The cell biology of aging

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ABSTRACT **One of the original hypotheses of organismal longevity posits that aging is the natural result of entropy on the cells, tissues, and organs of the animal—a slow, inexorable slide into nonfunctionality caused by stochastic degradation of its parts. We now have evidence that aging is instead at least in part genetically regulated. Many mutations have been discovered to extend lifespan in organisms of all complexities, from yeast to mammals. The study of metazoan model organisms, such as *Caenorhabditis elegans*, has been instrumental in understanding the role of genetics in the cell biology of aging. Longevity mutants across the spectrum of model organisms demonstrate that rates of aging are regulated through genetic control of cellular processes. The regulation and subsequent breakdown of cellular processes represent a programmatic decision by the cell to either continue or abandon maintenance procedures with age. Our understanding of cell biological processes involved in regulating aging have been particularly informed by longevity mutants and treatments, such as reduced insulin/IGF-1 signaling and dietary restriction, which are critical in determining the distinction between causes of and responses to aging and have revealed a set of downstream targets that participate in a range of cell biological activities. Here we briefly review some of these important cellular processes.**

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INTRODUCTION

To achieve lifespan extension in humans, we must understand which cellular programs are responsible for aging and how their dysregulation directs senescence and decline. In many degenerative diseases associated with aging, the specific, proximal etiologies of the disease, such as protein aggregation, stem from dysregulation of processes responsible for regulation of healthy aging, such as autophagy and proteostasis. Addressing the role of such cellular processes not only with age but also in the context of Alzheimer's disease and Parkinson's disease will provide valuable insight into the fundamental biology of aging, as well as directly aid in increasing the quality of life of a population aging at high risk for these diseases.

Here we review a number of crucial processes responsible for regulating cellular health in aging and the link between many of those diseases and aging. Cellular health is controlled at various points in the cell, starting in the nucleus through chromosome structure/organization, transcriptional regulation, and nuclear export/import, ranging outward to protein translation and quality control, autophagic recycling of organelles, maintenance of cytoskeletal structure, and finally maintenance of the extracellular matrix and extracellular signaling (Figure 1). Each regulatory system receives information from every other system, resulting in an intricate interplay of regulation controlling the aging of the cell.

CHROMOSOME AND TELOMERE REGULATION

Telomeres cap each chromosome with a repetitive sequence, protecting chromosomes from damage caused by shortening (due to end-replication problems on the lagging strand and oxidative damage; Richter and von Zglinicki, 2007) at each replicative cycle (Richter and von Zglinicki, 2007). Telomere length, which is inversely correlated with lifespan (Gomes *et al.*, 2011), and rate of accumulation of short telomeres are predictors of lifespan in zebra finch and mice (Heidinger *et al.*, 2012; Vera *et al.*, 2012), and the longest-lived organisms have long telomeres (Heidinger *et al.*, 2012). Long telomeres are linked to increased stress resistance in *Caenorhabditis elegans* (Park *et al.*, 2010), and increased stress in humans leads to increased telomere shortening (Shalev *et al.*, 2013), suggesting that

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Abbreviations used: CMA, chaperone-mediated autophagy; DMQ, demethoxyubiquinone; DR, dietary restriction; ECM, extracellular matrix; ER, endoplasmic reticulum; ERAD, ER-associated decay; ETC, electron transport chain; IGF-1, insulin-like growth factor 1; IIS, insulin/IGF-1 signaling; NPC, nuclear pore complex; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; TOR, target of rapamycin; UPR, unfolded protein response.

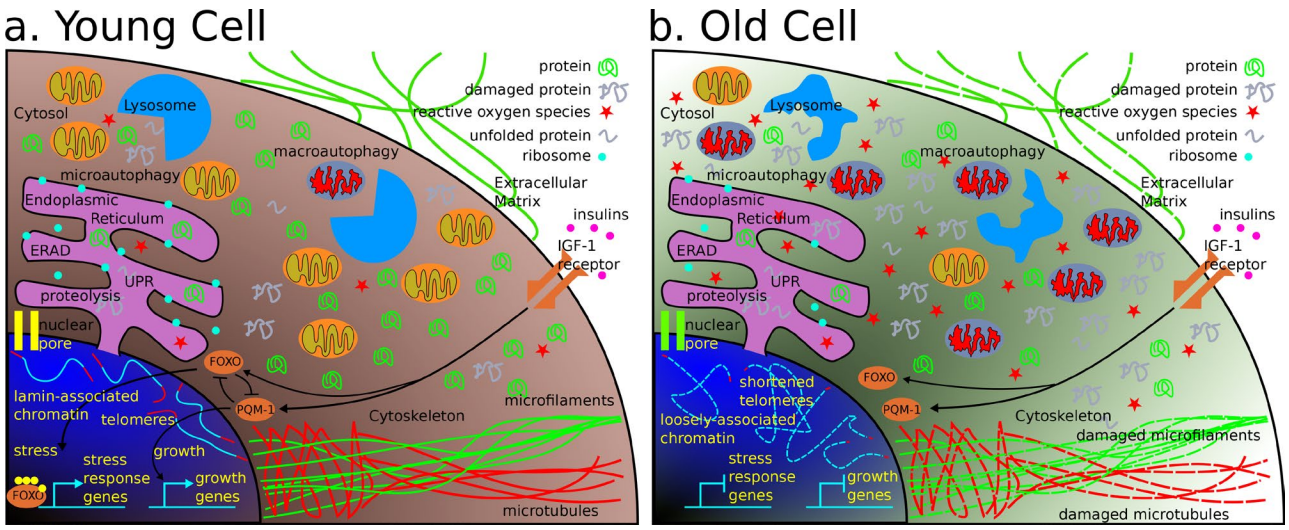

FIGURE 1: Major features of cellular aging. As the cell ages, translational defects and entropy progressively increase the amount of cellular damage, and clearance and quality control mechanisms grow less effective. (a) In a young cell, most organelles are very healthy, and when proteins are translated and misfolded or acquire damage in the cytosol, they are cleared either by ERAD (in the ER) or autophagy (in the cytosol). When organelles become too damaged, they are degraded to component parts by macroautophagy. (b) In an older cell, accumulated damage leads to a less healthy cell. ROS build up from damaged mitochondria and contribute to a greater fraction of the proteome consisting of damaged proteins and protein aggregates.

regulation of telomere length is predictive of longevity and influenced by longevity-related factors. Mammalian cell cultures enter senescence after 40–60 divisions (Hayflick, 1965), known as the Hayflick limit or replicative senescence (Hayflick and Moorhead, 1961). Shortening of the telomeres at each replication (Olovnikov, 1996; Shay and Wright, 2000) leads to cellular senescence (Harley *et al.*, 1992). This telomere shortening has been implicated in many age-related phenotypes, such as decline in innate immunity (Effros and Pawelec, 1997; Effros *et al.*, 2005), and even correlates with protein diseases, such as Alzheimer's disease (Panossian *et al.*, 2003).

The sirtuins *SIR3* and *SIR4* are associated with lifespan and nuclear organization in *Saccharomyces cerevisiae* (Kaeberlein *et al.*, 1999), regulating nucleolus fragmentation in aging yeast (Lewinska *et al.*, 2014) and leading to a relocation of the telomeres to the nucleolus in old cells (Lo *et al.*, 2006) and progressive dysregulation of the cell. Nuclear shape degrades, and heterochromatin becomes dissociated from the periphery in aged worms (Haithcock *et al.*, 2005) but these processes are slowed in long-lived insulin/insulin-like growth factor 1 (IGF-1) signaling (IIS) mutants (Haithcock *et al.*, 2005).

TRANSCRIPTIONAL REGULATION

Transcriptional regulation is key in coordinating the activation of many genes to extend lifespan. Most cellular processes that affect longevity are regulated at the transcriptional level through highly conserved signaling pathways (Kenyon, 2010a) including the IIS (Kenyon *et al.*, 1993; Ogg *et al.*, 1997; Lin *et al.*, 2001; Lee *et al.*, 2003; McElwee *et al.*, 2003; Murphy *et al.*, 2003) and target of rapamycin (TOR) pathways (Jia *et al.*, 2004; Kaeberlein and Shamieh, 2010), which regulate gene expression in response to stress and nutrient availability stimuli (Jia *et al.*, 2004). Regulation by the IIS pathway in *C. elegans* involves primarily the PQM-1 and DAF-16/FOXO transcription factors, which localize to the nucleus in a mutually exclusive manner (Tepper *et al.*, 2013) and promote either growth/development or stress response/longevity, respectively (Kenyon *et al.*, 1993; Lin *et al.*, 1997, 2001; Ogg *et al.*, 1997; Lee *et al.*, 2003; McElwee *et al.*, 2003; Murphy *et al.*, 2003; Tepper *et al.*, 2013); their mutually exclusive nuclear localization breaks down with age (Tepper *et al.*, 2013). The downstream targets of these pathways include genes implicated in regulation of cellular health (Murphy *et al.*, 2003). The heat shock factor HSF-1 is responsible for regulation of cytoskeletal integrity (Baird *et al.*, 2014), heat stress resistance (Hsu *et al.*, 2003; Morley and Morimoto, 2004), and protein quality control (Morley and Morimoto, 2004), all of which contribute to its effect on *C. elegans* longevity (Hsu *et al.*, 2003; Morley and Morimoto, 2004; Baird *et al.*, 2014). The Nrf/SKN-1 transcription factor mediates longevity (Tullet *et al.*, 2008; Robida-Stubbs *et al.*, 2012), as well as regulation of extracellular collagen matrices (Ewald *et al.*, 2015).

NUCLEAR TRAFFICKING AND ORGANIZATION

The eukaryotic nuclear pore complex (NPC), one of the most complex molecular devices, serves an essential role in exporting messages and proteins into and out of the nucleus and is critical to many aspects of cellular regulation and health (Nigg, 1997; D'Angelo and Hetzer, 2008; Toyama *et al.*, 2013), including tumor suppression (Pinkston-Gosse and Kenyon, 2007). mRNA is shuttled to the cytoplasm through the NPC (Cole and Scarcelli, 2006), and nuclear trafficking decreases with cellular senescence, leading to hyporesponsiveness to cellular stresses (Kim *et al.*, 2010). NPC proteins are long lived (Rout *et al.*, 2000), rendering them susceptible to age-related damage. Progressive degradation of nucleoporins further contributes to aging through leaking of proteins and messages (D'Angelo *et al.*, 2009).

Organization inside the nucleus is also important for cellular health. Incorrect organization of lamins at the nuclear envelope (Muchir *et al.*, 2000; Mounkes *et al.*, 2003), which spatially organize the genome, cause laminopathies, including "premature-aging" diseases (Broers *et al.*, 2006); for example, Hutchinson–Gilford progeria patients display extreme aging phenotypes while very young (Scaffidi and Misteli, 2005). Genome instability caused by laminopathies renders DNA sensitive to damaging agents, causing higher rates of breaks, relocations, and aneuploidies (Liu *et al.*, 2005a). Proper

regulation of nuclear lamins is essential for maintenance of tissues in healthy adults (Mounkes *et al.*, 2003; Hutchison and Worman, 2004), and lamin damage results in increased sensitivity to reactive oxygen species (ROS; Pekovic *et al.*, 2011), leading to oxidative damage (Pekovic *et al.*, 2011). Laminopathy-driven altered nuclear architectures are also observed in patients with cardiomyopathies (Muchir *et al.*, 2004; Nikolova-Krstevski *et al.*, 2011) and in aged (Zuo *et al.*, 2012) and damaged (Park *et al.*, 2011) stem cells.

PROTEIN TRANSLATION

Protein translation is a critical control mechanism in longevity regulation; down-regulation of translation upon reduced nutrient availability (Evans *et al.*, 2011) extends lifespan in many organisms (Syntichaki *et al.*, 2007), including worms (Hansen *et al.*, 2007) and flies (Partridge *et al.*, 2011), via TOR signaling in dietary restriction (DR) regimes (Hansen *et al.*, 2007; Katewa and Kapahi, 2011) and IIS/FOXO signaling (Hansen *et al.*, 2007). Loss of the *C. elegans* eukaryotic initiation factor 4F (eIF-4F)/*ife-2* extends lifespan (Hansen *et al.*, 2007), as does loss of ribosomal-protein S6 kinase (S6K)/*rsks-1* (Hansen *et al.*, 2007). Loss of TOR signaling, eIF-4E/*ife-2*, or S6K/*rsks-1* also increases heat stress resistance (Hansen *et al.*, 2007).

PROTEOSTASIS

Maintenance of protein quality, or proteostasis, is critical for the health and longevity of the cell. Proteostasis ensures a supply of high-quality protein by culling misfolded and damaged proteins from the cellular pool and replacing them with newly formed proteins (Powers *et al.*, 2009). Molecular chaperones direct amino acid chains to the correctly folded state (Hartl and Hayer-Hartl, 2002; Dobson, 2003; Kim *et al.*, 2013), direct misfolded proteins to degradation pathways (Bukau *et al.*, 2006; Hartl *et al.*, 2011), and refold misfolded proteins (Wickner *et al.*, 1999) before they enter the wider population of cellular proteins. Disruption of proteostasis alters the proteome (David *et al.*, 2010; Walther *et al.*, 2015), is hastened by stress (Ben-Zvi *et al.*, 2009), and signals organismal aging in *C. elegans* (Ben-Zvi *et al.*, 2009; David *et al.*, 2010) but is forestalled by HSF-1 and DAF-16/FOXO activity (Ben-Zvi *et al.*, 2009). IIS and FOXO are critical regulators of healthy aging across eukaryotes (Demontis and Perrimon, 2010; Haigis and Yankner, 2010), increasing resistance to oxygenation damage (Adachi *et al.*, 1998), decreasing accumulation of carbonylated proteins (Adachi *et al.*, 1998), and slowing proteome decline (Walther *et al.*, 2015). Chaperones, including small heat shock proteins, as well as superoxide dismutase and catalase, are upregulated in long-lived *daf-2* mutants by DAF-16/FOXO (Murphy *et al.*, 2003) and HSF-1 (Hsu *et al.*, 2003; Morley and Morimoto, 2004; Ben-Zvi *et al.*, 2009). Increased proteostasis is necessary for the longevity of *daf-2* mutants (Matilainen *et al.*, 2013). Protein aggregation is decreased in human cells with reduced IIS (O'Neill *et al.*, 2012), and reducing IGF-1 signaling in mice slows the onset of dysregulation of proteostasis, increasing healthy aging (Ben-Zvi *et al.*, 2009).

Many age-related diseases, including Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis, are associated with aggregated and misfolded proteins. Conformational defects allow the seeding of protein aggregates (Polymeropoulos *et al.*, 1997), which can expand into macroscopic plaques (Jarrett *et al.*, 1993), leading to tissue degeneration. Thus proper regulation of proteostasis is strongly correlated with healthy aging (Balch *et al.*, 2008).

UNFOLDED PROTEIN RESPONSE

The unfolded protein response (UPR) monitors quality of unfolded amino acid chains primarily in the endoplasmic reticulum (ER), where much of translation occurs (Ron and Walter, 2007), and is linked with ER-associated protein quality regulation processes, particularly the ER-associated degradation (ERAD) pathway (Travers *et al.*, 2000). UPR dysregulation is linked to several diseases (Walter and Ron, 2011), especially age-related protein conformational diseases such as Alzheimer's and Parkinson's (Yoshida, 2007). Low nutrient sensing through the TOR pathway (Vellai *et al.*, 2003), rapamycin treatment (Harrison *et al.*, 2009), and low insulin signaling regulate the UPR (Jia *et al.*, 2004), whereas the protein/histone deacetylase SIR-2.1 acts in insulin signaling–dependent (Berdichevsky *et al.*, 2006) and –independent manners to regulate the UPR (Viswanathan *et al.*, 2005). In *C. elegans* IIS mutants, the ER stress response is up-regulated by XBP-1 and the DAF-16/FOXO (Henis-Korenblit *et al.*, 2010), leading to better clearance of damaged proteins by UPR. ER stress in mouse fibroblasts also increases the UPR through Xbp-1 (Akha *et al.*, 2011).

AUTOPHAGY

In much the same way as proteostasis is maintained through degradation and resynthesis of proteins, organelles are consumed by the cell through autophagy (Klionsky and Emr, 2000). In macroautophagy, the damaged organelle is encased in a double membrane to form the autophagosome, which traffics to the lysosome, where the organelle is broken down (Cesen *et al.*, 2012). In microautophagy, cytosol is taken up in bulk directly to the lysosome (Massey *et al.*, 2006), and in chaperone-mediated autophagy (CMA), specific proteins are targeted for transport to the lysosome (Cuervo *et al.*, 2005; Massey *et al.*, 2006; Mizushima *et al.*, 2008).

Autophagy is required for longevity paradigms across many species (Gelino and Hansen, 2012), including DR (Jia and Levine, 2007; Hansen *et al.*, 2008), and IIS mutants (Melendez *et al.*, 2003), and inhibition of autophagy generates hallmarks of aging at an accelerated rate (Cuervo *et al.*, 2005; Rubinsztein *et al.*, 2011). Dependence on autophagy for longevity suggests that autophagic clearing of damaged proteins, protein aggregates, organelles, lipids, and other cargo is required to provide new raw material (Kenyon, 2010b) for a healthy cell.

Autophagy plays a complex role in neurodegenerative disease as well (Nixon, 2013). In Parkinson's disease brains, autophagy is down-regulated (Alvarez-Erviti *et al.*, 2010) and CMA is dysregulated (Massey *et al.*, 2006). However, autophagy is up-regulated in the brains of patients with Alzheimer's disease (Lipinski *et al.*, 2010) and ALS (Sasaki, 2011). Regulatory differences occur at different steps in the autophagy pathway, suggesting a complex role of autophagy in maintaining health.

MITOCHONDRIAL FUNCTION, BIOGENESIS, AND MITOPHAGY

Maintenance of mitochondrial function is critical for cellular and organismal health, due to both the critical nature of their primary role in energy generation for the cell (McBride *et al.*, 2006) and toxic by-products and side and intermediate products of energy generation (Richter *et al.*, 1988), generating free radicals that cause damage (Harman, 1972). Mitochondria have their own mechanisms for proteostasis and regulation of unfolded proteins (Haynes and Ron, 2010), through chaperones and ubiquitin-mediated degradation (Kriegenburg *et al.*, 2012). Mitophagy (mitochondrial autophagy) and mitochondrial biogenesis are coordinated and extended with age in *C. elegans daf-2* mutants (Pinkston-Gosse and Kenyon, 2007) through the activity of DCT-1, a DAF-16/FOXO target, and the Nrf2 homologue SKN-1 (Palikaras *et al.*, 2015).

Defects in the oxidative phosphorylation chain extend lifespan in *C. elegans* (Kayser *et al.*, 2004) and mice (Lapointe and Hekimi, 2008). Mutants in mitochondrial function, such as the DMQ

hydroxylase *clk-1* in *C. elegans* (Ewbank *et al.*, 1997), affect biological timing, including longevity, development, and reproduction (Branicky *et al.*, 2000; Stepanyan *et al.*, 2006), which is also true in mice (Liu *et al.*, 2005b). Mutations in the *C. elegans clk-1* gene lead to modest lifespan gains at the expense of small and unhealthy mutants (Stepanyan *et al.*, 2006) in a manner independent of more robust lifespan gains from insulin signaling mutations (Stepanyan *et al.*, 2006). The mechanism is hypothesized to be related to ROS (Harman, 1972) but is incompletely understood (Shibata *et al.*, 2003). However, increased expression of certain electron transport chain (ETC) components increases lifespan in *Drosophila* (Zid *et al.*, 2009). This extension seems to be linked to the relative expression of different ETC components and the buildup of oxidative intermediates in the mitochondria (Rea *et al.*, 2007). By contrast, *C. elegans* IIS mutants display healthier organelles overall by well-regulated autophagy (Melendez *et al.*, 2003; Rubinsztein *et al.*, 2011), resulting in overall better health than *clk-1* mutants.

Mitochondria have been associated with diseases stemming from direct pathology (Boffoli *et al.*, 1994), aging-related diseases (de Grey, 2004), and neurological diseases such as Alzheimer's and Parkinson's (Devi and Anandatheerthavarada, 2010). Defects in autophagy are linked to multiple myopathies such as Pompe and Danon diseases (Masiero *et al.*, 2009), primarily due to the highly toxic nature of decaying mitochondria (Wu *et al.*, 2009) enriched in mammalian muscle (Wenz *et al.*, 2009; Wu *et al.*, 2009). Beyond the consequences of disruption of energy production, mitochondrial decay puts the cell at risk of leaking ROS and mitochondria-specific enzymes into the cytosol, generating stress that may lead to apoptosis (Green *et al.*, 2011).

CYTOSKELETAL INTEGRITY

The cytoskeleton is critical in maintaining cell shape and integrity, and its dysregulation is an indicator of cellular aging (Gourlay and Ayscough, 2005). In yeast, actin turnover increases with increased ROS (Gourlay *et al.*, 2004) and disruption of the Ras pathway with age (Ho and Bretscher, 2001). ROS (Gourlay and Ayscough, 2005), ischemia (Genesca *et al.*, 2006), ultraviolet treatment (Kulms *et al.*, 2002), or introduction of a toxin (Korsnes *et al.*, 2007) can lead to cytoskeletal stress, which activates apoptosis (Ashkenazi and Dixit, 1998). The SM22 actin filament cross-linking protein (Prinjha *et al.*, 1994) has been identified as a biomarker of aging across a range of organisms, including yeast, *Drosophila*, and humans (Prinjha *et al.*, 1994; Camoretti-Mercado *et al.*, 1998). In worms, loss of *pat-10*/troponin leads to cytoskeletal collapse, whereas overexpression leads to enhanced cytoskeletal stability and stress resistance (Baird *et al.*, 2014).

Cytoskeletal disruptions can cause degenerative neural diseases characteristic of aging. The apolipoprotein E4 (apoE4) is a risk indicator for early-onset Alzheimer's disease in humans (Sando *et al.*, 2008). ApoE4 is proteolyzed in neurons, forming toxic fragments that interact with the actin cytoskeleton (Mahley *et al.*, 2006), hastening cell aging and oxidative stress (Aksenov *et al.*, 2001), and eventually triggering decline and apoptosis. Par-4, which is increased in neurons of Alzheimer's patients (Guo *et al.*, 1998), interacts with Dlk to form stress fibers and cause apoptosis (DiazMeco *et al.*, 1996; Sells *et al.*, 1997; Vetterkind *et al.*, 2005). Hyperphosphorylation of the microtubule-associated tau protein leads to formation of neurofibrillary tangles (Braak and Braak, 1991), another hallmark of Alzheimer's disease, and inhibits proper proteasome activity (Keller *et al.*, 2000a,b), allowing tangles to grow unchecked (Keck *et al.*, 2003).

THE CELL MEMBRANE AND THE EXTRACELLULAR MATRIX

Extracellular signals pass into and out of the cell through the membrane, providing critical context for the health of the cell. Cells acquire geometric aberrations, which are driven by degradation and stress on the cytoskeleton (Kulms *et al.*, 2002; Vetterkind *et al.*, 2005), as they age (Kulms *et al.*, 2002; Vetterkind *et al.*, 2005), which can change surface texture in aging erythrocytes (Girasole *et al.*, 2010). Cell signaling molecule recycling in the cell membrane becomes dysregulated with age (Meissner *et al.*, 2004), leading to disruption of longevity-promoting cell signaling pathways (Meissner *et al.*, 2004; Samuelson *et al.*, 2007).

The extracellular matrix (ECM) is an important contributor to health and longevity and is also an indicator of the health inside the cell. Regulation of collagens, an ECM component, is shared from invertebrates to humans (Myllyharju and Kivirikko, 2004). Collagen expression in *C. elegans* declines with age (Tullet *et al.*, 2008; Ewald *et al.*, 2015), and regulation of specific collagens is required for *daf-2*–mediated lifespan extension (Ewald *et al.*, 2015). Aging humans also experience glycosylation and other proteomic damage to the ECM proteins (Brownlee, 1995; Kristic *et al.*, 2014), a process that is accelerated in type 2 diabetes patients (Evans *et al.*, 2002; Giacco and Brownlee, 2010) due to buildup of oxidative damage products and ROS (Giacco and Brownlee, 2010).

REPLICATIVE AGING, SENESCENCE, AND RENEWAL

In addition to decline of health with time, cells also experience aging linked to the number of divisions they have undergone (replicative aging). *S. cerevisiae* reproduces by budding a new cell off of the mother cell and can undergo ~26 such divisions before succumbing to detrimental effects of age (Kaeberlein, 2010), whereas the daughter is not limited by the number of previous divisions of the mother cell (Kaeberlein, 2010), due to renewal of its replicative potential. Replicative aging can be modified by disruption of TOR signaling (Kaeberlein *et al.*, 2005), dietary restriction (Kaeberlein *et al.*, 2005), and modifications to intercellular pH (Schleit *et al.*, 2013). During replicative aging, oxidative damage products such as carbonylated proteins and accumulated cellular damage build up in the yeast mother cell (Reverter-Branchat *et al.*, 2004; Unal *et al.*, 2011; Cabiscol *et al.*, 2014) and are retained by the mother cell through a Sir2-dependent mechanism, allowing the newborn daughter cell to be born without this hallmark of aging (Aguilaniu *et al.*, 2003; Wood *et al.*, 2004). (Although carbonylated protein clearance also occurs in *C. elegans* oocytes [Goudeau and Aguilaniu, 2010], this process is not dependent on *sir-2* [Viswanathan *et al.*, 2005; Berdichevsky *et al.*, 2006].) Resetting of replicative potential has clear parallels in mammalian and invertebrate gametogenesis. Stem cells undergo asymmetric divisions that segregate new mitochondria to the daughter cell, affecting their ability to maintain "stemness" (Katajisto *et al.*, 2015).

As cells age, they communicate their internal status—DNA damage (Kuilman *et al.*, 2010), oncogene activation (Kuilman *et al.*, 2010), and proteomic dysregulation (Walther *et al.*, 2015)—to their neighbors by the senescence-associated secretory phenotype (SASP; Coppe *et al.*, 2010; Kuilman *et al.*, 2010). SASP has been reported in flies, mice, and humans (Coppe *et al.*, 2008; Neves *et al.*, 2015), but particular SASP profiles vary based on cell type and context (Gu and Kitamura, 2012). SASP regulates tumor formation (Lehmann *et al.*, 2008) and may play a role in regulating organismal aging (Childs *et al.*, 2014), as well as in age-related pathologies (van Deursen, 2014; Demaria *et al.*, 2015), including neurodegenerative aging diseases (Chinta *et al.*, 2015).

Dysregulation of replicative lifespan is characteristic of diseases of aging, particularly cancer (Reya *et al.*, 2001). Stem cells maintain a balance between multipotency and tumorogenicity by careful internal regulation (Thomson *et al.*, 1998; Pittenger *et al.*, 1999) and by sensing external stimuli (Engler *et al.*, 2006). In cells induced to recover their stem cell–like state through coordinated factor expression (Takahashi and Yamanaka, 2006; Takahashi *et al.*, 2007), chromosomal abnormalities quickly arise (Mayshar *et al.*, 2010), as in normally aging cells (Aubert and Lansdorp, 2008) and immortalized cell lines (Landry *et al.*, 2013). This tendency toward tumor formation suggests that aging and senescence plays an important role in limiting the chance of runaway errors that compromise the overall health of the organism.

CONCLUSION

Cellular health is regulated by a number of cell biological processes. Conserved gene-regulatory pathways coordinate separate processes of cellular aging to maintain cellular health. Because cellular health is regulated across a wide range of scales from molecular to cellular and across every spatial division of the cell, the processes of regulating cellular health are linked: poor protein quality leads to defective organelles, defective organelles lead to increased ROS, and increased ROS leads to further low protein quality. Each of these is linked to regulation of aging on the cellular level, ultimately impinging on the control of aging of the whole organism.

The deeply conserved nature of the IIS pathway, the TOR pathway, and dietary restriction–induced longevity across eukaryotes suggests that regulation of aging is fundamental to eukaryotic evolution. The links between longevity, nutrient availability, and reproduction suggest that longevity pathways evolved to link somatic health to delayed reproduction in periods of low nutrient availability (Luo and Murphy, 2011). The robust, healthy-longevity phenotypes of DR and reduced IIS are the result of the systemic, coordinated change of many cell biological processes that together extend longevity.

Understanding the global regulatory processes that control the cell's health will lead to a greater understanding of aging, which may allow us to better treat and prevent aging-related degenerative diseases such as Alzheimer's and Parkinson's, diseases of incorrect senescence or failure to senesce, such as cancer, and slow aging itself, improving quality of life with age.

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