

Review Article

RECENT TRENDS IN TREATING NEURONAL PROTEINOPATHIES

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Abstract: Neurodegenerative diseases (ND) such as Alzheimer's disease, Parkinson's disease, Huntington disease, amyotrophic lateral sclerosis, Creutzfeldt-Jacob Disease, spongiform encephalopathies, etc. are some of the most devastating human disorders affecting almost half of the world elderly population. All these disorders seem to share the same etiology of existence of cerebral accumulation of misfolded protein aggregates in neuronal inclusions and plaques. These aggregates can initiate a toxic cascade in the cell, causing vesicle dystrafficking, synaptic and cell organelle dysfunction, and ultimately cell death. Currently, there is no treatment available that promises complete cure for these neurodegenerative disorders, which makes it necessary to review the recent research updates for therapeutic insights. Here we review and discuss all major strategies to modulate these toxic inclusions/amyloids. All clinical developments have been elaborately mentioned. Progresses on various pre-clinical drugs against these proteiopathies have also been highlighted.

Keywords: Alzheimer's disease; Neurodegenerative disorders; Protein misfolding; Protein aggregation; Therapeutics.

1. Accumulation of Protein aggregates: A Basic Cause of Neurological Proteinopathies

Neurodegenerative diseases (ND) are some of the most debilitating disorders, affecting thinking, skilled movements, feelings, cognition, and memory. Despite significant dissimilarities in clinical manifestation, this diverse group of disease shares some common features such as their advent late in life, the widespread neuronal loss and synaptic aberrations, and the existence of cerebral accumulation of misfolded protein aggregates in neuronal inclusions and plaques. These deposits are emblematic signature of most of the neurological disorders, and can trigger cascade of events ultimately resulting in synaptic dysfunction and consequent neuronal death with

devastating clinical consequences. However, in each proteinopathy, the distribution and composition of protein aggregate is distinct. In Alzheimer's disease (AD), amyloid plaques formed by β amyloid ($A\beta$) protein are deposited extracellularly in the brain parenchyma, and around the cerebral vessel walls, and neurofibrillary tangles containing aggregates of hyper phosphorylated tau protein are located in the cytoplasm of degenerating neurons (Smith, 1998). The patients with Parkinson's disease (PD) have α -synuclein (aSyn) aggregates deposited in Lewy bodies present in the cytoplasm of neurons of the substantia nigra (SN) in the brain (Schulz-Schaeffer, 2010). On the other hand, polyglutamine-rich (polyQ) version of huntingtin protein deposits inside the nucleus are a typical feature in the brain of patients of Huntington disease (HD) (Walker, 2007), and the brains of humans and animals with diverse forms of transmissible spongiform encephalopathy are illustrated by accretion of protease-resistant

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aggregates of the prion protein (PrP) (Aguzzi and Calella, 2009). Whereas, patients with amyotrophic lateral sclerosis (ALS), superoxide dismutase aggregates are observed in cell bodies and axons of motor neurons (Soto and Estrada, 2008). Recently, ubiquitin positive, tau negative and α -synuclein negative frontotemporal lobar degeneration (FTLD-U), a neurodegenerative disease also has been revealed to be a proteinopathy caused due to ubiquitinated inclusion of a protein TAR DNA binding protein 43 (TDP-43) (Chen-Plotkin et al., 2010). Table 1 shows a list of neuronal proteinopathies along with the associated genes and proteins.

Another common thread among these diseases is mutations in the respective genes, as an underlying cause for protein aggregation. It is commonly believed that mutations lead to accumulation of kinetically trapped intermediates in the folding pathway of the protein (Singh et al., 2010). These intermediates, depending on the activity of the protein quality control system (PQC) may have different consequences in the cell namely, trafficking defect, haploinsufficiency due to enhanced degradation of misfolded protein, aggregation of disordered protein, and amyloid formation (Figure 1). Although the first two categories are not completely excluded, the latter two are the common hallmark of central nervous system (CNS) disorders. Almost all processes of amyloid formation are explained based on the nucleation-polymerization model (Powers and Powers, 2008). According to this model, amyloid formation requires a lag phase (or the nucleation step), log phase (or oligomerization step) and finally a stationary phase (represented by the formation of ordered fibrils).

Oligomers are one of the diverse ultrastructures displayed by protein assemblies, and are usually diffusible, non-fibrillary, small-order aggregates that are believed to be responsible for synaptic aberrations and neuronal death (the toxic oligomer hypothesis) (Ferreira et al., 2007). This “toxic oligomer” hypothesis is supported by the finding that a single-domain antibody can recognize a common conformational epitope that is displayed by several disease-associated proteins, including A β , aSyn, tau protein, prions, and polyglutamine containing

peptides (Jellinger, 2009). The precise size and type of the toxic oligomeric species that is deleterious for the cell is not fully understood (Stefanis, 2012). In a recent study, it has been shown that in the presence of A β trimers, tau protein is abnormally phosphorylated resulting in the breakdown of the cellular scaffolding to produce widespread brain cell degeneration and dysfunction (Handoko et al., 2013). Another reason for toxicity is that the small intermediates created during the oligomer to fibril transition built ‘pore-like’ structures which may disrupt ionic homeostasis, and influence synaptic dysfunction, while large insoluble deposits may function as reservoirs of the oligomers that can lead to synaptic and mitochondrial dysfunction, neuronal apoptosis and cell death (Gadad et al., 2011). This line of thought is further supported by another recent report that demonstrated increased fibrillation rate to correlate well with the enhanced neurotoxicity in aSyn (Wan and Chung, 2012).

In contrast to the generally accepted theory of proteinaceous oligomers/aggregates to be toxic in nature, some investigators suggest that these inclusions may serve a cyto-protective role in certain circumstances. In one such study performed on experimental models of polyglutamine disorders, inclusion formation was observed to be alienated from neuronal toxicity (Saudou et al., 1998). Moreover, interruption of inclusion formation by mutant polyglutamine resulted in enhanced toxicity, suggesting that inclusion formation may be a mechanism to assist in the clearance of misfolded, noxious proteins (Muchowski et al., 2002). However, a defensive role for inclusions does not preclude the possibility that the inherent aggregability of a mutant protein either with itself or with other proteins is important to its toxicity (Taylor et al., 2002).

2. Protein Aggregates are Infectious

It has been suggested that protein oligomer propagation in CNS contributes not only to the spreading and progression of the disease, but also to neurodegeneration, and such prion-like protein aggregate spreading has been seen in AD, PD, FTLD and other NDs (Jellinger, 2012). For

Table 1
List of neuronal proteinopathies, associated protein and related genes

<i>Disease</i>	<i>Associated Protein</i>	<i>Related Genes</i>
Alzheimer's disease, Cerebral β -amyloid angiopathy	Amyloid- β , Tau Protein, ApoE4	APP, Presenilins 1 and 2, APOE ϵ 4, SORL1 and CLU
Amyotrophic lateral sclerosis	Superoxide dismutase 1	SOD1, VCP and FUS
Creutzfeldt Jakob Disease	Prion protein	PRNP
Dentatorubral-pallidoluysian atrophy (DRPLA)	Atrophin 1 (polyglutamine expansion)	ATN
familial amyloidotic neuropathies, Senile systemic amyloidosis	Transthyretin	FAP-I and FAP-II
Familial amyloid polyneuropathy III	Apolipoprotein A-1	FAP-III
Familial british dementia	Abri	ITM2B / BRI2
Familial encephalopathy with neuroserpin inclusion bodies	Neuroserpin	SERPINI1
Frontotemporal Dementia	Tau Protein	MAPT and GRN
Frontotemporal lobar degeneration	TDP-43	MAPT, PGRN and CHMP2B
Hereditary cerebral hemorrhage with amyloidosis	Cystatin C	CST3
Huntington's disease	Huntingtin (polyglutamine expansion)	IT15
Parkinson's disease and other synucleinopathies (multiple)	α -Synuclein	SNCA, PRKN, PINK, LRRK2, DJ-1 and ATP13A2
Spinocerebellar ataxia 17	TATA box-binding protein (polyglutamine expansion)	KCNC3
Spongiform encephalopathies	Prion protein	PRNP
Ubiquitin positive, tau negative and α -synuclein negative Frontotemporal dementia	TAR DNA-binding protein 43	TARBP

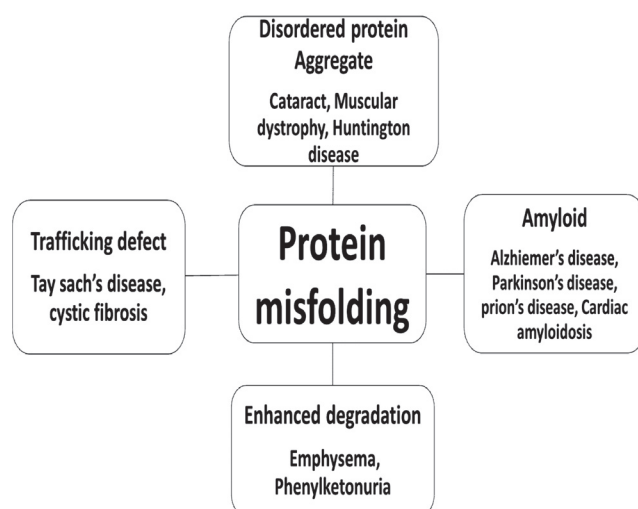


Figure 1: Consequences of Protein misfolding

instance, in brain of mouse models of AD, introduction of A β aggregates had shown the ability of passing between the living cells and infect them (Rosen et al., 2011). It has also been

deciphered that for Alzheimer's disease, the protein, tau spreads through connected areas of the brain by effectively "jumping" from one neuron to another (Adr_newsletter, 2012). In another interesting study, it has also been shown that a single injection of preformed fibrillar aSyn into the striatum of Wt mice not only induces intra-neuronal aSyn accumulation and Lewy body pathology but also enhance PD progression in a stereotypic fashion between connected brain regions hence, potentiating that aSyn promote disease by cell-to-cell transmission (Jellinger, 2011). The propagation of proteinaceous lesions has also been demonstrated in aggregates of SOD1 in ALS, cytosolic aggregates of TDP-43 which are present in ALS and FTL with TDP-43-positive inclusions (Luk et al., 2012). Interestingly, all these proteins have a prion-like domain, which is now considered as one of the alleged factor for the progressive spreading nature of such disorders (Cushman et al., 2010).

Furthermore, in other neurodegenerative diseases, where no infectivity has been definitely confirmed, a seeding activity of protein fibrils may describe the propagation of pathological changes within the affected tissues. These findings suggest that infectivity, which was earlier considered a unique feature of prion disease, may be a more general property of amyloids.

3. Therapeutic advances against proteinopathies

3.1. Immunotherapy

Active and passive immunizations are aimed at inhibiting generation of protein aggregates, or removal of aggregates that are already formed. The concept of passive immunotherapy includes raising monoclonal antibodies against toxic proteins which can then be injected into patients to decrease their amyloid or aggregate burden. Formerly, the so-called “first-in-man” and “first-in-kind” clinical trial for the development of a Parkinson’s vaccine, PD01A has been initiated. This vaccination aims to educate the immune system to generate antibodies directed against α Syn, and hence neutralize its toxic impact (PRNewswire, 2012). However, for Alzheimer’s disease, several types of immunotherapies directed against $A\beta$ peptide are under investigation, including direct immunization with synthetic intact $A\beta$ 1-42, active immunization involving the administration of synthetic fragments of $A\beta$ peptide conjugated to a carrier protein and passive administration with monoclonal antibodies directed against $A\beta$ peptide (Delrieu et al., 2012). The first clinical trial was performed with anti- $A\beta$ vaccine, AN1792 (Morgan, 2006), but due to development of meningoencephalitis in a small percentage of patients all study dosing was halted. However, immunization with $A\beta$ 1-42 was found efficient in clearing amyloid plaques in patients with AD, and prevented progressive neuro-degeneration (Delrieu et al., 2012). Several monoclonal antibodies for AD had also been tested (Moreth et al., 2013): bapineuzumab (AAB-001), solanezumab (LY-2062430), PF-04360365, GSK-933776, R-1450 (RO-4909832), and MABT-5102A. However, bapineuzumab and solanezumab had failed to meet clinical endpoints for Alzheimer’s

disease (for details see review Chowhan and Singh, 2012). Researchers are currently planning to test an $A\beta$ -clearing drug in older people thought to be in the pre-symptomatic stage of Alzheimer’s (Alzheimer research forum news, 2013).

Recently, a therapeutic monoclonal antibody that is reactive with all types of amyloid has been developed by targeting Serum Amyloid A protein (SAP) because it is a universal constituent of all amyloid deposits and an excellent immunogen. To ensure that anti-SAP antibodies reach residual SAP in the amyloid deposits, circulating human SAP can be depleted by the bis-d-proline compound, CPHPC. This novel combined therapy has shown encouraging results in mice models and is expected to be effective for all forms of human systemic and local amyloidosis (Bodin et al., 2010).

3.2. Anti-oxidative therapy

It has been known that one of the basic causes of the intra-cellular toxicity of protein aggregates is due to oxidative stress leading to the generation of many reactive oxygen species (ROS) (Tabner et al., 2001). ROS are generally harmful, which makes antioxidant defenses essential, and makes antioxidants as promising therapeutic agents. These agents can be classified on the basis of their mode of action (a) compounds that prevent the formation of free radicals; (b) compounds that chemically interfere with formed free radicals; and (c) compounds which limit the damage extent to the cell by alleviating the secondary metabolic burden of increased levels of free radicals. Indeed, the increase in antioxidant glutathione (GSH) availability in neurons infected by protein aggregates is a logical therapeutic target in neural impairment related to oxidative stress. Recently L-dopa-GSH co-drugs have been developed which can easily cross blood brain barrier, and has shown ability to protect against the oxidative stress deriving from autoxidation and the monoamine oxidase mediated metabolism of Dopamine (Cacciatore et al., 2012). Methionine sulfoxide reductase (MsrA), an antioxidant repair enzyme had also been shown to assist the inhibition of α Syn fibrillation, and neurotoxicity by repairing oxidatively damaged protein and by

depleting ROS (Liu et al., 2008). Antioxidant therapy has also been tried to treat AD either by increasing the pool of endogenous antioxidants (e.g. vitamins, co-enzyme Q10 or melatonin) or by the intake of dietary antioxidants, such as phenolic compounds of flavonoid or non-flavonoid type (Gilgun-Sherki et al., 2003). However, in clinical trials these agents had shown limited success, which may be because of poor distribution or agent's inherent difficulty to cross the brain-blood barrier.

3.3. Modulating PQC mechanisms

3.3.1. Ubiquitin Proteasome system

Proteasome is one of the major therapeutic targets as its inhibition is often reported to increase the risk of neurodegeneration development (Richardson et al., 2005). Thus, activating proteasome is considered an efficient way to decrease the load of aggregated protein species in the cell. This could be achieved by use of endogenous activators of the 20S proteasome (PA700, PA200 and PA28) or by overexpressing the proteasome maturation protein (POMP), the accessory factor for proteasome assembly in humans (Huang and Figueiredo-Pereira, 2010). Using genome-wide association studies, negative regulator of ubiquitin-like protein 1 (NUB1) has been identified as a modifier of mutant htt abundance. In fact, NUB1 overexpression was seen to lower mutant htt in neuronal models, and rescue them from cell death by enhancing its polyubiquitination and proteasomal degradation (Lu et al., 2013). This study has made investigators hope that Interferon- β , a modulator of NUB1 can be used as a potential therapeutic agent in HD treatment.

3.3.2. Chaperone up-regulation

Up-regulation of molecular chaperones is considered to inhibit protein aggregation by facilitating the refolding of misfolded proteins or by directing the aggregated proteins to cellular clearance pathways. Using various cellular models and *in vitro* studies; upregulation of heat shock proteins like Hsp70, Hsp40 and Hsp27 have been shown to attenuate aSyn fibril formation (Rochet et al., 2012). Also, Hsp70 overexpression is found to be effective treatment in mouse model

of type 1 spinocerebellar ataxin (SCA1) disease and fly model of HD (Chaudhuri and Paul, 2006). Interestingly, intermediate concentrations of molecular chaperone Hsp104 are reported to propagate yeast non-Mendelian factor [psi+], analogue of mammalian prions, while overproduction or inactivation of Hsp104 cause loss of [psi+]. These results suggest that controlling Hsp104 expression may provide a therapy against prion disease (Chernoff et al., 1995).

Chemical chaperones are also known to have the capability to correct misfolded protein conformations, prevent their excessive degradation and consequently promote their intracellular functional activity by influencing the rate or fidelity of the protein folding reaction (Singh et al., 2011). They have been shown to reverse the intracellular retention of several different misfolded proteins such as CFTR (Cystic fibrosis transmembrane conductance regulator), prion protein, AAT, p53, etc. (Chaudhuri and Paul, 2006). In cystic fibrosis, the $\Delta F508$ mutation can be rescued by treating cells with chemical chaperones like glycerol, dimethyl sulfoxide (DMSO), trimethylamine-N-oxide (TMAO) and deuterated water (Brown et al., 1996). However, effects of some chaperones like TMAO on protein aggregation are concentration dependent. TMAO at higher concentration (>3M) leads to tight folding of aSyn eventually forming stable oligomers, and decreased fibrillation rate, but, at low concentrations it forms partially folded intermediate which accelerates fibrillation (Fink, 2006). Because of these complex effects of chemical chaperone on aggregation kinetics, utilizing it for treatment will require very stringent investigations.

3.3.3. Autophagy

Rapamycin is a potent autophagy inducer that works via inhibition of mTOR (mammalian target of rapamycin) kinase activity. In cell models rapamycin treatment has been shown to increase the clearance of many toxic aggregation prone proteins such as mutant ataxin, aSyn, htt and tau (Hochfeld et al., 2013). In case of fly and mouse models of HD, it effectively cleared mutant huntingtin fragments, reduced aggregate

formation and protected against toxicity. These effects produced were solely based on autophagy induction as this drug was not much effective in the fly models of various proteinopathies with reduced activity of autophagy genes (Wang et al., 2009). Rapamycin analogue CCI-779 had also been shown to reduce levels of toxin proteins in drosophila models of HD and Spinocerebellar ataxia type-3 (Menziés et al., 2010; Ravikumar et al., 2004). Since, mTOR is also involved in ribosome biogenesis and protein translation, inhibiting its activity can lead to deleterious side-effects in long-term use (Kranz et al., 2013). Therefore, novel autophagy inducers have been introduced that work via decreasing inositol triphosphate levels, such as lithium, sodium valproate, carbamazepine, xestospongine B, and Rilmenidine. They have been shown to reduce toxicity and clear aggregates in fly models of HD (Hochfeld et al., 2013). However, rilmenidine being the drug with minimal side-effects is currently being tested in safety trial with HD patients (Rose et al., 2010).

3.4. Reduction/Inhibition of amyloid formation

3.4.1. RNA silencing or Anti-sense therapy

The theory behind using Anti-sense therapy is that the RNAi mediated allele-specific silencing of the disease associated gene will suppress the expression of the variant protein, and leave the Wt protein at heterozygous expression level. The first clinical trial of intrathecal delivery of an antisense oligonucleotide, ISIS 333611 against mutant SOD1 messenger RNA has revealed this antisense therapy to be safe in ALS patients (Miller et al., 2013). It is believed that the gene silencing strategy cannot be used in diseases where a PQC system is defective or where its efficiency has declined with age, such as in most cases of Parkinson and Alzheimer diseases (Gregersen, 2006). But, recently a new specific SOFA-Hepatitis Delta Virus ribozyme has been engineered that was exploited as RNA silencing tool against amyloid- β precursor protein (APP) gene in neuronal cell models, and demonstrated to be effective in decreasing APP mRNA and protein levels, as well as A β levels (Ben Aissa et al., 2012). Adeno-associated virus-mediated delivery of anti aSyn ribozyme has also been

investigated both *in vitro* and *in vivo* (Hayashita-Kinoh et al., 2006).

3.4.2. Stabilization of fibril precursor protein

It is known that amyloid formation requires conversion of respective precursor protein into a different conformation with high β structure to form fibril precursor protein which then accumulate and propagate via seeding reaction (Kumar and Udgaonkar, 2010). Speculatively, if we stabilize this soluble precursor protein by binding it to some pharmaceutical compounds, then this process of amyloidosis may be inhibited. This has been explored in systemic transthyretin amyloidosis with various drugs like diflunisal and tafamidis etc (Banyersad et al., 2012). Higher affinity superstabilizer, palindromic ligands has also been developed that can bind to native transthyretin and inhibit amyloid formation (Kolstoe et al., 2010). Few researchers are also developing small peptides to specifically bind to the pathogenic protein and block and/or reverse its abnormal conformational change (Estrada and Soto, 2006).

Several other small molecular compounds that have the potential to inhibit protein aggregation in common have also been discovered. These include 2, 4-dinitrophenol, di- and tri-substituted aromatic molecules, curcumin, cyclodextrin derivatives, hematin, meclocycline, indomethacin, and Congo red. Their inhibitory effect involves stabilization of the native fold of potentially amyloidogenic proteins or inhibition of their oligomerization or fibrillation processes (Mirov et al., 1996).

3.4.3. Modulation of cellular enzymes

A recent finding of a specific mutation in the gene for APP that can significantly decrease its cleavage by beta-secretase, and confer resistance to the development of AD in patients has reinforced the hypothesis that inhibition of A β cleaving secretases is an important disease modifying approach (Jonsson et al., 2012). Following this trend, Merck USA has started largest phase 3 clinical trial in 2010 of a gamma-secretase inhibitor drug, semagacestat for prodromal AD but failed due to its adverse effects seen on worsening of cognition in patients

(World_News, 2010). Interestingly, phase-II clinical trial of MK8931, a BACE-1 (β -secretase APP cleaving enzyme) was found successful in inhibiting AD progression (Business_wire, 2012).

Anti-cholinesterase inhibitors are currently approved by Food and Drug Association for AD treatment. They are believed to increase the levels of the neurotransmitter acetylcholine, which is depleted in AD brains or antagonize NMDA-type glutamate receptors to prevent aberrant neuronal stimulation (Birks, 2006). Since hyperphosphorylated tau is present in the neurofibrillary tangles in brains of AD patients, inhibitors of tau kinases are considered to be important therapeutic target (Mazanetz and Fischer, 2007). However, so far no tau kinase inhibitor appears to have advanced to a late-phase clinical trial for AD (Huang and Mucke, 2012).

Recently, viral vector-mediated increase in glucocerebrosidase enzyme (GCase) activity has been reported to reverse aSyn related pathological features and improve behavioural function in the D409V mouse model of gaucher disease (Sardi et al., 2011). It is believed that correcting GCase deficiency can directly influence SNCA and other protein metabolism in the brain in vivo (Schapira and Gegg, 2013).

3.5. Antibiotics in Proteinopathies

The tetracyclines are a family of broad-spectrum antibiotics that include tetracycline, doxycycline and minocycline. Studies done with transgenic mice models had revealed tetracycline to inhibit amyloid formation by hampering misfolding of soluble oligomers, and hence delay various neurodegeneration (Aitken et al., 2010). Tetracycline was observed to inhibit the conversion of prion protein, PrP^C into PrP^{Sc} form and hinder prion aggregation (Tagliavini et al., 2000). Minocycline has been shown to prevent A β and tau protein accumulation in AD models (Noble et al., 2009). Furthermore, doxycycline displayed prolonged survival and delayed onset of disease in animal models of prions (Forloni et al., 2002).

3.6. Modulation of polyamines levels

Effects of various naturally polyamines (spermine, spermidine and putresine) have been shown to alter protein aggregation processes

(Chowhan and Singh, 2012) indicating that these molecules might be of use as a therapeutic agent for neurodegenerative diseases. A recent gene expression analysis done on differentially affected brainstem regions of PD patients had implicated that higher polyamine levels are one of the causes for induction of aSyn aggregation (Lewandowski et al., 2010). Furthermore, it has also been reported that the pathological length polyglutamine proteins like mutated htt proteins, promote their own aggregation and cell death upon increasing the polyamine production pathway (Chowhan and Singh, 2012). These pieces of evidences indicate that the reduction of polyamine levels might be a potential therapeutic target for PD and HD.

4. Summary

Ongoing research in therapeutic interventions for neuronal proteinopathies is focused on various treatment approaches including immunotherapy, antioxidative therapy, modulation of polyamines and cellular enzyme levels, anti-sense therapy, antibiotic therapy, etc. However, none of them has been proved to be sufficient enough to provide cure against protein aggregation induced neurodegeneration.

Particularly, immunotherapy, antioxidative therapy and RNA silencing strategies have failed to work in clinical trials and more extensive studies are required to increase their efficiency. It appears that modulation of the levels of specific cellular enzyme (for instance, GCase for PD, Acetylcholine esterase for AD, etc.) has great therapeutic potential, but clinical trials are yet to be done. Developing strategies to target genes required for polyamine and osmolyte biosynthesis might stand as one of the best approach to control proteinopathies.

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Abbreviations

A β , Amyloid- β protein; AD, Alzheimer's disease; ALS, Amyotrophic lateral Sclerosis; APP, Amyloid- β precursor

protein; aSyn, Alpha-synuclein; CFTR, Cystic fibrosis transmembrane conductance regulator; FTL, Frontotemporal lobar degeneration; HD, Huntington disease; mTOR, mammalian target of rapamycin; ND, Neurodegenerative diseases; PD, Parkinson disease; PQC, Protein quality control system; PrP, Prion Protein; ROS, Reactive oxygen species; Wt, Wild type.

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