyphenol mitigates fluoride induced hepatotoxicity in rats: A possible mechanism. *BioFactors* 41, 90–100.
- Kane, R.C., Bross, P.F., Farrell, A.T., Pazdur, R., 2003. Velcade: U.S. FDA approval for the treatment of multiple myeloma progressing on prior therapy. *Oncologist* 8, 508–513.

- Kaushik, S., Cuervo, A.M., 2012a. Chaperone-mediated autophagy: a unique way to enter the lysosome world. *Trends Cell Biol.* 22, 407–417.
- Kaushik, S., Cuervo, A.M., 2012b. Chaperones in autophagy. *Pharmacol. Res.* 66, 484–493.
- Kaushik, S., Cuervo, A.M., 2015. Proteostasis and aging. *Nat. Med.* 21, 1406–1415.
- Kettern, N., Dreiseidler, M., Tawo, R., Hohfeld, J., 2010. Chaperone-assisted degradation: multiple paths to destruction. *Biol. Chem.* 391, 481–489.
- Khodakarami, A., Saez, I., Mels, J., Vilchez, D., 2015. Medication of organismal aging and somatic proteostasis by the germline. *Front Mol Biosci* 2, 3.
- Khurana, V., Lindquist, S., 2010. Modelling neurodegeneration in *Saccharomyces cerevisiae*: why cook with baker's yeast? *Nat. Rev. Neurosci.* 11, 436–449.
- Kikis, E.A., Gidalevitz, T., Morimoto, R.I., 2010. Protein homeostasis in models of aging and age-related conformational disease. *Adv. Exp. Med. Biol.* 694, 138–159.
- Kikis, E.A., 2016. The struggle by *Caenorhabditis elegans* to maintain proteostasis during aging and disease. *Biology Direct* 11, 58.
- Kim, I., Xu, W., Reed, J.C., 2008. Cell death and endoplasmic reticulum stress: disease relevance and therapeutic opportunities. *Nat. Rev. Drug Discov.* 7, 1013–1030.
- Kim, Y.E., Hipp, M.S., Bracher, A., Hayer-Hartl, M., Hartl, F.U., 2013. Molecular chaperone functions in protein folding and proteostasis. *Annu. Rev. Biochem.* 82, 323–355.
- Kimmyey, J.M., Stallings, C.L., 2016. Bacterial pathogens versus autophagy: implications for therapeutic interventions. *Trends Mol. Med.* 22, 1060–1076.
- Kirkwood, T.B.L., Austad, S.N., 2000. Why do we age? *Nature* 408, 233–238.
- Kirstein-Miles, J., Morimoto, R.I., 2010. *Caenorhabditis elegans* as a model system to study intercompartmental proteostasis: interrelation of mitochondrial function, longevity, and neurodegenerative diseases. *Dev. Dyn.* 239, 1529–1538.
- Kissova, I., Salin, B., Schaeffer, J., Bhatia, S., Manon, S., Camougrand, N., 2007. Selective and non-selective autophagic degradation of mitochondria in yeast. *Autophagy* 3, 329–336.
- Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., Yokochi, M., Mizuno, Y., Shimizu, N., 1998. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 392, 605–608.
- Klausner, R.D., Sitia, R., 1990. Protein degradation in the endoplasmic reticulum. *Cell* 62, 611–614.
- Klionsky, D.J., 2007. Autophagy: from phenomenology to molecular understanding in less than a decade. *Nat. Rev. Mol. Cell Biol.* 8, 931–937.
- Koegl, M., Hoppe, T., Schlenker, S., Ulrich, H.D., Mayer, T.U., Jentsch, S., 1999. A novel ubiquitination factor, E4, is involved in multiubiquitin chain assembly. *Cell* 96, 635–644.
- Komatsu, M., Waguri, S., Chiba, T., Murata, S., Iwata, J., Tanida, I., Ueno, T., Koike, M., Uchiyama, Y., Kominami, E., Tanaka, K., 2006. Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature* 441, 880–884.
- Kostova, Z., Tsai, Y.C., Weissman, A.M., 2007. Ubiquitin ligases, critical mediators of endoplasmic reticulum-associated degradation. *Semin. Cell Dev. Biol.* 18, 770–779.
- Koumenis, C., Naczki, C., Koritzinsky, M., Rastani, S., Diehl, A., Sonenberg, N., Koromilas, A., Wouters, B.G., 2002. Regulation of protein synthesis by hypoxia via activation of the endoplasmic reticulum kinase PERK and phosphorylation of the translation initiation factor eIF2alpha. *Mol. Cell. Biol.* 22, 7405–7416.
- Kozak, M., 1989. The scanning model for translation: an update. *J. Cell Biol.* 108, 229–241.
- Kraft, C., Reggiori, F., Peter, M., 2009. Selective types of autophagy in yeast. *Biochim. Biophys. Acta* 1793, 1404–1412.
- Kraus, M., Malenke, E., Gogel, J., Muller, H., Ruckrich, T., Overkleft, H., Ovaa, H., Koscielnik, E., Hartmann, J.T., Driessens, C., 2008. Ritonavir induces endoplasmic reticulum stress and sensitizes sarcoma cells toward bortezomib-induced apoptosis. *Mol. Cancer Ther.* 7, 1940–1948.
- Kreft, S.G., Wang, L., Hochstrasser, M., 2006. Membrane topology of the yeast endoplasmic reticulum-localized ubiquitin ligase Doa10 and comparison with its human ortholog TEB4 (MARCH-VI). *J. Biol. Chem.* 281, 4646–4653.
- Krick, R., Muhe, Y., Prick, T., Bredschneider, M., Bremer, S., Wenzel, D., Eskelinen, E.L., Thumm, M., 2009. Piecemeal microautophagy of the nucleus: genetic and morphological traits. *Autophagy* 5, 270–272.
- Kroemer, G., Marino, G., Levine, B., 2010. Autophagy and the integrated stress response. *Mol. Cell* 40, 280–293.
- Kryndushkin, D., Ihrke, G., Piermariti, T.C., Shewmaker, F., 2012. A yeast model of optineurin proteinopathy reveals a unique aggregation pattern associated with cellular toxicity. *Mol. Microbiol.* 86, 1531–1547.
- Kumatori, A., Tanaka, K., Inamura, N., Sone, S., Ogura, T., Matsumoto, T., Tachikawa, T., Shin, S., Ichihara, A., 1990. Abnormally high expression of proteasomes in human leukemic cells. *Proc. Natl. Acad. Sci. U. S. A.* 87, 7071–7075.
- Kunz, J.B., Schwarz, H., Mayer, A., 2004. Determination of four sequential stages during microautophagy in vitro. *J. Biol. Chem.* 279, 9987–9996.
- Kwak, M.K., Cho, J.M., Huang, B., Shin, S., Kensler, T.W., 2007. Role of increased expression of the proteasome in the protective effects of sulforaphane against hydrogen peroxide-mediated cytotoxicity in murine neuroblastoma cells. *Free Radic. Biol. Med.* 43, 809–817.
- Labbadia, J., Morimoto, R.I., 2014. Proteostasis and Longevity: When Does Aging Really Begin? *F1000Prime Reports* 6, 7..
- Labbadia, J., Morimoto, R.I., 2015. The biology of proteostasis in aging and disease. *Annu. Rev. Biochem.* 84, 435–464.
- Langer, T., Käser, M., Klanner, C., Leonhard, K., 2001. AAA proteases of mitochondria: quality control of membrane proteins and regulatory functions during mitochondrial biogenesis. *Biochem. Soc. Trans.* 29, 431–436.
- Lapierre, L.R., Gelino, S., Melendez, A., Hansen, M., 2011. Autophagy and lipid metabolism coordinately modulate life span in germline-less *C. elegans*. *Curr. Biol.* 21, 1507–1514.
- Lawson, B., Brewer, J.W., Hendershot, L.M., 1998. Geldanamycin, an hsp90/GRP94-binding drug, induces increased transcription of endoplasmic reticulum (ER) chaperones via the ER stress pathway. *J. Cell. Physiol.* 174, 170–178.
- Lawson, A.P., Long, M.J.C., Coffey, R.T., Qian, Y., Weerapana, E., El Oualid, F., Hedstrom, L., 2015. Naturally occurring isothiocyanates exert anticancer effects by inhibiting deubiquitinating enzymes. *Cancer Res.* 75, 5130–5142.
- Lee, Y.H., Chen, H.Y., Su, L.J., Chueh, P.J., 2015. Sirtuin 1 (SIRT1) deacetylase activity and NAD(+) /NADH ratio are imperative for capsaicin-mediated programmed cell death. *J. Agric. Food Chem.* 63, 7361–7370.
- Lemaître, J.F., Berger, V., Bonenfant, C., Douhard, M., Gamelon, M., Plard, F., Gaillard, J.M., 2015. Early-late life trade-offs and the evolution of ageing in the wild. *Proc. Biol. Sci.* 282, 20150209.
- Lemasters, J.J., 2014. Variants of mitochondrial autophagy: types 1 and 2 mitophagy and micromitophagy (Type 3). *Redox Biol.* 2, 749–754.
- Levine, B., Packer, M., Codogno, P., 2015. Development of autophagy inducers in clinical medicine. *J. Clin. Invest.* 125, 14–24.
- Li, X., Fan, Z., 2010. The epidermal growth factor receptor antibody cetuximab induces autophagy in cancer cells by downregulating HIF-1alpha and Bcl-2 and activating the beclin 1/hVps34 complex. *Cancer Res.* 70, 5942–5952.
- Li, Q., Li, H., Roughton, K., Wang, X., Kroemer, G., Blomgren, K., Zhu, C., 2010. Lithium reduces apoptosis and autophagy after neonatal hypoxia-ischemia. *Cell Death Dis.* 1, e56.
- Li, W.W., Li, J., Bao, J.K., 2012. Microautophagy: lesser-known self-eating. *Cell. Mol. Life Sci.* 69, 1125–1136.
- Li, Y.Y., Lam, S.K., Mak, J.C., Zheng, C.Y., Ho, J.C., 2013. Erlotinib-induced autophagy in epidermal growth factor receptor mutated non-small cell lung cancer. *Lung Cancer* 81, 354–361.
- Li, X., Tran, K.M., Aziz, K.E., Sorokin, A.V., Chen, J., Wang, W., 2016. Defining the protein-protein interaction network of the human protein tyrosine phosphatase family. *Mol. Cell. Proteomics* 15, 3030–3044.
- Li, X.Y., 1999. 1,25-Dihydroxyvitamin D<sub>3</sub> increases nuclear vitamin D<sub>3</sub> receptors by blocking ubiquitin/proteasome-mediated degradation in human skin. *Mol. Endocrinol.* 13, 1686–1694.
- Liberek, K., Lewandowska, A., Zietkiewicz, S., 2008. Chaperones in control of protein disaggregation. *EMBO J.* 27, 328–335.
- Lim, G.P., Calon, F., Moribara, T., Yang, F., Teter, B., Ubeda, O., Salem Jr., N., Frautschy, S. A., Cole, G.M., 2005. A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. *J. Neurosci.* 25, 3032–3040.
- Lin, B., Hasegawa, Y., Takane, K., Koibuchi, N., Cao, C., Kim-Mitsuyama, S., 2016. High-fat-diet intake enhances cerebral amyloid angiopathy and cognitive impairment in a mouse model of Alzheimer's disease, independently of metabolic disorders. *J. Am. Heart Assoc.* 5.
- Lindahl, T., Wood, R.D., 1999. Quality control by DNA repair. *Science* 286, 1897–1905.
- Lipinski, M.M., Zheng, B., Lu, T., Yan, Z., Py, B.F., Ng, A., Xavier, R.J., Li, C., Yankner, B.A., Scherzer, C.R., Yuan, J., 2010. Genome-wide analysis reveals mechanisms modulating autophagy in normal brain aging and in Alzheimer's disease. *Proc. Natl. Acad. Sci. U. S. A.* 107, 14164–14169.
- Lippincott-Schwartz, J., Bonifacino, J.S., Yuan, L.C., Klausner, R.D., 1988. Degradation from the endoplasmic reticulum: disposing of newly synthesized proteins. *Cell* 54, 209–220.
- Liu, H.Y., Pfleger, C.M., 2013. Mutation in E1, the ubiquitin activating enzyme, reduces *Drosophila* lifespan and results in motor impairment. *PLoS One* 8, e32835.
- Liu, Y., Ye, Y., 2011. Proteostasis regulation at the endoplasmic reticulum: a new perturbation site for targeted cancer therapy. *Cell Res.* 21, 867–883.
- Liu, B.-Q., Gao, Y.-Y., Niu, X.-F., Xie, J.-S., Meng, X., Guan, Y., Wang, H.-Q., 2010. Implication of unfolded protein response in resveratrol-induced inhibition of K562 cell proliferation. *Biochem. Biophys. Res. Commun.* 391, 778–782.
- Liu, H., Yang, J., Li, L., Shi, W., Yuan, X., Wu, L., 2016. The natural occurring compounds targeting endoplasmic reticulum stress. *Evid. Based Complement Altern. Med.* 2016, 783128.
- Lonskaya, I., Hebron, M.L., Desforges, N.M., Franjie, A., Moussa, C.E., 2013. Tyrosine kinase inhibition increases functional parkin-Becn1 interaction and enhances amyloid clearance and cognitive performance. *EMBO Mol. Med.* 5, 1247–1262.
- Lopez-Girona, A., Mendy, D., Ito, T., Miller, K., Gandhi, A.K., Kang, J., Karasawa, S., Carmel, G., Jackson, P., Abbasian, M., Mahmoudi, A., Cathers, B., Rychak, E., Gaidarov, S., Chen, R., Schafer, P.H., Handa, H., Daniel, T.O., Evans, J.F., Chopra, R., 2012. Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia* 26, 2326–2335.
- Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. *Cell* 153, 1194–1217.
- Lotito, S.B., Zhang, W.J., Yang, C.S., Crozier, A., Frei, B., 2011. Metabolic conversion of dietary flavonoids alters their anti-inflammatory and antioxidant properties. *Free Radic. Biol. Med.* 51, 454–463.
- Maeda, N., Hagihara, H., Nakata, Y., Hiller, S., Wilder, J., Reddick, R., 2000. Aortic wall damage in mice unable to synthesize ascorbic acid. *Proc. Natl. Acad. Sci. U. S. A.* 97, 841–846.
- Maheshwari, M., Shekhar, S., Singh, B.K., Jamal, I., Vatsa, N., Kumar, V., Sharma, A., Jana, N.R., 2014. Deficiency of Ube3a in Huntington's disease mice brain increases aggregate load and accelerates disease pathology. *Hum. Mol. Genet.* 23, 6235–6245.

- Maklakov, A.A., Immler, S., 2016. The expensive germline and the evolution of ageing. *Curr. Biol.* 26, R577–586.
- Malhotra, J.D., Miao, H., Zhang, K., Wolfson, A., Pennathur, S., Pipe, S.W., Kaufman, R.J., 2008. Antioxidants reduce endoplasmic reticulum stress and improve protein secretion. *Proc. Natl. Acad. Sci. U. S. A.* 105, 18525–18530.
- Malloy, K.L., Choi, H., Fiorilla, C., Valeriote, F.A., Matainaho, T., Gerwick, W.H., 2012. Hoiamide D, a marine cyanobacteria-derived inhibitor of p53/MDM2 interaction. *Bioorg. Med. Chem. Lett.* 22, 683–688.
- Manach, C., Williamson, G., Morand, C., Scalbert, A., Remesy, C., 2005. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am. J. Clin. Nutr.* 81 (230S–242S).
- Mangiarini, L., Sathasivam, K., Seller, M., Cozens, B., Harper, A., Hetherington, C., Lawton, M., Trottier, Y., Lehrach, H., Davies, S.W., Bates, G.P., 1996. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. *Cell* 87, 493–506.
- Manning-Bog, A.B., McCormack, A.L., Li, J., Uversky, V.N., Fink, A.L., Di Monte, D.A., 2002. The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: paraquat and alpha-synuclein. *J. Biol. Chem.* 277, 1641–1644.
- Maquat, L.E., 1995. When cells stop making sense: effects of nonsense codons on RNA metabolism in vertebrate cells. *RNA* 1, 453–465.
- Marinova, Z., Ren, M., Wendland, J.R., Leng, Y., Liang, M.-H., Yasuda, S., Leeds, P., Chuang, D.-M., 2009. Valproic acid induces functional heat-shock protein 70 via Class I histone deacetylase inhibition in cortical neurons: a potential role of Sp1 acetylation. *J. Neurochem.* 111, 976–987.
- Marti, E., 2016. RNA toxicity induced by expanded CAG repeats in Huntington's disease. *Brain Pathol.* 26 (6), 779–786.
- Martin, L.J., 2008. DNA damage and repair: relevance to mechanisms of neurodegeneration. *J. Neuropathol. Exp. Neurol.* 67, 377–387.
- Mathew, R., Karantza-Wadsworth, V., White, E., 2007. Role of autophagy in cancer. *Nat. Rev. Cancer* 7, 961–967.
- Maynard, S., Fang, E.F., Scheibe-Y Knudsen, M., Croteau, D.L., Bohr, V.A., 2015. DNA damage, DNA, repair, aging, and neurodegeneration. *Cold Spring Harb. Perspect. Med.* 5.
- McNaught, K.S., Belzaire, R., Isacson, O., Jenner, P., Olanow, C.W., 2003. Altered proteasomal function in sporadic Parkinson's disease. *Exp. Neurol.* 179, 38–46.
- Meacham, G.C., Patterson, C., Zhang, W., Younger, J.M., Cyr, D.M., 2001. The Hsc70 co-chaperone CHIP targets immature CFTR for proteasomal degradation. *Nat. Cell Biol.* 3, 100–105.
- Mehrpour, M., Esclatine, A., Beau, I., Codogno, P., 2010. Overview of macroautophagy regulation in mammalian cells. *Cell Res.* 20, 748–762.
- Merlo, D., Molinari, C., Racaniello, M., Garaci, E., Cardinale, A., 2016. DNA double strand Breaks: a common theme in neurodegenerative diseases. *Curr. Alzheimer Res.* 13 (11), 1208–1218.
- Meydani, M., 2001. Nutrition interventions in aging and age-associated disease. *Ann. N. Y. Acad. Sci.* 928, 226–235.
- Michels, A.J., Frei, B., 2013. Myths, artifacts, and fatal flaws: identifying limitations and opportunities in vitamin C research. *Nutrients* 5, 5161–5192.
- Mijaljica, D., Devenish, R.J., 2013. Nucleophagy at a glance. *J. Cell Sci.* 126, 4325–4330.
- Miklossy, J., 2008. Chronic inflammation and amyloidogenesis in Alzheimer's disease – role of Spirochetes. *J. Alzheimers Dis.* 13, 381–391.
- Miller, S.B., Mogk, A., Bukau, B., 2015. Spatially organized aggregation of misfolded proteins as cellular stress defense strategy. *J. Mol. Biol.* 427, 1564–1574.
- Miller-Fleming, L., Giorgini, F., Outeiro, T.F., 2008. Yeast as a model for studying human neurodegenerative disorders. *Biotechnol. J.* 3, 325–338.
- Missiroli, P.V., Liu, K., Zou, L., Ross, B.C., Zhao, G., Liu, J.S., Ge, H., 2009. Information flow analysis of interactome networks. *PLoS Comput. Biol.* 5, e1000350.
- Mizushima, N., Komatsu, M., 2011. Autophagy: renovation of cells and tissues. *Cell* 147, 728–741.
- Mizushima, N., Levine, B., Cuervo, A.M., Klionsky, D.J., 2008. Autophagy fights disease through cellular self-digestion. *Nature* 451, 1069–1075.
- Molinari, M., 2007. N-glycan structure dictates extension of protein folding or onset of disposal. *Nat. Chem. Biol.* 3, 313–320.
- Moreau, K., Luo, S., Rubinsztein, D.C., 2010. Cytoprotective roles for autophagy. *Curr. Opin. Cell Biol.* 22, 206–211.
- Morrow, K.A., Ochoa, C.D., Balczon, R., Zhou, C., Cauthen, L., Alexeyev, M., Schmalzer, K.M., Frank, D.W., Stevens, T., 2016. *Pseudomonas aeruginosa* exoenzymes U and Y induce a transmissible endothelial proteinopathy. *Am. J. Physiol. Lung Cell. Mol. Physiol.* 310, L337–353.
- Mowers, E.E., Sharifi, M.N., Macleod, K.F., 2017. Autophagy in cancer metastasis. *Oncogene* 36, 1619–1630.
- Muller, O., Sattler, T., Flottemeyer, M., Schwarz, H., Plattner, H., Mayer, A., 2000. Autophagic tubes: vacuolar invaginations involved in lateral membrane sorting and inverse vesicle budding. *J. Cell Biol.* 151, 519–528.
- Muller, H.G., Carey, J.R., Wu, D., Liedo, P., Vaupel, J.W., 2001. Reproductive potential predicts longevity of female Mediterranean fruitflies. *Proc. Biol. Sci.* 268, 445–450.
- Munteanu, A., Ricciarelli, R., Massone, S., Zingg, J.-M., 2007. Modulation of proteasome activity by vitamin E in THP-1 monocytes. *IUBMB Life* 59, 771–780.
- Nagy, T., Frank, D., Kátai, E., Yahiro, R.K.K., Poór, V.S., Montskó, G., Zrínyi, Z., Kovács, G. L., Miseta, A., 2013. Lithium induces ER stress and N-glycan modification in galactose-grown Jurkat cells. *PLoS One* 8, e70410.
- Nakamura, Y., Kato, H., Nishikawa, T., Iwasaki, N., Suwa, Y., Rotinsulu, H., Losung, F., Maarisit, W., Mangindaan, R.E., Morioka, H., Yokosawa, H., Tsukamoto, S., 2013. Sulfated serinol A-L: new sulfonated serinol derivatives from a tunicate as inhibitors of p53-Hdm2 interaction. *Org. Lett.* 15, 322–325.
- Narabayashi, K., Ito, Y., Eid, N., Maemura, K., Inoue, T., Takeuchi, T., Otsuki, Y., Higuchi, K., 2014. Indomethacin suppresses LAMP-2 expression and induces lipophagy and lipoapoptosis in rat enterocytes via the ER stress pathway. *J. Gastroenterol.* 50, 541–554.
- Narendra, D., Kane, L.A., Hauser, D.N., Fearnley, I.M., Youle, R.J., 2010. p62/SQSTM1 is required for Parkin-induced mitochondrial clustering but not mitophagy; VDAC1 is dispensable for both. *Autophagy* 6, 1090–1106.
- Naumann, P., Fortunato, F., Zentgraf, H., Buchler, M.W., Herr, I., Werner, J., 2011. Autophagy and cell death signaling following dietary sulforaphane act independently of each other and require oxidative stress in pancreatic cancer. *Int. J. Oncol.* 39, 101–109.
- Nawrocki, S.T., Carew, J.S., Dunner Jr., K., Boise, L.H., Chiao, P.J., Huang, P., Abbruzzese, J.L., McConkey, D.J., 2005. Bortezomib inhibits PKR-like endoplasmic reticulum (ER) kinase and induces apoptosis via ER stress in human pancreatic cancer cells. *Cancer Res.* 65, 11510–11519.
- Neuber, O., Jarosch, E., Volkwein, C., Walter, J., Sommer, T., 2005. Ubx2 links the Cdc48 complex to ER-associated protein degradation. *Nat. Cell Biol.* 7, 993–998.
- Niccoli, T., Cabecinha, M., Tillmann, A., Kerr, F., Wong, C.T., Cardenes, D., Vincent, A.J., Bettledi, L., Li, L., Grönke, S., 2016. Increased glucose transport into neurons rescues Aβ toxicity in Drosophila. *Curr. Biol.* 26, 2291–2300.
- Nomura, J., Hosoi, T., Kaneko, M., Ozawa, K., Nishi, A., Nomura, Y., 2016. Neuroprotection by endoplasmic reticulum stress-induced HRD1 and chaperones: possible therapeutic targets for Alzheimer's and Parkinson's disease. *Med. Sci.* 4, 14.
- Nosengo, N., 2016. Can you teach old drugs new tricks? *Nature* 534, 314–316.
- Nussbaum-Kramer, C.I., Morimoto, R.I., 2014. *Caenorhabditis elegans* as a model system for studying non-cell-autonomous mechanisms in protein-misfolding diseases. *Dis. Model. Mech.* 7, 31–39.
- O'Rourke, E.J., Kuballa, P., Xavier, R., Ruvkun, G., 2013. Omega-6 Polyunsaturated fatty acids extend life span through the activation of autophagy. *Genes Dev.* 27, 429–440.
- Ohsumi, Y., 2014. Historical landmarks of autophagy research. *Cell Res.* 24, 9–23.
- Okui, T., Shimo, T., Hassan, N.M., Fukazawa, T., Kurio, N., Takaoka, M., Naomoto, Y., Sasaki, A., 2011. Antitumor effect of novel HSP90 inhibitor NVP-AUY922 against oral squamous cell carcinoma. *Anticancer Res.* 31, 1197–1204.
- Omura, T., Asari, M., Yamamoto, J., Kamiyama, N., Oka, K., Hoshina, C., Maseda, C., Awaya, T., Tasaki, Y., Shiono, H., Shimizu, K., Matsubara, K., 2012. HRD1 levels increased by zonisamide prevented cell death and caspase-3 activation caused by endoplasmic reticulum stress in SH-SY5Y cells. *J. Mol. Neurosci.* 46, 527–535.
- Osman, C., Wilmes, C., Tatsuta, T., Langer, T., 2007. Prohibitins interact genetically with Atp23, a novel processing peptidase and chaperone for the F1Fo-ATP synthase. *Mol. Biol. Cell* 18, 627–635.
- Pal, R., Monroe, T.O., Palmieri, M., Sardiello, M., Rodney, G.G., 2014. Rotenone induces neurotoxicity through Rac1-dependent activation of NADPH oxidase in SHSY-5Y cells. *FEBS Lett.* 588, 472–481.
- Panasenko, O.O., 2014. The role of the E3 ligase Not4 in cotranslational quality control. *Front. Genet.* 5, 141.
- Pankiv, S., Clausen, T.H., Lamark, T., Brech, A., Bruun, J.A., Outzen, H., Overvatn, A., Bjorkoy, G., Johansen, T., 2007. p62/SQSTM1 binds directly to Atg8/LC3 to facilitate degradation of ubiquitinated protein aggregates by autophagy. *J. Biol. Chem.* 282, 24131–24145.
- Parenti, G., Andria, G., Valenzano, K.J., 2015. Pharmacological chaperone therapy: preclinical development, clinical translation, and prospects for the treatment of lysosomal storage disorders. *Mol. Ther.* 23, 1138–1148.
- Park, H.-R., Furihata, K., Hayakawa, Y., Shin-ya, K., 2002. Versipelostatin, a novel GRP78/Bip molecular chaperone down-regulator of microbial origin. *Tetrahedron Lett.* 43, 6941–6945.
- Park, Y.E., Hayashi, Y.K., Bonne, G., Arimura, T., Noguchi, S., Nonaka, I., Nishino, I., 2009. Autophagic degradation of nuclear components in mammalian cells. *Autophagy* 5, 795–804.
- Patterson, C., Höhfeld, J., 2008. Molecular chaperones and the ubiquitin-proteasome system. *Protein Science Encyclopedia*.
- Patton, W.F., 2002. Detection technologies in proteome analysis. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* 771, 3–31.
- Pechmann, S., Willmund, F., Frydman, J., 2013. The ribosome as a hub for protein quality control. *Mol. Cell* 49, 411–421.
- Pennington, S.R., Wilkins, M.R., Hochstrasser, D.F., Dunn, M.J., 1997. Proteome analysis: from protein characterization to biological function. *Trends Cell Biol.* 7, 168–173.
- Petiwal, S.M., Li, G., Bosland, M.C., Lantvit, D.D., Petukhov, P.A., Johnson, J.J., 2016. Carnosic acid promotes degradation of the androgen receptor and is regulated by the unfolded protein response pathway in vitro and in vivo. *Carcinogenesis* 37, 827–838.
- Pierce, A., Wei, R., Halade, D., Yoo, S.-E., Ran, Q., Richardson, A., 2010. A Novel mouse model of enhanced proteostasis: full-length human heat shock factor 1 transgenic mice. *Biochem. Biophys. Res. Commun.* 402, 59–65.
- Pierdominici, M., Barbat, C., Vomero, M., Locatelli, S.L., Carlo-Stella, C., Ortona, E., Malorni, W., 2014. Autophagy as a pathogenic mechanism and drug target in lymphoproliferative disorders. *FASEB J.* 28, 524–535.
- Pinto, B.A., Melo, T.M., Flister, K.F., Franca, L.M., Kajihara, D., Tanaka, L.Y., Laurindo, F.R., Paes, A.M., 2016. Early and sustained exposure to high-sucrose diet triggers hippocampal ER stress in young rats. *Metab. Brain Dis.* 31, 917–927.
- Piper, P.W., 2006. Long-lived yeast as a model for ageing research. *Yeast* 23, 215–226.
- Pisa, D., Alonso, R., Rabano, A., Rodal, I., Carrasco, L., 2015. Different brain regions are infected with fungi in Alzheimer's disease. *Sci. Rep.* 5, 15015.

- Pisarev, A.V., Skabkin, M.A., Pisareva, V.P., Skabkina, O.V., Rakotondrafara, A.M., Hentze, M.W., Hellen, C.U., Pestova, T.V., 2010. The role of ABCE1 in eukaryotic posttermination ribosomal recycling. *Mol. Cell* 37, 196–210.
- Plotkin, J.B., 2011. Cell biology. The lives of proteins. *Science* 331, 683–684.
- Poidevin, M., Zhang, F., Jin, P., 2015. Small-molecule screening using Drosophila models of human neurological disorders. *Methods Mol. Biol.* 1263, 127–138.
- Powolny, A.A., Bommareddy, A., Hahn, E.R., Normolle, D.P., Beumer, J.H., Nelson, J.B., Singh, S.V., 2011. Chemopreventative potential of the cruciferous vegetable constituent phenethyl isothiocyanate in a mouse model of prostate cancer. *J. Natl. Cancer Inst.* 103, 571–584.
- Preissler, S., Deuerling, E., 2012. Ribosome-associated chaperones as key players in proteostasis. *Trends Biochem. Sci.* 37, 274–283.
- Pujals, A., Favre, L., Pioche-Durieu, C., Robert, A., Meurice, G., Le Gentil, M., Chelouah, S., Martin-Garcia, N., Le Cam, E., Guettier, C., Raphael, M., Vassilev, L.T., Gaulard, P., Codogno, P., Lipinski, M., Wiels, J., 2015. Constitutive autophagy contributes to resistance to TP53-mediated apoptosis in Epstein-Barr virus-positive latency III B-cell lymphomproliferations. *Autophagy* 11, 2275–2287.
- Puri, P., Chandra, A., 2014. Autophagy modulation as a potential therapeutic target for liver diseases. *J. Clin. Exp. Hepatol.* 4, 51–59.
- Pyo, J.O., Yoo, S.M., Ahn, H.H., Nah, J., Hong, S.H., Kam, T.I., Jung, S., Jung, Y.K., 2013. Overexpression of Atg5 in mice activates autophagy and extends lifespan. *Nat. Commun.* 4, 2300.
- Qin, Y., Yalamanchili, H.K., Qin, J., Yan, B., Wang, J., 2015. The current status and challenges in computational analysis of genomic big data. *Big Data Res.* 2, 12–18.
- Qiu, S., Sun, H., Zhang, A.H., Xu, H.Y., Yan, G.L., Han, Y., Wang, X.J., 2014. Natural alkaloids: basic aspects, biological roles, and future perspectives. *Chin. J. Nat. Med.* 12, 401–406.
- Quiros, P.M., Langer, T., Lopez-Otin, C., 2015. New roles for mitochondrial proteases in health, ageing and disease. *Nat. Rev. Mol. Cell Biol.* 16, 345–359.
- Ramalho, M.J., Loureiro, J.A., Gomes, B., Frasco, M.F., Coelho, M.A., Pereira, M.C., 2015. PLGA nanoparticles as a platform for vitamin D-based cancer therapy. *Beilstein J. Nanotechnol.* 6, 1306–1318.
- Ramirez-Alvarado, M., Kelly, J.W., Dobson, C.M., 2010. Protein Misfolding Diseases: Current and Emerging Principles and Therapies. John Wiley & Sons.
- Rao, K.S., 1993. Genomic damage and its repair in young and aging brain. *Mol. Neurobiol.* 7, 23–48.
- Ravikumar, B., Duden, R., Rubinsztein, D.C., 2002. Aggregate-prone proteins with polyglutamine and polyalanine expansions are degraded by autophagy. *Hum. Mol. Genet.* 11, 1107–1117.
- Ravikumar, B., Sarkar, S., Davies, J.E., Futter, M., Garcia-Arencibia, M., Green-Thompson, Z.W., Jimenez-Sanchez, M., Korolchuk, V.I., Lichtenberg, M., Luo, S., Massey, D.C., Menzies, F.M., Moreau, K., Narayanan, U., Renna, M., Siddiqui, F.H., Underwood, B.R., Winslow, A.R., Rubinsztein, D.C., 2010. Regulation of mammalian autophagy in physiology and pathophysiology. *Physiol. Rev.* 90, 1383–1435.
- Ravindran, S., Kuruvilla, V., Wilbur, K., Munusamy, S., 2016. Nephroprotective effects of metformin in diabetic nephropathy. *J. Cell. Physiol.* 232 (4), 731–742.
- Reddy, L., Odhav, B., Bhoola, K.D., 2003. Natural products for cancer prevention: a global perspective. *Pharmacol. Ther.* 99, 1–13.
- Renna, M., Schaffner, C., Brown, K., Shang, S., Tamayo, M.H., Hegyi, K., Grimsey, N.J., Cusens, D., Coulter, S., Cooper, J., Bowden, A.R., Newton, S.M., Kampmann, B., Helm, J., Jones, A., Haworth, C.S., Basaraba, R.J., DeGroote, M.A., Ordway, D.J., Rubinsztein, D.C., Floto, R.A., 2011. Azithromycin blocks autophagy and may predispose cystic fibrosis patients to mycobacterial infection. *J. Clin. Invest.* 121, 3554–3563.
- Reyes-Turcu, F.E., Ventii, K.H., Wilkinson, K.D., 2009. Regulation and cellular roles of ubiquitin-specific deubiquitinating enzymes. *Annu. Rev. Biochem.* 78, 363–397.
- Rincon-Limas, D.E., Jensen, K., Fernandez-Funez, P., 2012. Drosophila models of proteinopathies: the little fly that could. *Curr. Pharm. Des.* 18, 1108–1122.
- Roberts, P., Moslitch-Moshkovitz, S., Kvam, E., O'Toole, E., Winey, M., Goldfarb, D.S., 2003. Piecemeal microautophagy of nucleus in *Saccharomyces cerevisiae*. *Mol. Biol. Cell* 14, 129–141.
- Rodrigues, T., Reker, D., Schneider, P., Schneider, G., 2016. Counting on natural products for drug design. *Nat. Chem.* 8, 531–541.
- Rodriguez, M., Snoek, L.B., De Bono, M., Kammenge, J.E., 2013. Worms under stress: *C. elegans* stress response and its relevance to complex human disease and aging. *Trends Genet.* 29, 367–374.
- Romisch, K., 2006. Cdc48p is UBX-linked to ER ubiquitin ligases. *Trends Biochem. Sci.* 31, 24–25.
- Rongo, C., 2015. Better to burn out than it is to rust: coordinating cellular redox states during aging and stress. *EMBO J.* 34, 2310–2311.
- Ross, C.A., Poirier, M.A., 2004. Protein aggregation and neurodegenerative disease. *Nat. Med.* S10–S17.
- Rossi, M., Rotblat, B., Ansell, K., Amelio, I., Caraglia, M., Misso, G., Bernassola, F., Cavasotto, C.N., Knight, R.A., Ciechanover, A., Melino, G., 2014. High throughput screening for inhibitors of the HECT ubiquitin E3 ligase ITCH identifies antidepressant drugs as regulators of autophagy. *Cell. Death. Dis.* 5, e1203.
- Roth, D.M., Balch, W.E., 2011. Modeling general proteostasis: proteome balance in health and disease. *Curr. Opin. Cell Biol.* 23, 126–134.
- Rual, J.F., Venkatesan, K., Hao, T., Hirozane-Kishikawa, T., Dricot, A., Li, N., Berriz, G.F., Gibbons, F.D., Dreze, M., Ayivi-Guedehoussou, N., Klitgord, N., Simon, C., Boxem, M., Milstein, S., Rosenberg, J., Goldberg, D.S., Zhang, L.V., Wong, S.L., Franklin, G., Li, S., Albala, J.S., Lim, J., Fraughton, C., Llamasas, E., Cevik, S., Bex, C., Lamesch, P., Sikorski, R.S., Vandenhoutte, J., Zoghbi, H.Y., Smolyar, A., Bosak, S., Sequerra, R., Doucette-Stamm, L., Cusick, M.E., Hill, D.E., Roth, F.P., Vidal, M., 2005. Towards a proteome-scale map of the human protein-protein interaction network. *Nature* 437, 1173–1178.
- Rubinsztein, D.C., Gestwicki, J.E., Murphy, L.O., Klionsky, D.J., 2007. Potential therapeutic applications of autophagy. *Nat. Rev. Drug Discov.* 6, 304–312.
- Rubinsztein, D.C., Marino, G., Kroemer, G., 2011. Autophagy and aging. *Cell* 146, 682–695.
- Rugarli, E.I., Langer, T., 2012. Mitochondrial quality control: a matter of life and death for neurons. *EMBO J.* 31, 1336–1349.
- Saez, I., Vilchez, D., 2014. The mechanistic links between proteasome activity, aging and age-related diseases. *Curr. Genomics* 15, 38–51.
- Saghafelian, A., Cravatt, B.F., 2005. Assignment of protein function in the postgenomic era. *Nat. Chem. Biol.* 1, 130–142.
- Sahu, R., Kaushik, S., Clement, C.C., Cannizzo, E.S., Scharf, B., Follenzi, A., Potolicchio, I., Nieves, E., Cuervo, A.M., Santambrogio, L., 2011. Microautophagy of cytosolic proteins by late endosomes. *Dev. Cell* 20, 131–139.
- Sarkar, R., Mukherjee, S., Biswas, J., Roy, M., 2012. Sulforaphane, a naturally occurring isothiocyanate induces apoptosis in breast cancer cells by targeting heat shock proteins. *Biochem. Biophys. Res. Commun.* 427, 80–85.
- Scarffe, L.A., Stevens, D.A., Dawson, V.L., Dawson, T.M., 2014. Parkin and PINK1: much more than mitophagy. *Trends Neurosci.* 37, 315–324.
- Schaeffer, C., Creatore, A., Rampoldi, L., 2014. Protein trafficking defects in inherited kidney diseases. *Nephrol. Dial. Transplant.* 29 (Suppl. 4), iv33–iv44.
- Schneider, K., Bertolotti, A., 2015. Surviving protein quality control catastrophes—from cells to organisms. *J. Cell Sci.* 128, 3861–3869.
- Schuberth, C., Buchberger, A., 2005. Membrane-bound Ubx2 recruits Cdc48 to ubiquitin ligases and their substrates to ensure efficient ER-associated protein degradation. *Nat. Cell Biol.* 7, 999–1006.
- Scotter, E.L., Chen, H.J., Shaw, C.E., 2015. TDP-43 proteinopathy and ALS: insights into disease mechanisms and therapeutic targets. *Neurotherapeutics* 12, 352–363.
- Sekijima, Y., Dendale, M.A., Kelly, J.W., 2006. Orally administered diflunisal stabilizes transthyretin against dissociation required for amyloidogenesis. *Amyloid* 13, 236–249.
- Sekizawa, R., Ikeno, S., Nakamura, H., Naganawa, H., Matsui, S., Inuma, H., Takeuchi, T., 2002. Panepophenanthrin, from a mushroom strain, a novel inhibitor of the ubiquitin-activating enzyme. *J. Nat. Prod.* 65, 1491–1493.
- Selkoe, D.J., 2004. Cell biology of protein misfolding: the examples of Alzheimer's and Parkinson's diseases. *Nat. Cell Biol.* 6, 1054–1061.
- Shah, M., Stebbins, J.L., Dewing, A., Qi, J., Pellecchia, M., Ronai, Z.E.A., 2009. Inhibition of Siab2 ubiquitin ligase by vitamin K3 (menadione) attenuates hypoxia and MAPK signaling and blocks melanoma tumorigenesis. *Pigm. Cell Melanoma Res.* 22, 799–808.
- Shao, S., von der Malsburg, K., Hegde, R.S., 2013. Listerin-dependent nascent protein ubiquitination relies on ribosome subunit dissociation. *Mol. Cell* 50, 637–648.
- Sherer, T.B., Betarbet, R., Stout, A.K., Lund, S., Baptista, M., Panov, A.V., Cookson, M.R., Greenamyre, J.T., 2002. An *in vitro* model of Parkinson's disease: linking mitochondrial impairment to altered alpha-synuclein metabolism and oxidative damage. *J. Neurosci.* 22, 7006–7015.
- Shevchenko, A., Jensen, O.N., Podtelejnikov, A.V., Sagliocco, F., Wilm, M., Vorm, O., Mortensen, P., Shevchenko, A., Boucherie, H., Mann, M., 1996. Linking genome and proteome by mass spectrometry: large-scale identification of yeast proteins from two dimensional gels. *Proc. Natl. Acad. Sci. U. S. A.* 93, 14440–14445.
- Shevchenko, A., Tomas, H., Havlis, J., Olsen, J.V., Mann, M., 2006. In-gel digestion for mass spectrometric characterization of proteins and proteomes. *Nat. Protoc.* 1, 2856–2860.
- Shibler, A., Ravid, T., 2014. Chaperoning proteins for destruction: diverse roles of Hsp70 chaperones and their co-chaperones in targeting misfolded proteins to the proteasome. *Biomolecules* 4, 704–724.
- Shimazaki, H., Watanabe, K., Veeraveedu, P.T., Harima, M., Thandavarayan, R.A., Arozal, W., Tachikawa, H., Kodama, M., Aizawa, Y., 2010. The antioxidant edaravone attenuates ER-stress-mediated cardiac apoptosis and dysfunction in rats with autoimmune myocarditis. *Free Radic. Res.* 44, 1082–1090.
- Shoemaker, C.J., Green, R., 2011. Kinetic analysis reveals the ordered coupling of translation termination and ribosome recycling in yeast. *Proc. Natl. Acad. Sci. U. S. A.* 108, E1392–E1398.
- Shyng, S.I., Ferrigni, T., Shepard, J.B., Nestorowicz, A., Glaser, B., Permutt, M.A., Nichols, C.G., 1998. Functional analyses of novel mutations in the sulfonylurea receptor 1 associated with persistent hyperinsulinemic hypoglycemia of infancy. *Diabetes* 47, 1145–1151.
- Si, X., Wang, Y., Wong, J., Zhang, J., McManus, B.M., Luo, H., 2007. Dysregulation of the ubiquitin-proteasome system by curcumin suppresses coxsackievirus B3 replication. *J. Virol.* 81, 3142–3150.
- Siddiqui, A., Hanson, I., Andersen, J.K., 2012. Mao-B elevation decreases parkin's ability to efficiently clear damaged mitochondria: protective effects of rapamycin. *Free Radic. Res.* 46, 1011–1018.
- Sklirou, A.D., Ralli, M., Dominguez, M., Papassideri, I., Skaltsounis, A.L., Trougakos, I.P., 2015. Hexapeptide-11 is a novel modulator of the proteostasis network in human diploid fibroblasts. *Redox Biol.* 5, 205–215.
- Sleigh, S.H., Barton, C.L., 2010. Repurposing strategies for therapeutics. *Pharm. Med.* 24, 151–159.
- Smuder, A.J., Kavazis, A.N., Min, K., Powers, S.K., 2011. Exercise protects against doxorubicin-induced oxidative stress and proteolysis in skeletal muscle. *J. Appl. Physiol.* 110, 935–942.
- Sommerweiss, D., Gorski, T., Richter, S., Garten, A., Kiess, W., 2013. Oleate rescues INS-1E beta-cells from palmitate-induced apoptosis by preventing activation of the unfolded protein response. *Biochem. Biophys. Res. Commun.* 441, 770–776.

- Song, Y.M., Lee, J.-W., Kim, Y.-h., Ham, D.-S., Kang, E.-S., Cha, B.S., Lee, H.C., Lee, B.-W., 2014. Metformin alleviates hepatosteatosis by restoring SIRT1-mediated autophagy induction via an AMP-activated protein kinase-independent pathway. *Autophagy* 11, 46–59.
- Soti, C., Csermely, P., 2007. Aging cellular networks: chaperones as major participants. *Exp. Gerontol.* 42, 113–119.
- Steele, A.D., Hutter, G., Jackson, W.S., Heppner, F.L., Borkowski, A.W., King, O.D., Raymond, G.J., Aguzzi, A., Lindquist, S., 2008. Heat shock factor 1 regulates lifespan as distinct from disease onset in prion disease. *Proc. Natl. Acad. Sci. U. S. A.* 105, 13626–13631.
- Strong, M.J., Kesavapany, S., Pant, H.C., 2005. The pathobiology of amyotrophic lateral sclerosis: a proteopathy. *J. Neuropathol. Exp. Neurol.* 64, 649–664.
- Suaud, L., Miller, K., Panichelli, A.E., Randell, R.L., Marando, C.M., Rubenstein, R.C., 2011. 4-Phenylbutyrate stimulates hsp70 expression through the elp2 component of elongator and STAT-3 in cystic fibrosis epithelial cells. *J. Biol. Chem.* 286, 45083–45092.
- Suzuki, Y., 2014. Emerging novel concept of chaperone therapies for protein misfolding diseases. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* 90, 145–162.
- Tan, W., Lu, J., Huang, M., Li, Y., Chen, M., Wu, G., Gong, J., Zhong, Z., Xu, Z., Dang, Y., Guo, J., Chen, X., Wang, Y., 2011. Anti-cancer natural products isolated from Chinese medicinal herbs. *Chin. Med.* 6, 27.
- Tan, C.-C., Yu, J.-T., Tan, M.-S., Jiang, T., Zhu, X.-C., Tan, L., 2014. Autophagy in aging and neurodegenerative diseases: implications for pathogenesis and therapy. *Neurobiol. Aging* 35, 941–957.
- Tan, Y.Q., Zhang, J., Zhou, G., 2016. Autophagy and its implication in human oral diseases. *Autophagy* 1–12.
- Tanaka, K., Matsuda, N., 2014. Proteostasis and neurodegeneration: the roles of proteasomal degradation and autophagy. *Biochim. et Biophys. Acta (BBA)-Mol. Cell Res.* 1843, 197–204.
- Tang, C., Yang, L., Jiang, X., Xu, C., Wang, M., Wang, Q., Zhou, Z., Xiang, Z., Cui, H., 2014. Antibiotic drug tigecycline inhibited cell proliferation and induced autophagy in gastric cancer cells. *Biochem. Biophys. Res. Commun.* 446, 105–112.
- Tapia, H., Morano, K.A., 2010. Hsp90 nuclear accumulation in quiescence is linked to chaperone function and spore development in yeast. *Mol. Biol. Cell* 21, 63–72.
- Tatsuta, T., Langer, T., 2008. Quality control of mitochondria: protection against neurodegeneration and ageing. *EMBO J.* 27, 306–314.
- Taylor, R.C., Dillin, A., 2011. Aging as an event of proteostasis collapse. *Cold Spring Harb. Perspec. Biol.* 3.
- Taylor, C.F., Paton, N.W., Garwood, K.L., Kirby, P.D., Stead, D.A., Yin, Z., Deutsch, E.W., Selway, L., Walker, J., Riba-Garcia, I., Mohammed, S., Deery, M.J., Howard, J.A., Dunkley, T., Aebersold, R., Kell, D.B., Lilley, K.S., Roepstorff, P., Yates 3rd, J.R., Brass, A., Brown, A.J., Cash, P., Gaskell, S.J., Hubbard, S.J., Oliver, S.G., 2003. A systematic approach to modeling, capturing, and disseminating proteomics experimental data. *Nat. Biotechnol.* 21, 247–254.
- Todde, V., Veenhuis, M., van der Klei, I.J., 2009. Autophagy: principles and significance in health and disease. *Biochim. Biophys. Acta* 1792, 3–13.
- Tokarz, P., Kauppinen, A., Kaarniranta, K., Blasiak, J., 2013. Oxidative DNA damage and proteostasis in age-related macular degeneration. *J. Biochem. Pharmacol. Res.* 1, 106–113.
- Trancikova, A., Ramonet, D., Moore, D.J., 2011. Genetic mouse models of neurodegenerative diseases. *Prog. Mol. Biol. Transl. Sci.* 100, 419–482.
- Treaster, S.B., Ridgway, I.D., Richardson, C.A., Gaspar, M.B., Chaudhuri, A.R., Austad, S.N., 2014. Superior proteome stability in the longest lived animal. *Age (Dordr)* 36, 9597.
- Tropak, M.B., Mahuran, D., 2007. Lending a helping hand, screening chemical libraries for compounds that enhance  $\beta$ -hexosaminidase A activity in GM2 gangliosidosis cells. *FEBS J.* 274, 4951–4961.
- Trott, A., West, J.D., Klaic, L., Westerheide, S.D., Silverman, R.B., Morimoto, R.I., Morano, K.A., 2008. Activation of heat shock and antioxidant responses by the natural product celastrol: transcriptional signatures of a thiol-targeted molecule. *Mol. Biol. Cell* 19, 1104–1112.
- Tsakiri, E.N., Trougakos, I.P., 2015. The amazing ubiquitin-proteasome system: structural components and implication in aging. *Int. Rev. Cell Mol. Biol.* 314, 171–237.
- Tsakiri, E.N., Sykiotis, G.P., Papassideri, I.S., Gorgoulis, V.G., Bohmann, D., Trougakos, I.P., 2013. Differential regulation of proteasome functionality in reproductive vs somatic tissues of Drosophila during aging or oxidative stress. *FASEB J.* 27, 2407–2420.
- Tsukamoto, S., Yokosawa, H., 2010. Inhibition of the ubiquitin-Proteasome system by natural products for cancer therapy. *Planta Med.* 76, 1064–1074.
- Tsukamoto, S., Yoshida, T., Hosono, H., Ohta, T., Yokosawa, H., 2006. Hexylitaconic acid: a new inhibitor of p53-HDM2 interaction isolated from a marine-derived fungus, *Arthrinium* sp. *Bioorg. Med. Chem. Lett.* 16, 69–71.
- Tsukamoto, S., Takeuchi, T., Rotinsulu, H., Mangindaan, R.E., van Soest, R.W., Ukai, K., Kobayashi, H., Namikoshi, M., Ohta, T., Yokosawa, H., 2008. Leucettamol A: a new inhibitor of Ubc13-Uev1A interaction isolated from a marine sponge: leucetta aff. microrhaphis. *Bioorg. Med. Chem. Lett.* 18, 6319–6320.
- Tsukamoto, S., Yamanokuchi, R., Yoshitomi, M., Sato, K., Ikeda, T., Rotinsulu, H., Mangindaan, R.E., de Voogd, N.J., van Soest, R.W., Yokosawa, H., 2010. Aaptamine, an alkaloid from the sponge Aaptos suberitoides, functions as a proteasome inhibitor. *Bioorg. Med. Chem. Lett.* 20, 3341–3343.
- Tsukamoto, S., 2016. Search for inhibitors of the ubiquitin-proteasome system from natural sources for cancer therapy. *Chem. Pharm. Bull.* 64, 112–118.
- Tyedmers, J., Mogk, A., Bukau, B., 2010. Cellular strategies for controlling protein aggregation. *Nat. Rev. Mol. Cell Biol.* 11, 777–788.
- Udan-Johns, M., Bengoechea, R., Bell, S., Shao, J., Diamond, M.I., True, H.L., Weihl, C.C., Baloh, R.H., 2014. Prion-like nuclear aggregation of TDP-43 during heat shock is regulated by HSP40/70 chaperones. *Hum. Mol. Genet.* 23, 157–170.
- Ungermannova, D., Parker, S.J., Nasveschuk, C.G., Wang, W., Quade, B., Zhang, G., Kuchta, R.D., Phillips, A.J., Liu, X., 2012. Largazole and its derivatives selectively inhibit ubiquitin activating enzyme (e1). *PLoS One* 7, e29208.
- Upadhyay, A., Amanullah, A., Chhangani, D., Joshi, V., Mishra, R., Mishra, A., 2016a. Ibuprofen induces mitochondrial-mediated apoptosis through proteasomal dysfunction. *Mol. Neurobiol.* 53, 6968–6981.
- Upadhyay, A., Amanullah, A., Chhangani, D., Mishra, R., Prasad, A., Mishra, A., 2016b. Mahogunin ring finger-1 (MGRN1), a multifaceted ubiquitin ligase: recent unraveling of neurobiological mechanisms. *Mol. Neurobiol.* 53, 4484–4496.
- Urra, H., Dufey, E., Avril, T., Chevet, C., 2016. Endoplasmic reticulum stress and the hallmarks of cancer. *Trends Cancer* 2, 252–262.
- Usenovic, M., Niroomand, S., Drolet, R.E., Yao, L., Gaspar, R.C., Hatcher, N.G., Schachter, J., Renger, J.J., Parmentier-Batteur, S., 2015. Internalized tau oligomers cause neurodegeneration by inducing accumulation of pathogenic tau in human neurons derived from induced pluripotent stem cells. *J. Neurosci.* 35, 14234–14250.
- Uversky, V.N., Li, J., Fink, A.L., 2001. Metal-triggered structural transformations, aggregation, and fibrillation of human alpha-synuclein: a possible molecular link between Parkinson's disease and heavy metal exposure. *J. Biol. Chem.* 276, 44284–44296.
- Uytterhoeven, V., Lauwers, E., Maes, I., Miskiewicz, K., Melo, M.N., Swerts, J., Kuenen, S., Wittcox, R., Corthout, N., Marrink, S.J., Munck, S., Verstreken, P., 2015. Hsc70-4 deforms membranes to promote synaptic protein turnover by endosomal microautophagy. *Neuron* 88, 735–748.
- Varshavsky, A., 2012. The ubiquitin system, an immense realm. *Annu. Rev. Biochem.* 81, 167–176.
- Vassilev, L.T., Vu, B.T., Graves, B., Carvajal, D., Podlaski, F., Filipovic, Z., Kong, N., Kammlott, U., Lukacs, C., Klein, C., Fotouhi, N., Liu, E.A., 2004. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. *Science* 303, 844–848.
- Venkatraman, P., Wetzel, R., Tanaka, M., Nukina, N., Goldberg, A.L., 2004. Eukaryotic proteasomes cannot digest polyglutamine sequences and release them during degradation of polyglutamine-containing proteins. *Mol. Cell* 14, 95–104.
- Vergani, L., Barile, M., Angelini, C., Burlina, A.B., Nijtmans, L., Freda, M.P., Brizio, C., Zerbetto, E., Dabbeni-Sala, F., 1999. Riboflavin therapy: biochemical heterogeneity in two adult lipid storage myopathies. *Brain* 122 (Pt 12), 2401–2411.
- Visconti, P., Caron, A., Guicheney, P., Li, Z., Prevost, M.C., Faure, A., Chateau, D., Chapon, F., Tome, F., Dupret, J.M., Paulin, D., Fardeau, M., 1998. A missense mutation in the alphaB-crystallin chaperone gene causes a desmin-related myopathy. *Nat. Genet.* 20, 92–95.
- Vidal, R.L., Matus, S., Bargsted, L., Hetz, C., 2014. Targeting autophagy in neurodegenerative diseases. *Trends Pharmacol. Sci.* 35, 583–591.
- Vilchez, D., Morante, I., Liu, Z., Douglas, P.M., Merkowitz, C., Rodrigues, A.P., Manning, G., Dillin, A., 2012. RPN-6 determines *C. elegans* longevity under proteotoxic stress conditions. *Nature* 489, 263–268.
- Vogel, C., Marcotte, E.M., 2012. Insights into the regulation of protein abundance from proteomic and transcriptomic analyses. *Nat. Rev. Genet.* 13, 227–232.
- Voorhees, P.M., Orlowski, R.Z., 2006. The proteasome and proteasome inhibitors in cancer therapy. *Annu. Rev. Pharmacol. Toxicol.* 46, 189–213.
- Voos, W., Rottgers, K., 2002. Molecular chaperones as essential mediators of mitochondrial biogenesis. *Biochim. Biophys. Acta* 1592, 51–62.
- Wang, T., Hebert, D.N., 2003. EDEM as an ER quality control receptor. *Nat. Struct. Biol.* 10, 319–321.
- Wang, M., Kaufman, R.J., 2016. Protein misfolding in the endoplasmic reticulum as a conduit to human disease. *Nature* 529, 326–335.
- Wang, F., Segatori, L., 2013. Remodeling the proteostasis network to rescue glucocerebrosidase variants by inhibiting ER-associated degradation and enhancing ER folding. *PLoS One* 8, e61418.
- Wang, J., Tanila, H., Puolivali, J., Kadish, I., van Groen, T., 2003. Gender differences in the amount and deposition of amyloid $\beta$  in APPswe and PS1 double transgenic mice. *Neurobiol. Dis.* 14, 318–327.
- Wang, F., Song, W., Brancati, G., Segatori, L., 2011. Inhibition of endoplasmic reticulum-associated degradation rescues native folding in loss of function protein misfolding diseases. *J. Biol. Chem.* 286, 43454–43464.
- Wang, T., ECHEVERRIA, P.C., Picard, D., 2013. Overview of Molecular Chaperones in Health And. Inhibitors of Molecular Chaperones As Therapeutic Agents 37, 1.
- Wang, Y.J., Di, X.J., Mu, T.W., 2014. Using pharmacological chaperones to restore proteostasis. *Pharmacol. Res.* 83, 3–9.
- Wang, K., Hu, L., Jin, X.-L., Ma, Q.-X., Marcucci, M.C., Netto, A.A.L., Sawaya, A.C.H.F., Huang, S., Ren, W.-K., Conlon, M.A., Topping, D.L., Hu, F.-L., 2015. Polyphenol-rich propolis extracts from China and Brazil exert anti-inflammatory effects by modulating ubiquitination of TRAF6 during the activation of NF- $\kappa$ B. *J. Funct. Foods* 19, 464–478.
- Wang, P., Sheng, M., Li, B., Jiang, Y., Chen, Y., 2016. High osmotic pressure increases reactive oxygen species generation in rabbit corneal epithelial cells by endoplasmic reticulum. *Am. J. Transl. Res.* 8, 860–870.
- Webb, A.E., Brunet, A., 2014. FOXO transcription factors: key regulators of cellular quality control. *Trends Biochem. Sci.* 39, 159–169.
- Westerheide, S.D., Morimoto, R.I., 2005. Heat shock response modulators as therapeutic tools for diseases of protein conformation. *J. Biol. Chem.* 280, 33097–33100.

- White, E., 2012. Deconvoluting the context-dependent role for autophagy in cancer. *Nat. Rev. Cancer* 12, 401–410.
- White, E., 2015. The role for autophagy in cancer. *J. Clin. Invest.* 125, 42–46.
- Whitesell, L., Lindquist, S.L., 2005. HSP90 and the chaperoning of cancer. *Nat. Rev. Cancer* 5, 761–772.
- Whitesell, L., Santagata, S., Mendillo, M.L., Lin, N.U., Proia, D.A., Lindquist, S., 2014. HSP90 empowers evolution of resistance to hormonal therapy in human breast cancer models. *Proc. Natl. Acad. Sci. U. S. A.* 111, 18297–18302.
- Wickner, S., Maurizi, M.R., Gottesman, S., 1999. Posttranslational quality control: folding, refolding, and degrading proteins. *Science* 286, 1888–1893.
- Wiertz, E.J., Tortorella, D., Bogyo, M., Yu, J., Mothes, W., Jones, T.R., Rapoport, T.A., Ploegh, H.L., 1996. Sec61-mediated transfer of a membrane protein from the endoplasmic reticulum to the proteasome for destruction. *Nature* 384, 432–438.
- Williams, A., Jahreiss, L., Sarkar, S., Saiki, S., Menzies, F.M., Ravikumar, B., Rubinsztein, D.C., 2006. Aggregate-prone proteins are cleared from the cytosol by autophagy: therapeutic implications. *Curr. Top. Dev. Biol.* 76, 89–101.
- Williams, A., Sarkar, S., Cuddon, P., Ttofi, E.K., Saiki, S., Siddiqi, F.H., Jahreiss, L., Fleming, A., Pask, D., Goldsmith, P., O'Kane, C.J., Floto, R.A., Rubinsztein, D.C., 2008. Novel targets for Huntington's disease in an mTOR-independent autophagy pathway. *Nat. Chem. Biol.* 4, 295–305.
- Willisie, J.K., Clegg, J.S., 2002. Small heat shock protein p26 associates with nuclear lamins and HSP70 in nuclei and nuclear matrix fractions from stressed cells. *J. Cell. Biochem.* 84, 601–614.
- Wisniewski, J.R., Zougmor, A., Nagaraj, N., Mann, M., 2009. Universal sample preparation method for proteome analysis. *Nat. Methods* 6, 359–362.
- Włodkowic, D., Skommer, J., McGuinness, D., Hillier, Darzynkiewicz, C.Z., 2009. ER-Golgi network—a future target for anti-cancer therapy. *Leuk. Res.* 33, 1440–1447.
- Wolff, S., Weissman, J.S., Dillin, A., 2014. Differential scales of protein quality control. *Cell* 157, 52–64.
- Won, K.J., Im, J.Y., Kim, B.K., Ban, H.S., Jung, Y.J., Jung, K.E., Won, M., 2017. Stability of the cancer target DDIAS is regulated by the CHIP/HSP70 pathway in lung cancer cells. *Cell. Death. Dis.* 8, e2554.
- Wong, Y.Y., Moon, A., Duffin, R., Barthet-Barateig, A., Meijer, H.A., Clemens, M.J., de Moor, C.H., 2009. Cordycepin inhibits protein synthesis and cell adhesion through effects on signal transduction. *J. Biol. Chem.* 285, 2610–2621.
- Wu, S., Sun, J., 2011. Vitamin D, vitamin D receptor, and macroautophagy in inflammation and infection. *Discov. Med.* 11, 325–335.
- Wu, S., Schalk, M., Clark, A., Miles, R.B., Coates, R., Chappell, J., 2006. Redirection of cytosolic or plastidic isoprenoid precursors elevates terpene production in plants. *Nat. Biotechnol.* 24, 1441–1447.
- Xilouri, M., Stefanis, L., 2015. Chaperone mediated autophagy to the rescue: a new-fangled target for the treatment of neurodegenerative diseases. *Mol. Cell. Neurosci.* 66, 29–36.
- Yamagishi, N., Ueda, T., Mori, A., Saito, Y., Hatayama, T., 2012. Decreased expression of endoplasmic reticulum chaperone GRP78 in liver of diabetic mice. *Biochem. Biophys. Res. Commun.* 417, 364–370.
- Yamawaki, T.M., Arantes-Oliveira, N., Berman, J.R., Zhang, P., Kenyon, C., 2008. Distinct activities of the germline and somatic reproductive tissues in the regulation of *caenorhabditis elegans*' longevity. *Genetics* 178, 513–526.
- Yang, Z., Klionsky, D.J., 2010. Eaten alive: a history of macroautophagy. *Nat. Cell Biol.* 12, 814–822.
- Yang, Y., Ludwig, R.L., Jensen, J.P., Pierre, S.A., Medaglia, M.V., Davydov, I.V., Safiran, Y. J., Oberoi, P., Kenten, J.H., Phillips, A.C., Weissman, A.M., Vousden, K.H., 2005. Small molecule inhibitors of HDM2 ubiquitin ligase activity stabilize and activate p53 in cells. *Cancer Cell* 7, 547–559.
- Yang, F., Chen, W.L., Zheng, M.Z., Yu, G.W., Xu, H.J., Shen, Y.L., Chen, Y.Y., 2011. Heat shock protein 90 mediates anti-apoptotic effect of diazoxide by preventing the cleavage of Bid in hypothermic preservation rat hearts. *J. Heart Lung Transplant.* 30, 928–934.
- Yang, A.W., Sachs, A.J., Nystuen, A.M., 2015. Deletion of Inpp5a causes ataxia and cerebellar degeneration in mice. *Neurogenetics* 16, 277–285.
- Yerbury, J.J., Ooi, L., Dillin, A., Saunders, D.N., Hatters, D.M., Beart, P.M., Cashman, N. R., Wilson, M.R., Ecroyd, H., 2016. Walking the tightrope: proteostasis and neurodegenerative disease. *J. Neurochem.* 137, 489–505.
- Yi, J.J., Ehlers, M.D., 2007. Emerging roles for ubiquitin and protein degradation in neuronal function. *Pharmacol. Rev.* 59, 14–39.
- Yoo, B.C., Kim, S.H., Cairns, N., Fountoulakis, M., Lubec, G., 2001. Deranged expression of molecular chaperones in brains of patients with Alzheimer's disease. *Biochem. Biophys. Res. Commun.* 280, 249–258.
- Yook, S.H., Oltvai, Z.N., Barabasi, A.L., 2004. Functional and topological characterization of protein interaction networks. *Proteomics* 4, 928–942.
- Yoshimori, T., Yamamoto, A., Moriyama, Y., Futai, M., Tashiro, Y., 1991. Baflomycin A1, a specific inhibitor of vacuolar-type H(+)-ATPase, inhibits acidification and protein degradation in lysosomes of cultured cells. *J. Biol. Chem.* 266, 17707–17712.
- Youle, R.J., Narendra, D.P., 2011. Mechanisms of mitophagy. *Nat. Rev. Mol. Cell Biol.* 12, 9–14.
- Young, L., Leonhard, K., Tatsuta, T., Trowsdale, J., Langer, T., 2001. Role of the ABC transporter Mdr1 in peptide export from mitochondria. *Science* 291, 2135–2138.
- Yue, W., Chen, Z., Liu, H., Yan, C., Chen, M., Feng, D., Yan, C., Wu, H., Du, L., Wang, Y., Liu, J., Huang, X., Xia, L., Liu, L., Wang, X., Jin, H., Wang, J., Song, Z., Hao, X., Chen, Q., 2014. A small natural molecule promotes mitochondrial fusion through inhibition of the deubiquitinase USP30. *Cell Res.* 24, 482–496.
- Zhang Wang, H., 2000. MDM2 oncogene as a novel target for human cancer therapy. *Curr. Pharm. Des.* 6, 393–416.
- Zhang, Z., Wang, S., Zhou, S., Yan, X., Wang, Y., Chen, J., Mellen, N., Kong, M., Gu, J., Tan, Y., Zheng, Y., Cai, L., 2014. Sulforaphane prevents the development of cardiomyopathy in type 2 diabetic mice probably by reversing oxidative stress-induced inhibition of LKB1/AMPK pathway. *J. Mol. Cell. Cardiol.* 77, 42–52.
- Zhang, Y., Chen, M.-l., Zhou, Y., Yi, L., Gao, Y.-x., Ran, L., Chen, S.-h., Zhang, T., Zhou, X., Zou, D., Wu, B., Wu, Y., Chang, H., Zhu, J.-d., Zhang, Q.-y., Mi, M.-t., 2015. Resveratrol improves hepatic steatosis by inducing autophagy through the cAMP signaling pathway. *Mol. Nutr. Food Res.* 59, 1443–1457.
- Zhang, J., Cheng, Y., Gu, J., Wang, S., Zhou, S., Wang, Y., Tan, Y., Feng, W., Fu, Y., Mellen, N., Cheng, R., Ma, J., Zhang, C., Li, Z., Cai, L., 2016. Fenofibrate increases cardiac autophagy via FGF21/SIRT1 and prevents fibrosis and inflammation in the hearts of Type 1 diabetic mice. *Clin. Sci.* 130, 625–641.
- Zhao, Q., Wang, J., Levichkin, I.V., Stasinopoulos, S., Ryan, M.T., Hoogenraad, N.J., 2002. A mitochondrial specific stress response in mammalian cells. *EMBO J.* 21, 4411–4419.
- Zhao, Y., Chen, H., Shang, Z., Jiao, B., Yuan, B., Sun, W., Wang, B., Miao, M., Huang, C., 2012. SD118-Xanthocillin X(1), a novel marine agent extracted from penicillium commune, induces autophagy through the inhibition of the MEK/ERK pathway. *Mar. Drugs* 10, 1345–1359.
- Zhao, L., Gao, Y., Cao, X., Gao, D., Zhou, S., Zhang, S., Cai, X., Han, F., Wilcox, C.S., Li, L., Lai, E.Y., 2016. High-salt diet induces outward remodelling of efferent arterioles in mice with reduced renal mass. *Acta Physiol. (Oxf.)* 219 (3), 652–659.
- Zhou, H., Ranish, J.A., Watts, J.D., Aebersold, R., 2002. Quantitative proteome analysis by solid-phase isotope tagging and mass spectrometry. *Nat. Biotechnol.* 20, 512–515.
- Zorzi, E., Bonvini, P., 2011. Inducible hsp70 in the regulation of cancer cell survival: analysis of chaperone induction, expression and activity. *Cancers (Basel)* 3, 3921–3956.
- de Godoy, L.M., Olsen, J.V., de Souza, G.A., Li, G., Mortensen, P., Mann, M., 2006. Status of complete proteome analysis by mass spectrometry: SILAC labeled yeast as a model system. *Genome Biol.* 7, R50.