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The Role of the Proteasome in Limiting Cellular Stress Associated with Protein Accumulation

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Contributed as a perspective in the IJC Special Issue: Getting in Shape: Targeting the Molecular Etiology of Protein Folding Diseases.

Abstract: The proteasome is comprised of multiple subunits that catalyze the degradation of proteins to maintain cellular homeostasis. The proteasome targets protein substrates by two different pathways. The ubiquitin-dependent pathway requires proteins to be labeled with a ubiquitin tag to signal for degradation by the 26S isoform of the proteasome. Protein degradation through this pathway declines during age progression. The ubiquitin-independent pathway utilizes the 20S proteasome isoform. It can degrade misfolded and intrinsically disordered proteins to decrease cellular stress. Age-related protein accumulation and aggregation can occur due to the decreased activity and expression of the proteasome. Protein accumulation causes increased cellular stress which can contribute to disease progression. Increasing proteasome activity could serve as a solution to eliminating and preventing protein accumulation. Studies have shown the value of the proteasome as a therapeutic entity to mitigate cellular stress. This perspective explores the link between proteasome activity and cellular stress caused by age-related misfolded protein accumulation.

Keywords: proteasome · proteasome activation · aging · senescence · misfolded protein degradation

1. Introduction

Protein misfolding diseases have become more prevalent in recent decades, however the molecular etiology is still poorly understood. Protein misfolding occurs due to a variety of reasons that can stem from cellular aging and stress.[1] Protein homeostasis is sustained by cellular systems such as the ubiquitin-proteasome system (UPS), chaperone proteins, chaperone-mediated autophagy, and macroautophagy.[2,3] The decline of the proteostasis network is considered to be one of the hallmarks of aging.[4,5] Molecular aging can be defined as the accumulation of molecular damage to proteins or DNA/RNA.[6,7] The balance of maintaining cellular proteins can slowly deteriorate with age and can collapse when the stress of disease occurs. Misfolded or damaged proteins have been linked to age-related diseases such as Alzheimer's (AD), Parkinson's (PD), Huntington's disease (HD).[8] A solution to reduce cell stress and aging, associated with protein misfolding and aggregation, could achieved through an increase in proteasome activity.

The proteasome is a protein complex that is responsible for catalyzing the degradation of proteins the cell no longer requires. Proteasome degradation pathways partially contribute to preventing the accumulation of intrinsically disordered and misfolded protein.[9] Age progression can naturally diminish the activity of the proteasome which has been noted as a contributing factor to the cause of age-related disease.[3] A reduction in proteasome activity can lead to molecular damage to cellular maintenance and repair pathways. This in turn can induce cellular stress and promote the increase in senescent cells.[10] In this perspective we discuss the general principals of cellular stress and aging that demonstrate the link between proteasome activity and cellular homeostasis/longevity. We also describe genetic and small molecule therapeutic approaches that can modulate the proteasome to potentially decrease cell stress associated with unwanted protein accumulation.

1.1 Background: Structure of the 20S CP and 26S Proteasome

The proteasome is a large multi-catalytic complex that catalyzes the majority of protein degradation in mammalian cells.[11] There are different proteasome isoforms within the cell, however in this perspective we discuss the 20S and 26S proteasome isoforms. The 20S core particle (CP) is an isoform that performs ubiquitin-independent degradation and does not rely on the use of ATP. The structure of the 20S CP is constructed of heptameric subunit rings denoted as alpha and beta (α1-α7, β1-β7). The two outer alpha rings form the gate opening of the proteasome structure while the beta rings contain the catalytic subunits that facilitate protein degradation

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(β1, β2, and β5), Figure 1. The structure of the 26S proteasome contains a 19S regulatory particle (RP) located at the end of the barrel structure and functions to recognize and remove the ubiquitin tag on proteins. It then initiates the alpha ring of the 20S CP to open to allow the protein to be degraded in the catalytic core. The 26S proteasome performs ubiquitin-dependent degradation and relies on ATP binding/hydrolysis. This system functions by degrading proteins that have been labeled with a poly-ubiquitin chain. The mechanism of substrate recognition for non-ubiquitinated protein substrates is unclear, however there have been recent reports of degron sequences within a protein that could lead to its degradation.[12,13] The proteasome's primary role in cells is to maintain cellular homeostasis by eliminating damaged, misfolded, or excess proteins that can accumulate and lead to cellular stress.

1.2 Background: Aging and Cellular Stress Response

[Ageing can cause significant changes to the cellular environment, including a decrease in metabolic rates.[14] Normal aging can lead to an increase in the levels of proteins with abnormal structure and function. The occurrence of abnormal/damaged proteins has been linked to a variety of stressors. Oxidative stress has been labeled as a major contributor to the increase of abnormal proteins.[7] The accumulation of abnormal proteins can mediate impaired cellular function and the accumulation of age-related abnormal proteins.[7] Insufficient degradation of these proteins by the proteasomal or lysosomal systems can be considered the main reason for protein accumulation during aging.[6]

During natural age progression, cells will reach a state of cellular senescence which is an irreversible cell cycle arrest.[15] Senescent cells are still able to function metabolically and have a longevity dependent on its ability to maintain cellular homeostasis. It is known that proteasome activity declines naturally during age progression, and there are changes in the composition amounts of the proteasome isoforms.[16] As aging progresses the proportion of 26S proteasome decreases, increasing the proportion of 20S CP. The reason for this is due to a reduced expression of the 19S RP. This is indicative of senescent cells transitioning from utilizing ubiquitin-dependent degradation to ubiquitin-independent degradation to survive. The 20S CP has limitations on the types of proteins that can be degraded due to the size of the structural opening of the gate. Without the 19S RP, the alpha ring of the 20S CP remains in a closed off state. This limits the 20S CP to degrading proteins that lack a complex tertiary structure. This limitation can contribute to reduced overall protein degradation and accumulation of proteins that are unable to fit through the gate. Reduced protein degradation due to age progression can lead to other cellular effects that cause cellular stress.

The proteasome is known to be an important component in stress response pathways and cellular homeostasis.[17,18] Previous research has shown that the inhibition of the proteasome causes cells to have increased endoplasmic reticulum (ER) and oxidative stress that can lead to apoptosis.[19] ER stress can be caused by the accumulation of unfolded or misfolded proteins within the ER. During a stress response, the ER is unable to accept and fold newly synthesized proteins. This can lead to the accumulation of unfolded proteins outside of the ER in the cell cytosol.[20,21] ER stress can activate the unfolded protein response (UPR) pathway if the function of the ER is compromised.[20] The UPR enhances the ER's ability to refold proteins correctly or send them into the cytosol to undergo endoplasmic-reticulum-associated protein degradation (ERAD) involving the proteasome.[12] The accumulation of unfolded/misfolded proteins that causes ER stress can also contribute to oxidative stress.[20]

Oxidative stress involves the production of reactive oxygen species (ROS) or free radicals in the cell, which can further damage proteins. Specifically, oxidative stress occurs when there is an imbalance between reactive oxygen species and the naturally present antioxidant defenses.[22] The relationship between chronic oxidative stress and inflammation can lead to an inflammatory state leading to protein accumulation.[23] Many studies have been conducted have demonstrated the link between proteasome activity and longevity *in vitro* and *in vivo*.[24,24–26] Cellular senescence and stress are two types of biological processes where increased proteasome activity can be beneficial for survival.[27–30]

2. Damaged Proteasome Activity

The hallmarks of aging include loss of proteostasis, cellular senescence, mitochondrial dysfunction, genomic instability, epigenetic alterations, telomere attrition, stem cell exhaustion, and disrupted intracellular communication.[4] As aging pro-

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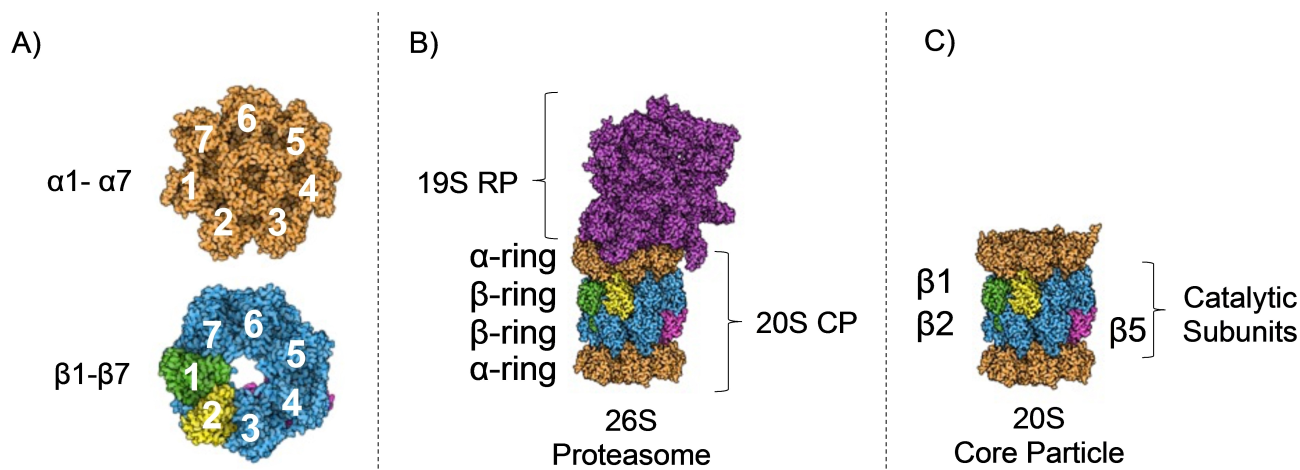

Figure 1. Structure of the 26S proteasome and 20S core particle. a) The proteasome is comprised of rings, denoted as alpha or beta, that contain seven distinct subunits. b) Structural components of the 26S proteasome. The 26S possesses a 19S regulatory particle (RP) that functions to remove the ubiquitin tag from substrates prior to degradation. The two alpha rings form the gate of the substrate entry pore. The two beta rings contain the catalytic subunits. c) Structural components of the 20S core particle. PDB: 8CVT

gresses, the cells' ability to sustain cellular maintenance declines. Ultimately, this can lead to accumulated proteins that can overburden proteasomal degradation pathways, Figure 2. This section discusses different explanations on why proteasome activity can become impaired or inhibited related to cellular stress and aging.

2.1 Attenuation of Senescence and Proteasome Activity Impairment

Cellular senescence is a state that is characterized by the ending of cellular division. Age progression is known to cause a reduction of proteasome activity and a decrease in the ubiquitin-dependent degradation system.[31] An investigation on the effects of aging on proteasome function was performed that focused on the aging of slow-twitch muscles in rats.[25] This study specifically evaluated 20S CP activity and content within aging muscle. Researchers found that during age progression there was an increase in the amount of the 20S CP, but the catalytic activity remained the same. The conclusion of this study determined that there is a reduction in hydrolysis activity of all three catalytic subunits of the proteasome and overall activity does not increase when the amount of 20S CP increases in this cell type.[25]

[However, a recent study has discovered that senescent cells have increased formation of nuclear foci that contain an increased amount of 26S proteasome.32] It is suggested that the formation of senescence-associated nuclear proteasome foci (SANPs) play an important role in senescent cell maintenance and health.[32] This study observed the effects of inhibiting the formation of SANPs.[33] They observed a significant increase in ROS production when SANPs formation was inhibited through RAD23B knockdown. The study concluded that SANPs formation potentially can help protect the senescent cells from ROS production. The formation of SANPs in senescent cells allows for the recruitment of the 26S proteasome for the purpose of promoting protein and ROS maintenance. SANPs are an adaptation of senescent cells to protect against excessive ROS and protein accumulation.

2.2 Misfolded proteins and Age-Related Neurodegenerative Diseases

Protein misfolding has been conclusively identified as a significant factor in diseases through many neuropathologic and genetic studies, as well as the development of transgenic animal models.[34] Aggregation of proteins has been noted in early Alzheimer's (AD) and Parkinson's disease (PD).[15,16] Impairment of the proteasome activity has also been indicated in these diseases.[32,37–39]

The misfolded protein that is linked to PD is α-synuclein. The proteasome can degrade α-synuclein through both ubiquitin-dependent and -independent pathways.[40] However, α-synuclein can aggregate and directly affect proteasome activity. In a study conducted by Cuanalo-Contreras *et.al*, they revealed that accumulation of α-synuclein occurs during natural aging and cellular senescence.[1] Similarly, AD has observable protein aggregates that contribute to the disease pathology.[41] In AD, misfolded proteins termed amyloid β (Aβ) and tau can form secondary structures that cause more misfolded protein accumulation.[42] Aβ can lead to plaque formation in between nerve cells and the hyperphosphorylation of tau can result in neurofibrillary tangles.[43]

There have been conflicting accounts of how the proteasome is affected by these toxic protein aggregates. Some studies have been able to show that Aβ serves as a proteasome

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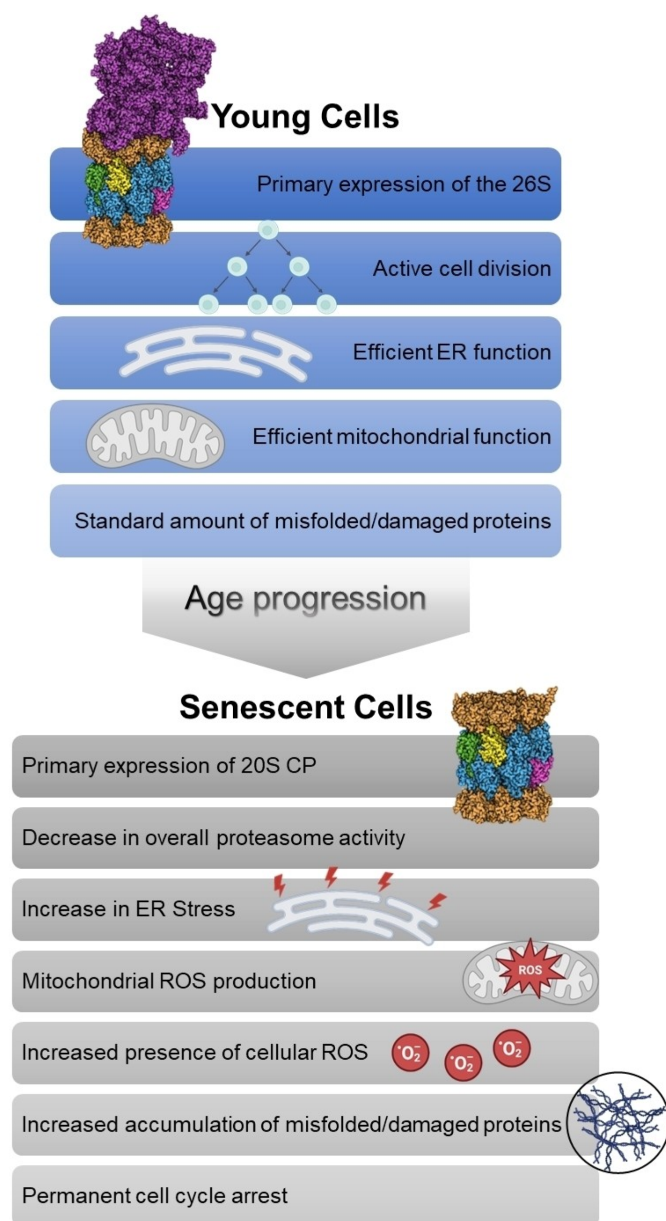

Figure 2. Effects of age progression on the cell and proteasome. Young cells can replicate and maintain cellular proteasome degradation performed primarily by the ATP-dependent 26S proteasome. Expression of proteasome activators, such as PA28, is present in young cells. Senescent cells lose the ability to replicate and maintain cellular protein homeostasis. The cell shifts to utilizing the ATP-independent 20S core particle (CP) to degrade proteins. There is a natural reduction of proteasome activity and expression of proteasome activators during age progression. This leaves the cell vulnerable to the accumulation/aggregation of proteins that can lead to an increased production of reactive oxygen species (ROS), such as superoxide.

substrate[44] while others observe proteasome impairment due to interaction with Aβ.[45] It has been determined that the monomeric form of Aβ is able to be degraded by the proteasome, but the oligomeric form leads to proteasome inhibition.[45] More research is required to understand how the activity of the 20S and 26S proteasome is damaged in this diseases.

2.3 Genetic Disorders That Alter Proteasome Function

The proteasome is a highly conserved multi-catalytic enzyme that is involved in several cellular processes. Each structural component of the 20S CP and the 19S RP must be correctly encoded to be functional. Mutations that occur in the genes encoding proteasome structure can lead to alterations in proteasome activity/function and are likely to be a contributing factor in diseases.

Polymorphisms in the genes that encode the alpha-ring of the 20S CP have been associated with human diseases. Changes in the gene PSMA6 that codes for the protein alpha-1 have been associated with myocardial infarction,[46] type 2 diabetes,[47,48] ischemic stroke,[49] and coronary artery disease.[50] The location of PSMA6 occurs within a region of DNA containing microsatellites; a tract of repetitive DNA that has a higher mutation rate than other areas.[51] This could explain the occurrence of polymorphisms in this gene.

The occurrence of a polymorphism in the 19S RP has been discovered, as well as other *de novo* mutations, in a male patient diagnosed with severe intellectual disability.[52] While searching for mutations within known intellectual-disability genes a missense mutation, A112D, was found in the PSMA7 gene of this patient.[52] There is still more research that must be conducted to show the relationship of this mutation to proteasome activity.

Genetic polymorphisms in proteins that interact with the proteasome have also been associated with rare diseases. Proteasome maturation protein (POMP) behaves as a chaperone protein and is an essential component to the maturation of the 20S CP. POMP specifically associates with alpha and beta subunit intermediates and coordinates the assembly of beta subunits onto alpha subunits.[53,54] A single base pair deletion in POMP is linked to diseases such as keratosis linearis, ichthyosis congenital, and sclerosing keratoderma (KLICK syndrome) in a pool of European families.[55] Research performed to study KLICK syndrome reveled that skin biopsies from patients had altered distribution of POMP.[55] It is assumed from these results that KLICK syndrome is likely associated with altered proteasome assembly, which can effect proteasome activity and function.

Down syndrome (DS) is the most frequent chromosomal abnormality that causes intellectual disability.[56] DS is characterized by presence of three copies of chromosome 21.[56] A feature of DS is early onset AD after the age of 40.[57,58] DS patients and control patients were evaluated for proteasome expression and proteasome activity.[59] It was revealed that DS patients have a higher expression of the 20S CP and there was an overall decrease in proteasome activity compared to control subjects.[59] These results are significant because it presents

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proteostasis dysfunction as a feature of DS. Since reduced proteasome activity is a contributing factor to the development of AD,[41] it could potentially explain the development of early onset AD in DS subjects.

Progeroid syndromes are a type of genetic disorder where premature aging characteristics are observed.[60] These syndromes are linked to defects in DNA repair machinery or a defective nuclear envelop,[61,62] which leads to the accumulation of DNA damage and chromosome instability.[63] The DNA damage response (DDR) pathway is a signal transduction pathway that has the purpose of detecting and repairing damaged DNA.[64] Most DDR pathways are controlled by the UPS.[65] This is by the post-translation alteration of protein subunits involved with machinery of DNA damage, DNA repair, and check point response.[65] Progeroid syndromes such as Werner syndrome,[66,67] Hutchinson-Gilford syndrome, Rothmund-Thomson syndrome,[68,69] and Ataxia Telangiectasia[70] have been linked subsequently to alterations in ubiquitin-dependent protein quality control,[67] accumulation of mutated RECQL4[68,69] (involved in maintaining genome stability[71]), decline in caspase-like proteasome activity,[72] and increased ubiquitination activity.[70] Future research is needed to understand the extent of the UPS's effect on these disorders and if reinstating proteasome function could have a positive outcome in changing the aging features of these disorders.

3. Age-Related Proteasome Activity

Research studies that have focused on the effects of aging on the proteasome have used a variety of *in vitro* and *in vivo* experimental models. This section discusses multiple studies that have shown consistent results of the importance of proteasome activity in cellular longevity. The overall conclusion of these studies shows the reduction of all three catalytic subunits of the proteasome with age progression and the restoration of proteasome activity increases the lifespan of the model. These various experimental models for proteasome studies are summarized in Table 1.

3.1 Plants

Plant models for proteasome aging studies have primarily focused on the plant species *Arabidopsis thaliana* due to its entire genome sequence being available for genomic studies.[73] Genomic studies have explored the link between autophagy and the ubiquitin-proteasome system, two pathways that are important for plant survival and stress response. In plants senescence serves as a positive cellular response that triggers tissue remodeling and minimizes the damage caused by stress.[74–76] Similarly to mammals, in *Arabidopsis thaliana* there is a decrease in 26S proteasome and a higher presence of 20S proteasome after age progression.[35,37]

The effects of oxidative stress on proteasome content, structure, and activity were also studied utilizing *Arabidopsis thaliana.* The results of the study determined that after exposure to oxidative stress for 24 hours the content of proteasome shifted from 26S to the 20S CP, cellular ATP content was reduced, and there was an increase in the activity of the 20S CP.[78]

3.2 Yeast

Budding yeast, *Saccharomyces cerevisiae*, has served as a valuable model that has been able to produce similar results to mammalian experimental models (mice, rats, etc.).[79] The elevation of proteasome activity in yeast was shown to increase the lifespan and provide resistance against [oxidative stress conditions compared to control yeast. [28,79,80] The effects of stoichiometry loss in protein complexes have also been studied in yeast. The results, similar to other models, show that loss of stoichiometry in complexes such as the proteasome, nuclear pore complexes, and mitochondria, and contribute to a decrease in yeast life span.[81]

Genetically modified strains of yeast have been generated that have decreased proteasome capacity. The most commonly used is a knockdown strain of RPN4, a transcription factor that controls expression of proteasomal subunits. This yeast strain has reduced proteasome activity and can be used to study the effects of proteasome activity on the lifespan of yeast.[28,82,83] A study utilizing this model was able to show that yeast with RPN4 knockdown had shortened a life span.[83] Genetically modified yeast strains to study proteasome activity are excellent tools, but it should be cautioned that results do not always translate to human/mammalian proteasomes.

3.3 Caenorhabditis Elegans

C. elegans have been used as a model to study aging due to their relatively short lifespans (~3 weeks).[84] Proteasome research involving *C. elegans* as an animal model have explored the effects of increased proteasome activity on longevity and the effects of aging on the UPS.

Rpn-6 is an essential component of the 26S proteasome because it makes interactions to associate the 19 RP to the 20S CP.[85] Overexpression or knockdown of Rpn-6 can affect the overall assembly of the proteasome. A study utilized this concept and observed the effects it had on *C. elegans.* Overexpression of Rpn-6 increased proteasome activity, provided resistance to oxidative ad heat stress, and extended lifespan in a heat stress environment.[27] Increasing Rpn-6 levels allowed for increased proteome maintenance and sustaining protein homeostasis.[27] These results were reproduced by Chondrogianni et al. 2015, using pbs-5 overexpression to achieve increased 20S CP proteasome activity.[80]

The effects of aging on the proteasome can also be observed in *C. elegans* and provides results consistent with other animal models. There is observable UPS impairment when comparing 7-day and 4-day old C. elegans.[86] Using a

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Table 1. Overview of experimental models used to study proteasome activity.

Species	TissueRegion	Cell Type	Focus	Isoform	Treatment	ProteasomeActivity Results	Results	Source
Mouse	Brain	Neuron	Aging	26S/20S	Age Observation	26S Decrease/ 20S Increase	Shift of primary proteasomal composition from 26S to 20S during aging.	93
Rat	Brain	Neuron	Aging	26S/20S	Age Observation	26S Decrease/ 20S Increase	Shift of primary proteasomal composition from 26S to 20S during aging.	93
Rat	Heart	Cardiomyocytes	Stress	11S	PA28α Overexpression	11S Increase	Reduction in oxidative stress and protein accumulation.	29
Rat (F344BN)	Muscle	Type I muscle fiber	Aging	20S	Age Observation	20S Decrease	Proteasome activity is observed to decrease with age.	25
Rat (LOU)	Muscle	Gastrocnemius medialis	Aging	20S	Age Observation	20S Decrease	Proteasome activity is observed to decrease with age.	26
Rat (Male Fischer 344)	Liver	Liver	Stress	20S	Metal-Catalyzed Oxidation	20S Decrease	Oxidative inactivation of the 20S proteasome.	94
Nothobranchius furzeri (killifish)	Brain	Neuron	Aging	26S/20S	Age Observation	26S Decrease/ 20S Increase	Decrease in the correlation between RNA transcripts and proteins as age progressed.	95
Nothobranchius furzeri (killifish)	Brain	Neuron	Aging	26S/20S	Age Observation	26S Decrease/ 20S Increase	Decrease in the expression of proteasome transcripts correlates with an increase in risk of morality.	88
Human	Skin	Dermal fibroblasts	Aging	20S	Age Observation	20S Decrease	Restoration of the normal level of proteasome catalytic subunits decreased the severity of age markers.	96
Human	Skin	Epidermal cells	Aging	20S	Age Observation	20S Decrease	Proteasome is decreased during replacive senescence	97
Human	Skin	Dermal fibroblasts	Aging	26S/20S	UVB Exposure	26S/20S Inactivation	Decrease in overall proteasome activity and an increase in ROS.	98
Human	Skin	Dermal fibroblasts	Aging	26S/20S	Mitochondria Inhibition	26S/20S Decrease	Inhibition of mitochondria function reduced proteasome activity. Proteasome inhibition also reduced mitochondrial function.	99
Caenorhabditis elegans	Brain	Dorsorectal neurons	Aging	26S/20S	Age Observation	26S/20S Decrease	Older worms displayed impaired UPS activity.	86
Caenorhabditis elegans	Muscle	Body-wall muscle	Aging	26S/20S	Age Observation	26S/20S Decrease	No change was observed in proteasome activity.	86
Caenorhabditis elegans	–	–	Aging/ Stress	26S/30S	RPN-6 Overexpression	26S/30S Decrease	Increase in overall proteasome activity.	27
Caenorhabditis elegans	–	–	Aging/ Stress	26S/30S	RPN-6 Overexpression	26S/30S Decrease	Extension of lifespan and resistance to oxidative stress	27
Caenorhabditis elegans	–	–	Aging/ Stress	20S	*pbs-5* Overexpression	20S Increase	Extension of lifespan and resistance to oxidative stress	80
Drosophila melanogaster	–	–	Aging	26S/20S	RPN11 Overexpression	26S/20S Increase	Proteasome subunit overexpression was shown to prevent the age-related reduction in proteasome activity.	24
Arabidopsis thaliana	–	–	Stress	26S/20S	Abiotic Stress	26S Decrease/ 20S Increase	There is a switch in the predominant proteasome complex from the 26S to 20S CP occurs under oxidative or salt stress	78
Saccharomyces cerevisiae	–	–	Stress	26S	RPN4 Overexpression	26S/20S Increase	Extended Lifespan	28

fluorescent reporter substrate the degradation rate was able to be quantified.[86] 7-day old worms were only able to degrade 20% of the total substrate, while 4-day old worms degraded 60% of the total.[86]

3.4 Whole Animals

Proof of reduced 26S proteasome activity in an animal model was demonstrated by Tonoki *et.al.* 2009 using Drosophila melanogaster.[24] This study also found that 20S proteasome activity was unaffected by the attenuation of age.[24] Mouse models have also shown how increased activity of 26S or 20S

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proteasome allow for the achievement of a longer life span compared to those with a reduced expression of proteasome.[87–89] This study investigated the age-related changes to caspase- and chymotrypsin-like activity of the 20S proteasome in lung, heart, liver, kidney, axillary lymph nodes, and peritoneal leukocytes.[87] The conclusion of this study, consistent with other research, determined that age-related changes of 20S activity is dependent on the organ and the peptidase activity being considered.[87,90,91]

3.5 Brain

Brain aging has been associated with a reduced ability to degrade proteins, leading to the accumulation of misfolded proteins within neurons. This can cause the decline of proteasomal and lysosomal degradation activity. *Nothobranchius furzeri*, also known as a killifish, have been used as a novel model for aging research due to its resemblance of mammalian aging and its short-term lifespan.[92] Researchers have used this model to quantitate protein homeostasis by using transcriptomics with proteomics. Using RNA-Seq they compared the transcripts of three different age groups of killifish: sexually mature young, adult, and old killifish. The amount of protein was quantified using an algorithm called iBAQ (intensity-based absolute quantification). The results of this study determined that there was a decrease in the correlation between RNA transcripts and proteins as age progressed.[95] A follow up study observed the decrease in correlation between transcripts and proteasome subunit proteins and a reduction of 26S proteasome.[88] They evaluated the effects of inhibiting proteasome activity and aging phenotypes in the brains of killifish by using bortezomib, a small molecule proteasome inhibitor, to induce a ~50% reduction in proteasome activity.[88] The results showed that there was an effect in protein abundance because of changes to large subunits of ribosomes located in the cytosol and mitochondria. Whether decreased proteasome activity played a role in early life and the lifespan of killifish was also explored. Their investigation discovered a decreased expression of proteasomal transcripts correlated with an increased risk of mortality.[88] Killifish that had the largest reduction in transcripts encoding the subunits of the proteasome had shorter lifespan compared to those with largest upregulation of proteasomal transcripts.[88,100]

Brain tissue from mice and rats have also been tested for overall proteasome activity at different ages ranging from 6-weeks to 15 months. The brain regions tested in this study were the cortex, cerebellum, globus pallidus, and the substantia nigra. This study found that the overall proteasome activity in brain tissue decreased at 15 months of age compared to 6-week-old mice/rats.[93] Specifically the chymotrypsin-like activity was ~40% lower in the frontal cortex of aged rats and mice. Chymotrypsin-like activity was found to be reduced in all brain regions except for the cerebellum. Trypsin-like and peptidylglutamyl peptidase activity were also found to be reduced in the substantia nigra.[93]

3.6 Muscle

Aging can cause the reduction of sustaining muscle mass and promote deterioration.[101,102] Two different rat models were able to show an increase in the 20S proteasome isoform within muscle cells over the life span of the rats.[25,26] However, each study came to a different conclusion when it came to 20S proteasome activity. One concluded that 20S proteasome activity decreased and the other observed no change.[25,26] Even though the results of the rat studies provided conflicting results, it is clear that proteasome activity can change as animals age.

Another study investigated the activity of the three catalytic subunits of the 20S proteasome, specifically in muscle tissue of rats. The proteasome activity in the gastrocnemius medialis muscle of different aged rats ranging from 4 months to 34 months of age was measured and compared. It was observed that all three catalytic subunit activities of the proteasome increased until rats were 29 months and then decreased when they reached 34 months of age.[26] This study further supports that the decrease of proteasome activity can contribute to aging and the breakdown of healthy cells.

3.7 Skin

Damaged skin has also been shown to be related to changes in proteasome activity. The 20S proteasome activity in donor human dermal fibroblasts that were collected from 50 year old and 20 year old individuals and were compared.[96] The study determined that the chymotrypsin-like, trypsin-like, and peptidylglutamyl peptidase catalytic activities of the 20S proteasome was significantly decreased in the 50 year old individuals compared to 20 year old individuals.[96] It was also revealed through immunoblotting that older individuals had a decrease in two of the catalytic proteasome subunits, β1 and β5.[96] Two subunits within the 19S regulatory particle, Rpn3 and Rpn12, are also observed to decrease in older individuals leading to a decrease in degradation of proteins through the ubiquitin-dependent pathway as well.[96]

Oxidized proteins have been quantified in human epidermal cells to determine the effects of age and the connection to protein oxidation.[97] Cell samples were collected from young (17–25 years old), middle-age (39–42 years old), and older (50–67 years old) individuals.[97] The results showed that there was an increase in oxidized proteins in older individuals compared to young individuals.[97] The study also evaluated 20S proteasome activity and found that the chymotrypsin-like and peptidylglutamyl peptidase activities were decreased in older individuals.[97] The 20S proteasome subunit content was also reduced in older individuals.[97]

In a study done to evaluate the effects of UV irradiation on cell senescence human dermal fibroblasts were treated with irradiation and proteasome activity was quantified.[98] The results showed a decrease in overall proteasome activity and an increase in ROS. The researchers concluded that ROS

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potentially caused the proteasome to become inactive and reduce protein degradation. The loss of protein degradation leads to increased autophagy and induction of senescence.[98]

Overall, these studies highlight that the activity of the proteasome decreases naturally as one ages. Additional studies are required to determine if an increase in 20S proteasome activity, whose levels to not change during aging, can compensate for the decrease in 26S activity. It is likely that in some capacity this is possible, but the substrate scope of the 20S is not as broad as the 26S.103]

4. Proteasome Activity and Cellular Stress

Cells can experience molecular damage, protein accumulation, impairment of function, and apoptotic initiation caused by a variety of intrinsic and extrinsic stressors. Misfolded proteins can be partially associated with the cause and consequences of cellular stress. As discussed in the previous section, age-related failure of protein handling systems can be the cause of the aggregation of misfolded proteins that can progress into protein accumulation diseases. This section will describe how misfolded proteins cause cellular stress and the cellular mechanisms in place that allow the cell to re-establish homeostasis.

4.1 Unfolded Protein Response Pathways

Living cells contain molecular systems that allow for proper function and survival. Networks of protein quality control (PQC) systems maintain protein folding, structure, and function.[7] These networks contain molecular chaperones, intracellular proteases and antioxidant systems that assist with cellular maintenance. PQC systems are specifically located in the cytosol, endoplasmic reticulum (ER) and mitochondria.[7] While these pathways are involved with maintaining regular cell maintenance, they also possess specialized unfolded protein response (UPR) pathways. These UPR pathways are initiated to save functional nascent proteins and eliminate misfolded proteins when the organelles function, where the PQC systems are located, is compromised due to protein accumulation.[104]

The proteasome plays a role in the UPR by degrading oxidized proteins or un/misfolded proteins that are shuttled out of the ER or mitochondria. During the UPR process entry to the ER is prohibited for newly synthesized proteins, which can cause protein accumulation in the cytosol. The 20S CP proteasome is potentially able to degrade unfolded nascent proteins while the UPR is active due to the proteins lack of structure. Oxidatively modified or un/misfolded proteins can be directly degraded by 26S proteasome and 20S CP. Increasing proteasome activity could have the potential of assisting the UPR pathway and re-establish homeostasis at a faster rate.

The localization of the proteasome during a stress response has previously been studied. This research has not been able to conclusively determine proteasome localization in mammalian cells due to the variation of cell lines, cellular growth conditions and the dependence on antibodies used in indirect fluorescence microscopy.[105] However, a study in mammalian cells, under non-stress conditions, observed that the majority of proteasomes are located within the cytoplasm. This is different in comparison to yeast where most proteasomes are localized in the nucleus during non-stress conditions.[21,105,106] Under stress conditions there is evidence that shows the localization of proteasome and ubiquitinated proteins within and surrounding PQC compartments in the cell.[107] PCQ compartments serve as a location for protein degradation of misfolded proteins and have been linked to aiding in resistance to cellular stress.[55,56]

4.2 UPR Endoplasmic Reticulum

The ER contains a network that functions to fold newly synthesized proteins within the cell. Quality protein folding is essential for cell survival and function. When the homeostasis of the ER is altered, proteins that are misfolded or unfolded can accumulate within the ER lumen. This can occur during growth factor stimulation, cell proliferation, and senescence.[109] ER stress can also be induced directly if there are gene mutations that cause proteins to misfold or alter the UPR.[110] Prolonged ER stress leads to the activation of the UPR pathway. Activation of the UPR helps determine the fate of the cell by the promotion of cell survival or cell death.

The UPR pathway for the ER possesses three branches of transcriptional signaling pathways: IRE1, PERK and ATF6.[20,111,112] This transcriptional signaling leads the ER to increase its capacity to eliminate or attempt to re-fold un/misfolded proteins. The BiP chaperone will attempt to refold proteins and ones that are unable to be folded correctly are eliminated through ER-associated protein degradation (ERAD). ERAD is a process that is employed during regular ER maintenance as well as the UPR pathway. Proteins eliminated by ERAD are shuttled out of the ER into the cytosol where they undergo ubiquitination which signal for the protein to be degraded by the 26S proteasome; or directly degraded by the 20S proteasome without undergoing ubiquitination.[113] By eliminating protein accumulation within the ER, a homeostatic state can be reached, and protein folding can continue.

Chronic ER stress has recently become a topic of interest in being one of the key contributors in a list of human diseases such as diabetes, neurodegeneration, and cancer.[114–118] Genetic manipulation of UPR components has shown to influence disease outcome in rodent models.[118–120] More research must be conducted to understand how the UPR signals for life and death. We hypothesize that the proteasome could pose as a potential solution in assisting the UPR in re-establishing ER homeostasis.

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4.3 Reactive Oxygen Species and Protein Misfolding

ROS are free, unstable oxygen-based molecules that contain an unpaired electron, including hydrogen peroxide, hydroxyl radical, singlet oxygen, and superoxide. The unpaired electrons can interact with proteins, DNA, or other biological molecules and cause unnecessary modifications. ROS has the function of signaling cell growth, but excess can cause cellular damage and induce apoptosis.

The initiation of ROS production can be associated with a variety of different sources. A major source of ROS is the mitochondrial respiratory chain where ATP synthesis naturally generates ROS during regular oxygen metabolism.[121] Another reason ROS production can be initiated is the accumulation of misfolded proteins. Protein accumulation can cause oxidative stress through proteasome inhibition (Figure 3). Proteasome inhibition/overload by protein accumulation can lead to mitochondrial dysfunction, impairment of glycolysis, and increases mitochondrial turnover through lysosomal degradation in cells.[122] This mitochondrial dysfunction can initiate the production of ROS which can in turn damage proteins and lead to more protein accumulation. Oxidatively modified proteins can be directly degraded by 26S and 20S proteasomes.

5. Increasing Proteasome Activity

Proteasome activity is a vital factor in cellular health. Activation of the proteasome is a natural process caused by the presence of misfolded or disordered proteins. Increasing the rate of proteasome degradation can potentially serve as a solution where this process is impaired due to disease or age. Many studies have explored the different methods to increase proteasome activity within the cell. These methods are through genetic upregulation of proteasome assembly components, endogenous proteasome activators, and small molecule proteasome activators.

5.1 Genetic Upregulation (NRF2, POMP, PSMB5)

Genetic upregulation of proteasome catalytic subunits has been shown to increase proteasome activity within cells. 20S proteasome activation was observed in established (WI38/T and HL60) and primary (IMR90) human fibroblast cell lines when the catalytic β5 subunit was stably overexpressed.[123] This increase in proteasome activity was also observed when the catalytic subunit β1was overexpressed in cells.

It has also been reported that over expressing a subunit in the 19S RP of the 26S proteasome elicits elevated proteasome activity.[24] Rpn-11 is responsible for the de-ubiquitination of proteins before proteasome degradation by the 26S. The upregulation of Rpn-11 allows the proteasome to increase its processing of ubiquitin tagged proteins.

The process of proteasome assembly and formation is complicated and employs many modulators. Proteasome maturation protein (POMP), or human UMP1 (hUMP1), is an important chaperone of proteasome assembly in mammals. It plays a role in the final maturation steps of proteasome assembly that yield a fully functional proteasome. When POMP was over expressed in WI38/T-cells proteasome activity was increased due to the elevated presence of 20S proteasome formation.[124] Nuclear factor erythroid 2-related factor 2 (Nrf2) is a proteasome regulator that also controls the expression of POMP. When more proteasome is needed, Nrf2 can signal for an increase in POMP to promote proteasome assembly. Overexpression of Nrf2 can also elicit an increase in proteasome activity.[125]

5.2 Proteasome Activators

Cells contain endogenous proteasome activators that function to boost the activity of the proteasome. The 20S proteasome functions as a catalytic barrel with a gate that opens an axial pore for substrates to enter. Proteasome activators can bind to the alpha ring of the proteasome where the gate is located to

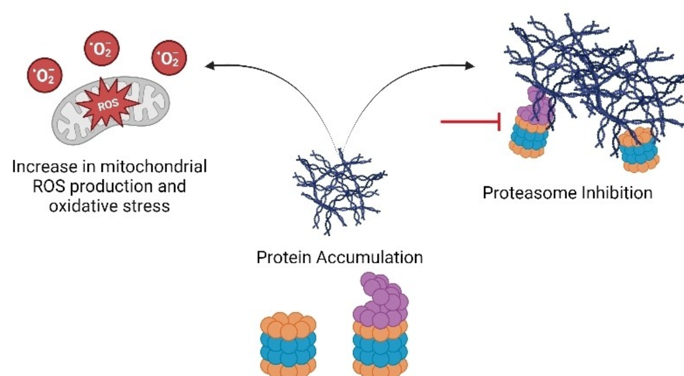

Figure 3. Direct proteasome inhibition/overload caused by the accumulation of misfolded, damaged, or unfolded proteins can increase oxidative stress by inducing mitochondrial dysfunction, impairment of glycolysis, and increases mitochondrial turnover that causes the production of ROS.

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stimulate proteasome activity. Proteasome activators can be separated into two categories that function through different mechanisms: ATP-dependent and ATP-independent. ATP-dependent activators can perform gate-opening, substrate unfolding and substrate translocation when bound to the 20S proteasome. ATP-independent activators stimulate the hydrolysis of model peptide substrates, and some can degrade unfolded proteins.[126] Though there is extensive structural information about how some proteasome activators bind, the mechanisms of how proteasome activators are recruited is unknown.

Notable research has been conducted on the proteasome activator PA28 in aging and cellular stress research. PA28 is a part of a class of 11S endogenous activators whose activation does not require the input of ATP.[25] The expression of PA28 has been observed to naturally increase during oxidative stress.[127] Overexpression of PA28 in rats and mice has demonstrated an increase in the expression of 11S proteasome and lead to a reduction in oxidative stress and protein accumulation.[29,128–130] During age progression there is no significant change observed in the expression of PA28.[25,131]

5.3 Phosphorylation Based Activation

Phosphorylation of the proteasome is another example of endogenous proteasome activation. The phosphorylation, induced by cAMP or cGMP, of proteasome subunits can enhance the rate of degradation of small proteins.[132,133] Previous research has shown that proteasome activation through phosphorylation has been sufficient in degrading accumulated pathological proteins.[134] Phosphorylation of the 26S proteasome subunits is a mechanism that can regulate protein degradation.[135] The two most established kinases that have demonstrated an effect on proteasome function is Protein Kinase A (PKA) and Dual Receptor Tyrosine Kinase 2 (DYRK2).[136] The phosphorylation site of PKA on the proteasome is located at serine 14 on the Rpn-6 subunit of the 19S RP.[132] Phosphorylation at this site by PKA has shown to increase proteasome activity. DYRK2 phosphorylates the 19S ATPase subunit Rpt-3 at threonine 25 which activates the proteasome. DYRK2 phosphorylation of the proteasome occurs during the S through M phases of the cell cycle and promotes cell proliferation.[137] The mechanism of how proteasome phosphorylation leads to enhanced protein degradation remains unclear. Proposed theories include the acceleration of proteolysis by inducing a more active form of the proteasome. More research is required to understand these and other reported post-translational modifications of the proteasome.

5.4 Small Molecules (Gate Openers, Catalytic Activators)

Proteasome activation by use of a small molecule was first recorded when researchers discovered the compound sodium dodecyl sulfate (SDS) was able to enhance proteasome activity at low concentrations.[103] It is known now that the mechanism of how SDS increases proteasome activity was by partial denaturation of the protein-protein interactions of the gate of the 20S CP.[138] Small molecules that interact with the proteasome isoforms to initiate proteasome activation can be associated with one of two proposed mechanisms. Small molecules can function as a gate-opener that promote substrate entry to the 20S CP catalytic subunits by inducing gate-opening (or stabilization of the open-conformation) of the 20S CP alpha ring. The second mechanism is when a small molecule can activate the proteasome by allosterically interacting with the one or more catalytic subunit.[139] A recently discovered proteasome activator, TCH-165, has shown the ability to stimulate proteasome assembly that results in increased amounts of 20S CP.[140] Other small molecules that have been discovered as proteasome activators are shown in Figure 4.

Previously discovered small molecule proteasome activators are compounds that have been repurposed to elicit increased proteasome activity. Currently, there is missing information on how and where small molecules bind to increase proteasome activity, limiting the ability to complete SAR campaigns.

6. Conclusion

Protein misfolding is involved in many age related diseases where their accumulation and aggregation harms cellular homeostasis.[141] It appears to be an important factor in aging, and increases suseptability to cellular stress. The failure of maintaining proper protein levels is a large contributing factor of aging, which can lead to the development of neruodegenerative diseases. The proteasome, a celluar enzyme complex, plays an important role in protein homeostasis. The preserva-

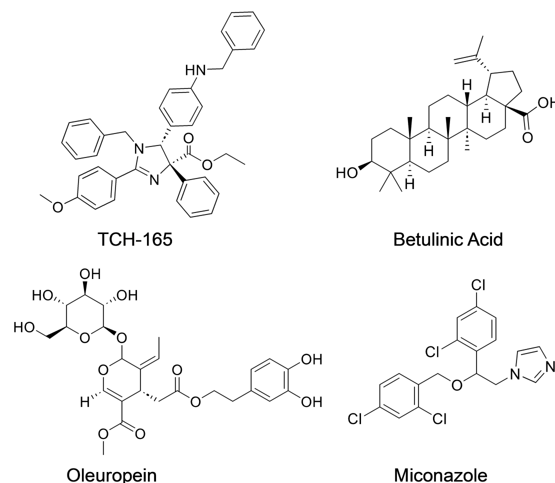

Figure 4. Small molecule stimulators of the 20S proteasome that can affect the rate of protein degradation.

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tion of proper protein turn over, degradation of misfolded proteins, and the integrity of the proteasome seems to be vital in protecting the cell against increased cellular stress and accelerated aging. This perspective has highlighted many studies on the importance of proteasome activity and in which disease types it could potentially be targeted as a therapy. The impact of impaired proteasome activity and the value of proteasome restoration for an organisms lifespan and cellular stress pathways has also been highlighted.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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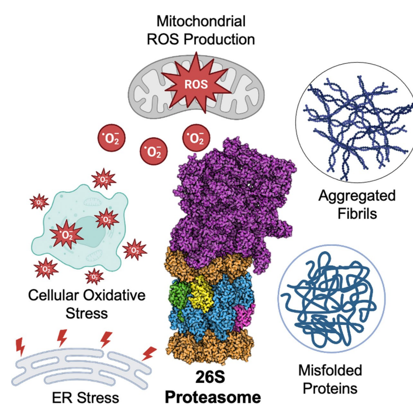

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