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REVIEW

Proteostasis in aging: mechanistic insights and therapeutic opportunities

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Abstract

Proteostasis, the dynamic balance of protein synthesis, folding, and degradation, is fundamental to cellular homeostasis and organismal health. Aging disrupts proteostasis networks, leading to the accumulation of misfolded and aggregated proteins, which plays a central role in age-related dysfunction and the onset of diseases such as neurodegenerative and metabolic disorders. This review comprehensively explores the components and regulatory mechanisms of proteostasis networks, including key proteolytic systems like the ubiquitin-proteasome system (UPS) and autophagy, as well as the role of molecular chaperones in maintaining protein folding. We discuss hallmark features of aging-related proteostasis dysfunction and highlight its implications in major age-associated diseases, particularly neurodegenerative conditions like Alzheimer's and Parkinson's, and metabolic disorders such as diabetes and obesity. Additionally, emerging therapeutic strategies aimed at restoring proteostasis for healthy aging are examined, focusing on targeting chaperones, enhancing proteolytic systems, and modulating protein folding pathways. Advances in transcription factor regulation, proteasome activators, and autophagy modulators, as well as promising approaches involving small molecules and gene therapy, are discussed. Finally, we outline future directions and conclude that targeting proteostasis represents a promising avenue for improving health span and mitigating age-related diseases.

Keywords: Proteostasis, proteolytic, dysfunction, neurodegenerative, age-related diseases

Introduction

Proteostasis, or protein homeostasis, is a critical process involving the synthesis, folding, trafficking, and degradation of proteins to maintain a functional proteome. It plays an essential role in cellular health by ensuring proteins achieve and retain their proper three-dimensional structure, which is necessary for their biological function [1]. The proteostasis network includes molecular chaperones that assist in protein folding, the ubiquitin-proteasome system for protein degradation, and pathways that address protein misfolding and aggregation. These systems work in concert to manage protein quality and prevent the accumulation of defective proteins, which can disrupt cellular functions and lead to diseases, particularly neurodegenerative conditions like Alzheimer's and Parkinson's [2, 3]. The efficiency of the proteostasis machinery is challenged by factors such as aging, environmental stress, and disease. As organisms age, the decline in proteostasis capacity contributes to the accumulation of misfolded or aggregated proteins, which are hallmarks of several age-related disorders. For example, molecular chaperones and proteasomal activity decline with age, making cells less capable of managing protein quality. Understanding the mechanisms of proteostasis and its regulation not only provides insights into fundamental biology but also has therapeutic implications for improving health and treating diseases associated with proteome instability [4-6].

As organisms age, the mechanisms that regulate proteostasis protein synthesis, folding, and degradation become less effective, leading to an accumulation of misfolded and damaged proteins. This imbalance, often termed "proteostasis collapse", significantly impacts cellular function, longevity, and susceptibility to diseases such

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as neurodegeneration, cancer, and cardiovascular disorders. Proteostasis is maintained by an intricate network of molecular chaperones, the ubiquitin-proteasome system (UPS), and autophagy pathways. With aging, these systems face increased oxidative stress, damage from reactive oxygen species (ROS), and a decline in efficiency [7]. The UPS, critical for degrading short-lived or misfolded proteins, becomes impaired, leading to an accumulation of ubiquitinated proteins and aggregates that disrupt cellular homeostasis. Similarly, autophagy, which removes large protein aggregates and damaged organelles, declines with age, further exacerbating proteotoxic stress. These deficiencies contribute to the hallmark signs of aging, such as cellular senescence, chronic inflammation, and tissue dysfunction. The decline in proteostasis significantly contributes to cellular aging and chronic diseases. For instance, in neurodegenerative diseases like Alzheimer's and Parkinson's, protein aggregates such as amyloid-beta and alpha-synuclein disrupt cellular function. In cancer, although proteostasis mechanisms are hyper activated to support the rapid proliferation of cells, aging reduces their efficacy, potentially leading to tumorigenesis. Moreover, systemic inflammation associated with aging, termed "inflammation," is partially driven by the phototoxic stress caused by impaired protein homeostasis. Interventions targeting these pathways, such as enhancing autophagy or proteasomal activity, have shown potential in extending lifespan and improving health span in model organisms [8, 9].

The primary objective of this review is to explore the intricate relationship between proteostasis and aging, emphasizing how the regulation of protein homeostasis impacts cellular health and overall longevity. It aims to examine the role of proteostasis in maintaining protein quality and stability and its deterioration as a hallmark of aging. Furthermore, the review investigates the implications of disrupted proteostasis for human health, with a focus on age-related diseases such as neurodegeneration, cancer, and cardiovascular disorders. By understanding the mechanisms underlying proteostasis collapse and its association with aging, the review seeks to highlight potential therapeutic strategies to enhance proteostasis, promote healthy aging, and mitigate the progression of age-related diseases.

Proteostasis networks: components and mechanisms

Molecular chaperones play an essential role in protein folding and quality control by assisting in the proper folding of newly synthesized proteins, ensuring their stability, and preventing the aggregation of misfolded proteins [3]. These chaperones act in several ways, such as by binding to nascent proteins and preventing their premature folding or degradation, or by facilitating the refolding of misfolded proteins under stress conditions like heat or oxidative stress. They help maintain proteostasis, which is crucial for cellular function, particularly in cells subjected to environmental stressors, such as neurons. Heat shock proteins (HSPs) are among the most well-known molecular chaperones, and they are named for their increased expression in response to heat stress. HSPs, including HSP70, HSP90, and small HSPs, provide a protective environment that allows proteins to adopt their functional conformations. When refolding is impossible, chaperones direct misfolded proteins to degradation pathways, such as the ubiquitin-proteasome system (UPS) or autophagy, preventing the accumulation of toxic aggregates that can impair cellular function [10, 11].Chaperones are involved in a range of protein quality control mechanisms, such as disaggregating protein clusters or guiding defective proteins to degradation pathways. For example, misfolded proteins are often marked by ubiquitination, which signals

Table 1. Various examples of Chaperone involved in protein folding and quality control.

Chaperone	Role	Function/Mechanism	References
HSP70	Protein folding, refolding, stabilization	HSP70 binds to nascent polypeptides, preventing premature folding and aggregation, and refolds misfolded proteins.	[3, 10]
HSP90	Protein maturation, stability	HSP90 assists in the maturation of client proteins, including kinases, and stabilizes misfolded proteins.	[11, 12]
sHSPs (small heat shock proteins)	Prevent aggregation, assist in protein folding	sHSPs prevent aggregation by binding to unfolded proteins under stress and facilitate their refolding.	[10, 12]
HSP60 (GroEL)	Protein folding and assembly	HSP60 acts as a molecular chaperonin, forming a chamber where proteins are enclosed and properly folded.	[13, 14]
HSP100	Protein disaggregation, proteostasis	HSP100 proteins assist in the disaggregation of protein complexes and refold proteins under stress conditions.	[15]
TriC/CCT	Protein folding, oligomeric assembly	TriC/CCT is a chaperonin complex that assists in the folding of actin, tubulin, and other cytoskeletal proteins.	[16, 17]
HSP40	Co-chaperone, assists HSP70	HSP40 interacts with HSP70, guiding substrate proteins to HSP70 for folding and preventing aggregation.	[18, 19]

the proteasome to degrade them, while other misfolded proteins are transported to lysosomes for breakdown through autophagy. This intricate system is particularly vital for preventing neurodegenerative diseases associated with protein misfolding, such as Alzheimer's and Parkinson's diseases [12] (Table 1).

Proteolytic systems

Ubiquitin-proteasome system (UPS)

The UPS is an essential intracellular proteolytic pathway that plays a central role in maintaining proteostasis the delicate balance of protein synthesis, folding, and degradation within cells. The UPS ensures the selective degradation of damaged, misfolded, or unnecessary proteins, preventing the accumulation of toxic aggregates that can disrupt cellular function. The system operates through a tightly regulated sequence of events. It begins with the activation of ubiquitin, a small regulatory protein, by the E1 ubiquitin-activating enzyme in an ATP-dependent manner. This activated ubiquitin is transferred to the E2 ubiquitin-conjugating enzyme, and finally, the E3 ubiquitin ligase facilitates the attachment of ubiquitin to specific substrate proteins, determining their fate (Figure 1). Proteins tagged with polyubiquitin chains are subsequently recognized and degraded by the 26S proteasome, a highly specialized protease complex. The degradation process releases peptides, which are further broken down into amino acids for recycling.

E1 (ubiquitin-activating enzyme): E1 is the initial enzyme in the ubiquitination cascade. It activates ubiquitin in an ATP-dependent manner, forming a high-energy thioester bond between the C-terminal glycine residue of ubiquitin and a cysteine residue on the E1 enzyme. This step primes ubiquitin for subsequent transfer and is critical for initiating the ubiquitination process. E1 exists in limited numbers in cells, as a single E1 enzyme can activate multiple ubiquitin molecules for further transfer to E2 enzymes. The activation involves two steps: adenylation of the ubiquitin molecule's C-terminal glycine using ATP, producing ubiquitin-AMP and Formation of the thioester bond between ubiquitin and the active site cysteine of E1, releasing AMP [20].

E2 (ubiquitin-conjugating enzyme): The E2 enzyme receives ubiquitin from E1 through a transthiolation reaction, where the activated ubiquitin is transferred to an active site cysteine on E2. E2 enzymes are responsible for carrying ubiquitin to E3 ligases and determining the type of ubiquitin chain linkage that will be added to the substrate. E2 enzymes also dictate the topology of the ubiquitin chain, influencing the fate of the ubiquitinated protein. There are multiple E2 enzymes in cells, each specialized for different functions, such as monoubiquitination, polyubiquitination, or specific chain formations like K48-linked chains (for degradation) or K63-linked chains (for signaling) [21, 22].

E3 (ubiquitin ligase): E3 ligases are responsible for the substrate specificity of ubiquitination. These enzymes recognize target proteins through specific degradation signals or motifs, such as phosphorylation tags or hydrophobic patches exposed due to protein misfolding. E3 ligases catalyze the transfer of ubiquitin from the E2 enzyme to the target protein, either directly or indirectly. Types of E3 ligases: HECT (homologous to E6-AP carboxyl terminus): These E3 ligases form a thioester intermediate with ubiquitin before transferring it to the substrate. RING (really interesting new gene) and RBR (RING-between-RING): These E3s facilitate the direct transfer of ubiquitin from E2 to the substrate without forming a thioester bond. The substrate recognition of E3 ligases is critical for cellular regulation, as it ensures that only proteins marked for degradation are ubiquitinated. Examples include the MDM2 ligase, which targets p53, and Parkin, associated with mitochondrial quality control. The coordinated action of E1, E2, and E3 enzymes ensures the selectivity and efficiency of the UPS. This specificity is vital for maintaining cellular homeostasis, regulating the cell cycle, controlling apoptosis, responding to stress, and modulating signal transduction. Dysregulation in any step of the ubiquitina-

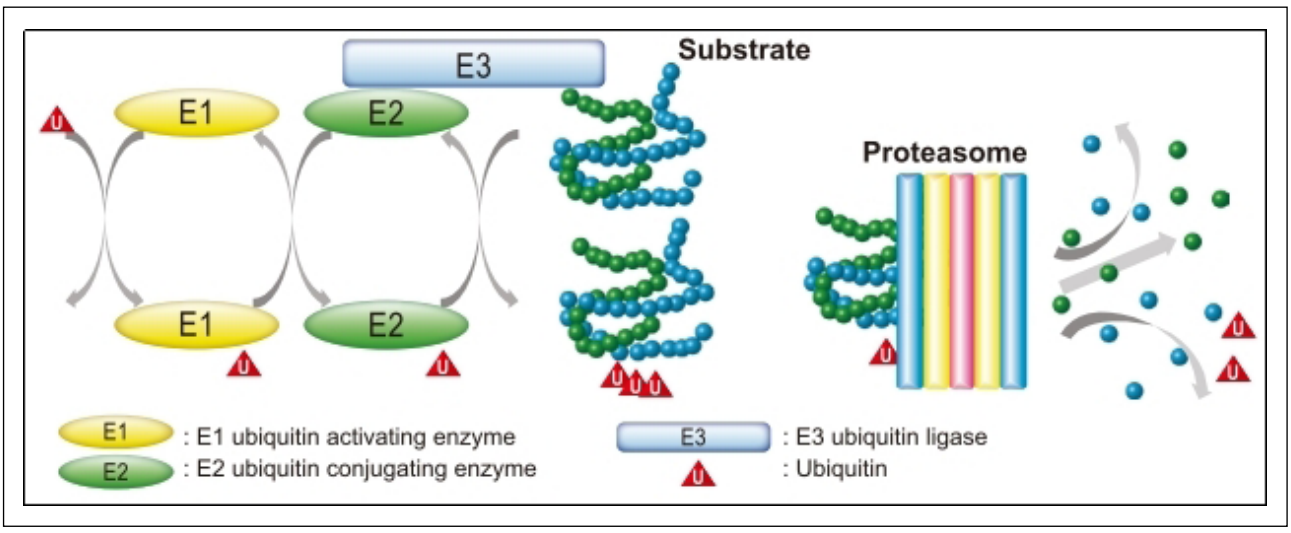

Figure 1. Ubiquitin-proteasome system (UPS).

tion process can lead to diseases such as cancer, neurodegenerative disorders (*e.g.*, Parkinson's disease due to Parkin dysfunction), and immune deficiencies [23, 24].

The UPS is fundamental to numerous biological processes, including cell cycle regulation, DNA repair, apoptosis, immune responses, and adaptation to stress. By removing oxidative damaged or misfolded proteins, the system protects cells from proteotoxicity, which is particularly critical in post-mitotic cells such as neurons. However, during aging, the efficiency of the UPS declines due to decreased expression of proteasomal subunits, reduced activity of E3 ligases, and accumulation of inhibitory substrates. This decline leads to the buildup of misfolded and aggregated proteins, contributing to cellular dysfunction and aging-related diseases, particularly neurodegenerative disorders. For instance, in Alzheimer's disease, the UPS struggles to manage the accumulation of amyloid-beta and tau proteins, while in Parkinson's disease; alpha-synuclein aggregates overwhelm the system. Similarly, Huntington's disease features polyglutamine expansions that resist proteasomal degradation, exacerbating the proteostasis imbalance [25, 26].

Research has also highlighted the interplay between the UPS and other proteolytic pathways, such as the autophagy-lysosome system, in managing cellular protein turnover. Together, these systems form a dynamic network to maintain proteostasis. However, with aging, this synergy is impaired, further exacerbating proteotoxic stress. Efforts to counteract this age-associated decline have inspired therapeutic approaches targeting the UPS. For example, small molecules that activate the proteasome or enhance the activity of E3 ligases show promise in clearing pathological proteins and restoring proteostasis [27]. Additionally, compounds that enhance the cross-talk between UPS and autophagy could provide dual benefits in promoting protein clearance. While proteasome inhibitors like bortezomib are effective in cancer therapies by inducing stress in rapidly dividing cells, their application in aging is limited due to the potential for exacerbating proteotoxic stress. Emerging research emphasizes the importance of understanding the molecular and structural intricacies of the UPS for developing precision therapies. Future strategies could include personalized approaches that target specific components of the UPS to enhance its activity in aging tissues or mitigate its dysfunction in disease states. The UPS remains a critical area of study for interventions aimed at extending health span and combating age-related pathologies [28, 29].

Autophagy-lysosome pathway (ALP)

The ALP is a fundamental cellular process that maintains homeostasis by degrading and recycling damaged proteins, dysfunctional organelles, and other cellular debris. This pathway operates by forming double-membraned vesicles, known as auto phagosomes, which engulf the targeted materials. Auto phagosomes subsequently fuse with lysosomes, specialized organelles containing hydrolytic enzymes, to form autolysosomes. Inside these autolysosomes, the contents are degraded into basic building blocks like amino acids and lipids, which are then recycled to support cellular functions and energy metabolism. This pathway is essential for maintaining proteostasis, adapting to stress, and regulating metabolism [30-32]. Autophagy is categorized into three types: macroautophagy, which targets large aggregates and organelles; microautophagy, where lysosomes directly engulf cytoplasmic material; and chaperone-mediated autophagy (CMA), a selective process where specific proteins are delivered to lysosomes by chaperones like Hsc70 and processed via LAMP-2A receptors. The ALP is tightly regulated by pathways such as mTOR, which inhibits autophagy under nutrient-rich conditions, and AMPK, which activates it

Table 2. Examples of proteolytic enzymes involved in aging, along with their roles.

Proteolytic enzyme	Function	Role in aging	References
Lon protease	Mitochondrial protease that degrades misfolded mitochondrial proteins	Decline in Lon protease activity with age contributes to mitochondrial dysfunction and oxidative stress, impacting cellular health	[39]
Proteasome	Multimeric enzyme complex that degrades damaged or unneeded proteins tagged by ubiquitin	Age-related decline in proteasomal activity leads to the accumulation of damaged proteins, contributing to age-related diseases like neurodegeneration	[40]
Aspartic proteases (*e.g.*, Cathepsin D)	Acidic proteases involved in protein degradation within lysosomes	Reduced cathepsin D activity in aging affects protein turnover and contributes to the build-up of damaged proteins in neurons, contributing to neurodegenerative diseases	[41]
Metalloproteinases (*e.g.*, MMP-9)	Enzyme responsible for breaking down extracellular matrix proteins	Overexpression of MMP-9 in aging promotes tissue degradation and has been implicated in diseases such as Alzheimer's and cardiovascular aging	[42]
Deubiquitinases (*e.g.*, USP14)	Proteases that remove ubiquitin from proteins, regulating protein degradation via the proteasome	Dysregulation of deubiquitinases like USP14 in aging can lead to the accumulation of damaged proteins and cellular dysfunction	[43]
Caspases	Cysteine-dependent proteases involved in apoptosis and cell death	Age-related activation of caspases contributes to neuronal loss and tissue degeneration seen in neurodegenerative diseases and other aging-associated pathologies	[44]
ClpXP protease	ATP-dependent protease that degrades abnormal proteins in bacteria and mitochondria	Decline in mitochondrial ClpXP activity during aging impairs protein quality control in mitochondria, contributing to mitochondrial dysfunction and cellular aging	[45]

under energy stress. Beclin-1 is a critical initiator of autophagosome formation [33].

Autophagy is a critical cellular process that relies on various proteolytic enzymes to maintain cellular homeostasis and function. These enzymes play essential roles in degrading damaged proteins and organelles, thereby supporting proteostasis and cellular health. As individuals age, the activity of these proteolytic enzyme declines, contributing to the accumulation of damaged proteins and dysfunctional cellular components. This decline in proteolytic activity is a key factor in the aging process and is linked to various age-related diseases. Table 2 provides examples of proteolytic enzymes involved in aging, along with their specific roles in maintaining cellular function. Autophagy efficiency declines with age, contributing to the accumulation of protein aggregates and damaged organelles. This decline exacerbates cellular dysfunction and is linked to age-related diseases. For example, in neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's, impaired autophagy leads to the accumulation of toxic protein aggregates. In metabolic disorders, autophagy dysfunction affects insulin signaling and lipid metabolism, aggravating conditions like diabetes and obesity. Interestingly, in cancer, autophagy has a dual role: it can suppress tumor initiation by clearing damaged components but may promote survival in established tumors under metabolic stress [34, 35]. Enhancing autophagy offers promising therapeutic potential. Pharmacological agents like rapamycin, which inhibits mTOR, and metformin, an AMPK activator, have shown efficacy in boosting autophagy and improving lifespan in preclinical models. Additionally, CMA enhancement by increasing LAMP-2A expression holds potential for selective degradation of toxic proteins. However, balancing autophagy is crucial to avoid excessive activation, which can lead to autophagic cell death. Continued research into autophagy modulation is key for developing therapies to combat aging-related diseases and improve health span [36-38].

Regulatory mechanisms of proteostasis

Transcription factors: HSF-1, Nrf2, and others

HSF-1 (heat shock factor 1) is a key transcription factor in the heat shock response (HSR), which is activated when cells experience proteotoxic stress, such as heat shock, oxidative damage, or heavy metal exposure. Under normal conditions, HSF-1 is kept inactive in the cytoplasm. When stress occurs, HSF-1 undergoes trimerization, a process that leads to its activation and translocation to the nucleus. Once in the nucleus, HSF-1 binds to heat shock elements (HSEs) in the promoter regions of heat shock protein (HSP) genes, initiating their transcription. These HSPs, such as HSP70 and HSP90, are molecular chaperones that help proteins fold correctly and protect against aggregation. HSF-1 activation has been linked to increased lifespan in organisms like *C. elegans* and *Drosophila* by enhancing cellular resistance to stress and reducing protein misfolding and aggregation, which are hallmarks of aging and neurodegenerative diseases. Furthermore, HSF-1 plays a role in regulating the expression of other stress-related genes, contributing to cellular maintenance during aging. Factor erythroid 2-related factor 2 (Nrf2) is a key regulator of the antioxidant response, orchestrating the expression of genes involved in oxidative stress defense. Under normal conditions, Nrf2 is kept inactive in the cytoplasm through binding to Keap1 (Kelch-like ECH-associated protein 1). Upon oxidative stress or electrophilic stress, Keap1 undergoes conformational changes that release Nrf2, allowing it to translocate to the nucleus. In the nucleus, Nrf2 binds to antioxidant response elements (AREs) in the promoter regions of genes encoding antioxidant enzymes (such as superoxide dismutase and glutathione S-transferase). Nrf2 activation is a critical response to counteract oxidative damage caused by reactive oxygen species (ROS). The decline in Nrf2 function during aging leads to an accumulation of oxidative damage, which accelerates aging and is implicated in neurodegenerative diseases such as Parkinson's and Alzheimer's disease. Boosting Nrf2 activity has been suggested as a therapeutic strategy to mitigate oxidative stress-related damage and enhance longevity [46-49].

Other transcrcontribute to stress responses and proteostasis regulation. For example, ATF4 (activating transcription factor 4) plays a central role in the unfolded protein response (UPR), a cellular mechanism activated under conditions of endoplasmic reticulum (ER) stress when misfolded proteins accumulate in the ER. ATF4 promotes the expression of genes that facilitate protein folding, degradation, and export, helping restore cellular homeostasis during stress. Additionally, FOXO transcription factors are involved in longevity regulation and the cellular response to stress. FOXO factors are activated by oxidative stress and promote autophagy, apoptosis, and the maintenance of cellular repair processes. Their role in aging is crucial, as they modulate both protein quality control and stress

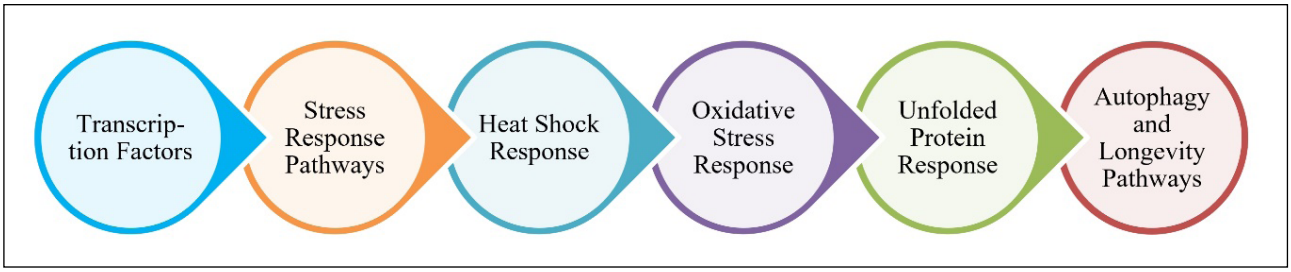

Figure 2. Regulatory mechanisms of proteostasis.

resilience (Figure 2) [50].

Stress response pathways

Stress response pathways are fundamental to maintaining proteostasis, especially under cellular stress conditions like oxidative stress, heat shock, nutrient deprivation, or the accumulation of damaged proteins. These pathways are regulated by transcription factors like HSF-1 and Nrf2, and their activation ensures cellular homeostasis. Below are key stress response pathways:

Heat shock response (HSR): The heat shock response, regulated by HSF-1, is one of the first lines of defense against proteotoxic stress, particularly when proteins begin to misfolded under high temperatures or stress conditions. HSF-1 activates the transcription of heat shock proteins (HSPs), which act as molecular chaperones to help in protein folding and prevent the aggregation of misfolded proteins. In aging, the efficiency of the heat shock response declines, contributing to the accumulation of misfolded proteins that exacerbate age-related diseases such as Alzheimer's, Huntington's, and Parkinson's diseases. Enhancing the heat shock response by activating HSF-1 has been shown to extend lifespan in model organisms and could be a therapeutic approach for combating age-related diseases [46, 51, 52].

Oxidative stress response: The oxidativrimarily regulated by Nrf2, is activated in response to increased levels of reactive oxygen species (ROS). ROS are byproducts of normal cellular metabolism, but their accumulation due to mitochondrial dysfunction, environmental stress, or aging can cause cellular damage. Nrf2 regulates the transcription of antioxidant genes that protect cells from oxidative damage. The ability to maintain Nrf2 activation diminishes with age, contributing to oxidative damage and inflammation, which accelerates aging and the development of neurodegenerative diseases. Nrf2 activation has thus become a promising target for therapies aimed at increasing cellular resistance to oxidative stress and promoting healthy aging [53, 54].

Unfolded protein response (UPR): The misfolded or unfolded proteins accumulate in the endoplasmic reticulum (ER). The UPR involves three key sensor proteins: IRE1, PERK, and ATF6, which help manage protein folding, quality control, and degradation. While the UPR can be

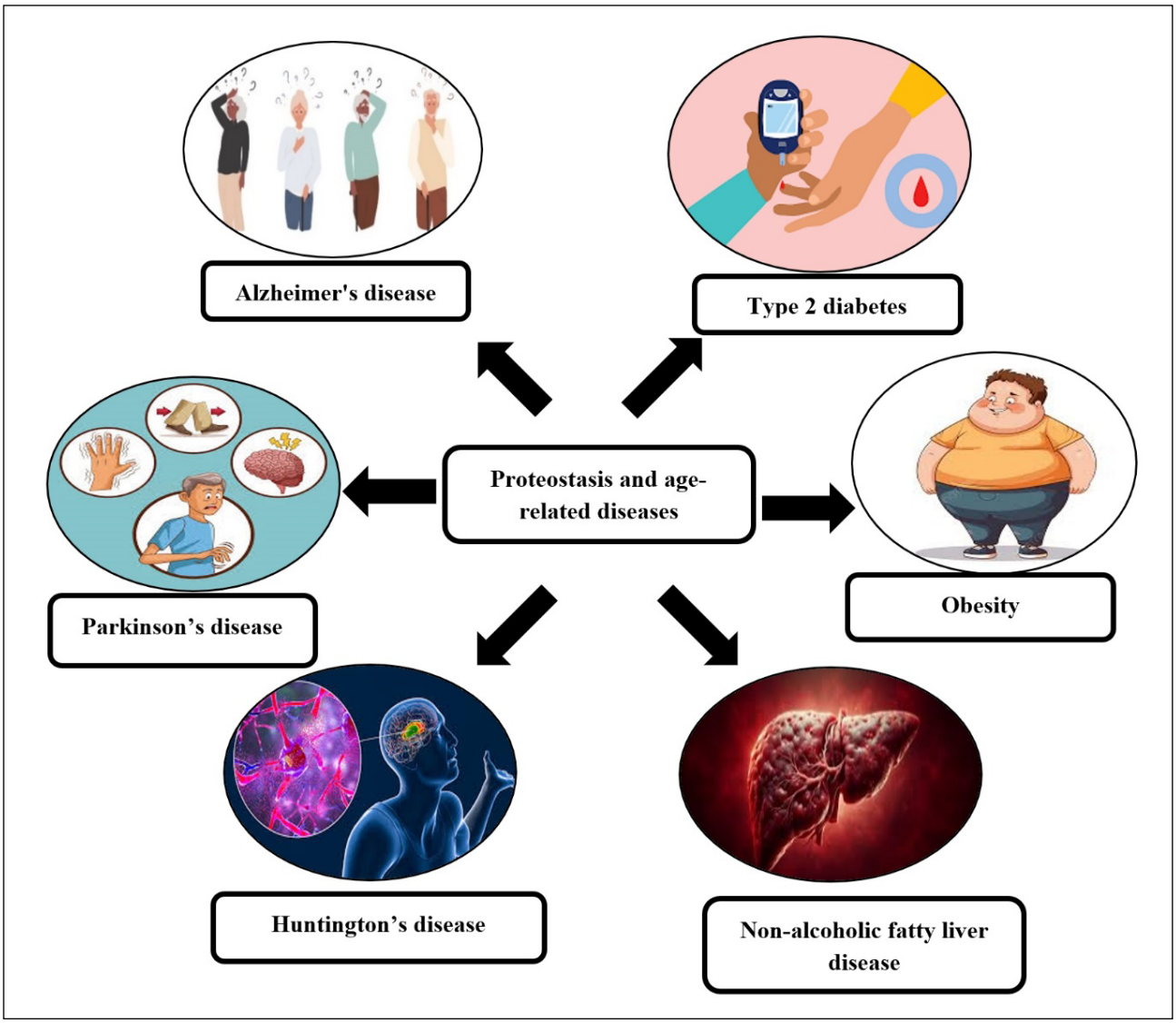

Figure 3. Proteostasis and age-related diseases.

protective by restoring cellular function and preventing damage, chronic or excessive UPR activation leads to apoptosis and has been linked to aging and diseases like Alzheimer's and Parkinson's. The efficiency of the UPR declines with age, contributing to protein aggregation and cellular dysfunction. Enhancing UPR signaling through modulation of its key components could hold therapeutic potential in aging-related diseases [55, 56].

Autophagy and longevity pathways: Auto degradation process that helps clear damaged proteins, organelles, and other cellular debris. Under stress, the autophagic process is upregulated, helping to maintain cellular homeostasis. The FOXO transcription factors play a critical role in promoting autophagy under stress conditions like oxidative damage or nutrient scarcity. In aging, the efficiency of autophagy decreases, leading to the accumulation of dysfunctional cellular components. This decline in autophagy has been linked to age-related diseases such as neurodegenerative disorders, cardiovascular diseases, and cancer. Strategies aimed at enhancing autophagic activity have shown promise in extending lifespan and mitigating the effects of aging. These transcription factors and stress response pathways are central to maintaining proteostasis, particularly under stress conditions [57].

Hallmarks of aging-related proteostasis dysfunction

Impaired protein folding

Proteins must fold into specific three-dimensional structures to perform their functions correctly. This folding process is highly dynamic and relies on molecular chaperones like HSP70, HSP90, and small heat shock proteins, which assist in maintaining the correct protein conformation under stressful conditions. With aging, the efficiency of these chaperones decreases, leading to an increased risk of proteins misfolding, which contributes significantly to aging-related diseases such as Alzheimer's, Parkinson's, and Huntington's diseases. As aging progresses, the cellular machinery that governs protein folding, including molecular chaperones and the endoplasmic reticulum (ER) chaperone system, deteriorates. This deterioration impairs the cell's ability to cope with misfolded proteins, leading to a decline in cellular function and an accumulation of proteotoxic species. These misfolded proteins can become toxic, disrupting cellular homeostasis and triggering pathways such as the unfolded protein response (UPR), which, when chronically activated, can lead to cellular apoptosis and tissue dysfunction [58, 59]. The unfolded protein response (UPR) is a critical cellular stress response triggered when the load of misfolded proteins overwhelms the protein folding machinery. In aging, the UPR becomes less effective, leading to a buildup of unfolded or misfolded proteins, which exacerbates the damage to cells and tissues. Chronic activation of the UPR is linked to various age-related diseases, including neurodegenerative disorders. The UPR and its relationship with aging highlights how impaired protein folding is a central feature of proteostasis dysfunction in aging [60, 61].

Accumulation of misfolded or aggregated proteins

The accumulation of misfolded and aggregated proteins is one of the most profound hallmarks of aging-related proteostasis dysfunction. Misfolded proteins, if not refolded correctly or degraded, tend to aggregate and form inclusion bodies, which are toxic to cells. These aggregates often resist degradation by the UPS or autophagy, which are the primary pathways responsible for the removal of damaged proteins. Over time, the accumulation of protein

Table 3. Systems affected by proteostasis decline.

System affected	Effect of proteostasis decline	Mechanisms involved	Disease implications	References
Neurons	Accumulation of misfolded proteins (*e.g.*, amyloid-β, tau, alpha-synuclein) leads to neurodegeneration, synaptic dysfunction, and cognitive decline.	Impaired protein folding, decreased chaperone function (HSP70, HSP90), and defective autophagy.	Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS.	[61]
Muscle cells	Decline in muscle function due to impaired protein turnover and aggregation of defective proteins such as in amyotrophic lateral sclerosis (ALS) and sarcopenia.	Decreased chaperone activity, proteasome dysfunction, and reduced autophagic activity.	Muscle atrophy, sarcopenia, ALS.	[63]
Heart	Proteostasis dysfunction impairs cardiac cells' ability to remove misfolded proteins, leading to heart failure and cardiomyopathy.	Impaired protein quality control (UPS and autophagy), reduced mitochondrial function, and accumulation of protein aggregates.	Heart failure, cardiomyopathy, and arrhythmias.	[64]
Liver	Accumulation of misfolded proteins disrupts liver cell function, leading to liver diseases such as fatty liver and fibrosis.	Decline in autophagic processes, proteasomal activity, and overall protein degradation efficiency.	Non-alcoholic fatty liver disease (NAFLD), liver fibrosis.	[65]
Kidneys	Proteostasis decline in renal cells leads to the accumulation of toxic protein aggregates and kidney dysfunction.	Impaired autophagic clearance, decreased proteasomal function, and mitochondrial stress in renal cells.	Chronic kidney disease, renal fibrosis, and glomerulosclerosis.	[66]

aggregates can overwhelm the cellular degradation systems, leading to cellular damage, inflammation, and organ dysfunction [46, 52]. A key example of this is amyloid plaques in Alzheimer's disease, composed primarily of amyloid-β (Aβ), which are the result of the aggregation of misfolded Aβ peptides. In Parkinson's disease, alpha-synuclein forms aggregates known as Lewy bodies. These aggregates interfere with normal cellular processes such as protein degradation and can lead to neurodegeneration and cell death. The accumulation of these protein aggregates is particularly problematic in neurons, which have limited regenerative capabilities. As cells age, their ability to clear protein aggregates diminishes, contributing to the onset of neurodegenerative diseases [62]. The role of impaired proteostasis in aging is especially evident in the context of the proteasome and autophagy, two key pathways that regulate the degradation of damaged proteins. With aging, the proteasome's efficiency decreases, and autophagic flux slows down, both of which contribute to the accumulation of protein aggregates. This impairment is a central feature of age-related diseases such as neurodegeneration, cardiovascular disease, and even cancer. For instance, impaired protein quality control mechanisms like chaperone function and autophagy can lead to the accumulation of misfolded proteins, which is especially detrimental in neurons and muscles. The consequences of proteostasis imbalance are evident across systems such as the nervous, cardiovascular, and metabolic systems. Table 3 outlines the key systems affected by the decline in proteostasis and their associated impact on cellular functions.

Proteostasis and age-related diseases: neurodegenerative diseases

Alzheimer's disease (AD)

Proteostasis, the cellular process that ensures proper protein synthesis, folding, and degradation, is critical for maintaining cellular function (Figure 3). In the context of AD, disruptions in proteostasis contribute significantly to the progression of the disease. As AD is characterized by the accumulation of misfolded proteins, the breakdown of proteostasis exacerbates the buildup of these toxic aggregates, leading to neuronal dysfunction, synaptic loss, and cognitive decline. The primary misfolded proteins involved in AD are Aβ and tau, which, when not properly managed by proteostasis mechanisms, form damaging plaques and tangles in the brain [67, 68]. The process of protein folding in AD is disrupted, with amyloid-beta and tau failing to achieve proper conformations and instead aggregating into toxic oligomers, fibrils, and plaques. Amyloid-beta is generated from the amyloid precursor protein (APP) by the sequential cleavage of secretases, but in AD, this peptide accumulates due to inefficient clearance mechanisms. Similarly, tau, a protein involved in stabilizing microtubules, becomes hyperphosphorylated in AD, causing it to detach from microtubules and form neurofibrillary tangles inside neurons. These tangles disrupt essential neuronal functions such as intracellular transport and synaptic communication, contributing to cognitive impairment and neurodegeneration [69-71]. In animal models, impaired protein folding, aggregation, and degradation pathways have been shown to exacerbate the accumulation of toxic proteins such as amyloid-beta and tau, which are central to AD pathology. These animal studies have provided valuable insights into how proteostasis decline accelerates the development and progression of AD. Table 4 summarizes several animal studies that investigate

Table 4. Animal studies investigating the progression of Alzheimer's disease (AD) due to proteostasis dysfunction in aging.

Animal model	Proteostasis mechanism studied	Findings	Reference
Transgenic mice (3xTg-AD)	Ubiquitin-proteasome system (UPS)	Aging worsens UPS dysfunction, increasing protein aggregation and neuroinflammation, leading to cognitive decline.	[81]
AβPP/PS1 transgenic mice	Autophagy	Impaired autophagy in aging promotes Aβ and tau accumulation, worsening memory.	[82]
AβPP/PS1 double transgenic mice	ER stress (UPR)	Aging increases ER stress, leading to tau phosphorylation and neuronal damage.	[83]
Tau transgenic mice (rTg4510)	Chaperones (HSP70, HSP90)	Reduced chaperone levels in aging increase tau aggregation.	[84]
APP/PS1 transgenic mice	Mitochondrial dysfunction	Mitochondrial dysfunction accelerates cognitive decline in aged mice.	[85]
Tg2576 mouse model	Autophagy and UPS	Impaired autophagy and UPS contribute to Aβ buildup and memory loss in aging.	[86]
5xFAD transgenic mice	Proteasome and autophagy cross-talk	Failure of both UPS and autophagy accelerates Aβ accumulation and cognitive decline.	[87]
AppNL-F/NL-F mice	Chaperone-assisted protein degradation	Aging reduces chaperone activity, leading to increased Aβ aggregation.	[88]
3xTg-AD mice	Proteasome function	Aging impairs proteasomal degradation, leading to neurotoxic protein accumulation.	[89]
Tg2576 mice	ER stress and UPR	Chronic ER stress in aging worsens Aβ pathology and cognitive decline.	[90]

the impact of proteostasis dysfunction on the progression of Alzheimer's disease in aging.

A critical aspect of proteostasis failure in AD is the impairment of two major protein degradation systems: the ubiquitin-proteasome system (UPS) and autophagy. The UPS is responsible for tagging misfolded proteins with ubiquitin and directing them for degradation in the proteasome. In AD, however, the efficiency of the UPS is reduced, leading to the accumulation of damaged proteins like amyloid-beta and tau. Similarly, autophagy, a process that degrades damaged proteins and organelles in lysosomes, is often impaired in AD, contributing to the build-up of protein aggregates. The inability to clear misfolded proteins accelerates neuronal damage, making it a central feature in the progression of the disease [72]. Molecular chaperones, such as HSP70 and HSP90, are proteins that assist in the proper folding of other proteins and prevent aggregation. However, in AD, the function of these chaperones is compromised, which exacerbates the accumulation of misfolded amyloid-beta and tau. Chaperones play an essential role in maintaining proteostasis, and when their activity is reduced, protein aggregation becomes more likely, accelerating disease progression. The loss of chaperone activity further compounds the problem, as it hampers the cell's ability to manage misfolded proteins, thus promoting the accumulation of toxic aggregates [73-76].

In addition to these disruptions, endoplasmic reticulum (ER) stress plays a significant role in AD. The ER is responsible for protein folding and quality control, but when overwhelmed by an excess of misfolded proteins like amyloid-beta, it activates the unfolded protein response (UPR). The UPR aims to restore proteostasis by halting protein synthesis and increasing protein degradation. However, in AD, the UPR is often prolonged, leading to neuronal dysfunction and death. Chronic ER stress can activate apoptotic pathways, further exacerbating synaptic loss and neurodegeneration. Proteostasis failure in AD also triggers an inflammatory response in the brain. The accumulation of amyloid-beta and tau aggregates activates glial cells, such as microglia and astrocytes, which play a role in neuroinflammation. While this response is intended to clear toxic proteins, chronic inflammation worsens proteostasis dysfunction by inhibiting protein degradation systems and promoting further protein aggregation. This inflammatory feedback loop contributes to disease progression and worsens the overall neuronal environment [77, 78]. Genetic and environmental factors also influence proteostasis failure in AD. Certain mutations, such as those in the APP gene or presenilins (PS1, PS2), lead to an overproduction of amyloid-beta or impair its clearance, further disrupting proteostasis. Environmental factors like

Table 5. Animal studies investigating the progression of Parkinson's disease (PD) due to proteostasis dysfunction in aging.

Animal model	Proteostasis mechanism studied	Findings	Reference
α-synuclein transgenic mice	Ubiquitin-proteasome system (UPS)	Aging leads to the accumulation of α-synuclein aggregates due to UPS dysfunction, contributing to neurodegeneration and motor deficits in PD.	[105]
MPTP-treated mice (Parkinson's model)	Autophagy	Impaired autophagic degradation of misfolded proteins such as α-synuclein accelerates dopaminergic neurodegeneration in aging mice.	[106]
Park2 knockout mice (Parkinson's model)	Parkin and mitophagy	Aging exacerbates mitochondrial dysfunction and impairments in Parkin-mediated mitophagy, leading to dopaminergic degeneration and motor deficits.	[107]
α-synuclein transgenic mice	Chaperones (HSP70, HSP90)	Decreased levels of HSP70 and HSP90 with aging lead to the accumulation of α-synuclein aggregates, promoting neurodegeneration and motor impairments.	[108]
α-synuclein transgenic mice	Proteasome function	Aging exacerbates proteasome dysfunction, leading to the accumulation of ubiquitinated α-synuclein and dopaminergic cell death.	[109]
α-synuclein transgenic mice	Autophagy and UPS	Both autophagy and UPS impairments in aging promote α-synuclein aggregation and neurodegeneration, contributing to PD pathogenesis.	[110]
MPTP-induced mice model	Mitochondrial dysfunction	Aging increases mitochondrial dysfunction and decreases mitophagy, exacerbating dopaminergic cell death and motor deficits in PD.	[111]
Park2 mutant mice (Parkinson's model)	Mitophagy	Defective mitophagy in aging leads to the accumulation of damaged mitochondria and dopaminergic neurodegeneration in PD models.	[112]
α-synuclein transgenic mice	Exosome-mediated protein degradation	Exosome secretion and the clearance of α-synuclein are impaired in aging, contributing to the accumulation of toxic aggregates and neurodegeneration.	[113]
α-synuclein transgenic mice	Chaperone-mediated autophagy (CMA)	CMA dysfunction in aging leads to α-synuclein aggregation and progressive dopaminergic neuronal death.	[114]

oxidative stress, metabolic dysfunction, and aging can also impair proteostasis mechanisms, making neurons more vulnerable to the toxic effects of misfolded proteins. Given the central role of proteostasis in AD, therapeutic strategies targeting protein aggregation, folding, and degradation pathways have emerged as potential treatments. Enhancing the activity of the proteasome and autophagy systems could help clear amyloid-beta and tau aggregates, potentially slowing or halting disease progression. Additionally, immunotherapies targeting amyloid-beta or tau have shown promise in reducing the buildup of these toxic proteins. Another potential approach involves boosting the activity of molecular chaperones to prevent the misfolding and aggregation of proteins. Further research into restoring proteostasis through these mechanisms offers hope for the development of disease-modifying therapies for AD [79, 80].

Parkinson's disease (PD)

In PD, proteostasis is compromised, leading to the accumulation of misfolded proteins, particularly α-synuclein, which aggregates into toxic forms known as Lewy bodies. These aggregates disrupt cellular functions, including synaptic activity, mitochondrial function, and axonal transport, contributing to the degeneration of dopaminergic neurons in the substantia nigra, the brain region most affected in PD. The failure of proteostasis in PD is primarily driven by dysfunction in key protein degradation pasthways, including the UPS and autophagy. The UPS is responsible for tagging misfolded or damaged proteins with ubiquitin, marking them for degradation by the proteasome. However, in PD, the efficiency of the UPS is often impaired. This is particularly evident in cases where mutations in the Parkin gene, which plays a key role in protein degradation, prevent the efficient clearance of damaged proteins. As a result, proteins like α-synuclein accumulate in neurons, forming toxic aggregates that interfere with normal cellular processes and contribute to neurodegeneration. Similarly, the ALP, which is responsible for clearing larger protein aggregates and damaged organelles, is also disrupted in PD. Impairment of autophagy prevents the clearance of α-synuclein and other misfolded proteins, accelerating the buildup of toxic aggregates and promoting neuronal damage [91-95].

One of the most prominent features of PD pathology is the aggregation of α-synuclein, a protein that under normal conditions helps regulate neurotransmitter release and synaptic function. However, in PD, α-synuclein becomes misfolded and aggregates into insoluble fibrils, forming Lewy bodies that are toxic to neurons. Normally, cellular chaperones such as HSP70 and HSP90 help prevent α-synuclein aggregation and facilitate its degradation. In PD, the activity of these chaperones is often insufficient, allowing α-synuclein to misfold and aggregate. These aggregates not only disrupt cellular functions but also spread from neuron to neuron, propagating the disease throughout the brain in a characteristic manner [96, 97]. Mitochondrial dysfunction is another hallmark of PD, and

Table 6. Animal studies investigating the progression of Huntington's disease (HD) due to proteostasis dysfunction in aging.

Animal model	Proteostasis mechanism studied	Findings	Reference
Huntington's disease knock-in mice (HDKI)	Ubiquitin-proteasome system (UPS)	Aging increases the accumulation of polyglutamine aggregates due to impaired UPS function, contributing to neuronal toxicity and motor deficits in HD.	[124]
R6/2 mice (HD model)	Autophagy	Autophagic dysfunction with age leads to the accumulation of Huntingtin aggregates, which contributes to neuronal degeneration and motor impairment in HD.	[125]
R6/2 transgenic mice	Proteasome function	Proteasome dysfunction in aging enhances the accumulation of Huntingtin aggregates, which leads to synaptic dysfunction and neuronal death.	[126]
R6/2 mice	Autophagy and the UPS	Defective autophagy and UPS function in aging contribute to the accumulation of toxic Huntingtin aggregates, leading to motor deficits and neurodegeneration.	[127]
ZQ175 mice (HD model)	Mitochondrial dysfunction	Aging leads to increased mitochondrial dysfunction, and impaired mitophagy, exacerbating the accumulation of Huntingtin aggregates and neuronal loss.	[128]
R6/2 transgenic mice	Protein aggregation	Aging accelerates Huntingtin protein aggregation, leading to neurodegeneration and motor dysfunction in HD models.	[129]
Q175 knock-in mice	Chaperone-mediated protein degradation	Age-related decline in HSP70 function exacerbates Huntingtin inclusion formation, promoting progressive motor deficits and neurodegeneration.	[130]
HdhQ150 mice (HD model)	Autophagy and lysosomal pathways	Autophagy defects in aging lead to the accumulation of toxic Huntingtin aggregates, contributing to striatal neurodegeneration and movement disorders.	[131]

it is closely linked to proteostasis failure. Mitochondria are responsible for generating energy and maintaining cellular homeostasis, but they are also susceptible to damage by misfolded proteins and oxidative stress. In PD, defective mitophagy—an autophagic process that specifically clears damaged mitochondria is a significant contributor to the progression of the disease. Mutations in genes like PINK1 and Parkin, which are involved in the regulation of mitophagy, result in the accumulation of dysfunctional mitochondria that increase oxidative stress and exacerbate neurodegeneration [98].

The impairment of proteostasis also triggers inflammation within the brain, further accelerating PD progression. The accumulation of misfolded α-synuclein aggregates activates microglia, the immune cells of the brain, which release pro-inflammatory cytokines that promote neuroinflammation. This inflammatory response not only worsens neuronal damage but also impairs the function of proteostasis systems, creating a vicious cycle that accelerates the degeneration of dopaminergic neurons. Chronic inflammation further exacerbates oxidative stress and disrupts cellular proteostasis, making it more difficult for neurons to clear misfolded proteins and damaged organelles [99-102].

Genetic mutations contribute to proteostasis failure in PD, particularly in familial forms of the disease. Mutations in genes such as Parkin, PINK1, and DJ-1 impair the cellular machinery responsible for protein degradation, making neurons more susceptible to the accumulation of misfolded proteins like α-synuclein. These mutations highlight the critical role of proteostasis in PD and provide insights into the molecular mechanisms driving the disease. Additionally, mutations in the α-synuclein gene itself can lead to an increased propensity for misfolding and aggregation, further promoting the accumulation of toxic proteins [103, 104]. Animal studies have demonstrated that disruptions in protein quality control mechanisms, such as impaired autophagy and proteasomal degradation, contribute to the accumulation of misfolded proteins like alpha-synuclein, which is a hallmark of PD pathology. These studies help elucidate how the decline in proteostasis over time accelerates the onset and progression of Parkinson's Disease (Table 5).

Huntington's disease (HD)

HD is a neurodegenerative disorder caused by an expansion of the CAG repeat in the HTT gene, which encodes the protein huntingtin. In HD, the polyglutamine (polyQ) tract within huntingtin becomes abnormally long, leading to the misfolding and aggregation of huntingtin, which in turn disrupts cellular proteostasis and contributes to neuronal dysfunction and death. The failure of proteostasis pathways, including the UPS and autophagy, plays a central role in HD progression by promoting the accumulation of misfolded huntingtin and other toxic proteins, thereby accelerating neurodegeneration. One of the primary contributors to proteostasis dysfunction in HD is the accumulation of misfolded mutant huntingtin (mHTT), which forms inclusions in neurons. These inclusions are highly toxic and disrupt various cellular processes, including vesicular trafficking, gene expression, and mitochondrial function. Normally, the UPS is responsible for tagging damaged or misfolded proteins with ubiquitin and targeting them for degradation by the proteasome. However, in HD, the UPS is overwhelmed by the accumulation of mHTT aggregates, leading to impaired clearance of the toxic protein. Studies have shown that the UPS is significantly impaired in HD, as the presence of mHTT interferes with the function of the proteasome, further exacerbating proteostasis failure and promoting the accumulation of other misfolded proteins [115-117].

In addition to the UPS, autophagy, a critical process that clears damaged proteins and organelles, is also compromised in HD. The autophagy-lysosome pathway (ALP), which is responsible for the degradation of large protein aggregates and dysfunctional organelles, is dysfunctional in HD. The presence of mHTT disrupts the normal function of autophagy, preventing the efficient clearance of aggregates. Autophagic impairment in HD contributes to the buildup of toxic aggregates and dysfunctional mitochondria, leading to increased oxidative stress, cellular damage, and neuronal death. Interestingly, enhancing autophagy has been shown in some models of HD to improve the clearance of mHTT aggregates and ameliorate some aspects of the disease, suggesting that restoring autophagic function may be a therapeutic strategy. Moreover, the failure of molecular chaperones, such as HSP70 and HSP90, which help in the proper folding of proteins and prevent aggregation, also contributes to proteostasis dysfunction in HD. In healthy cells, these chaperones assist in refolding misfolded proteins or targeting them for degradation. However, in HD, the chaperone system is overwhelmed by the excess of misfolded mHTT, reducing the ability of the cell to cope with protein misfolding. This leads to an increased burden of protein aggregation, which damages cellular components and accelerates the disease process. Additionally, chaperones like HSP70 can also help in clearing mHTT aggregates via autophagy, making them crucial players in maintaining proteostasis in HD [118-120].

The mitochondrial dysfunction observed in HD is another key aspect of proteostasis failure. Mitochondria are essential for energy production and cellular homeostasis, and their function is particularly important for neurons, which are highly energy-demanding. mHTT aggregates impair mitochondrial function by disrupting mitochondrial dynamics, including fission, fusion, and transport, and by increasing mitochondrial permeability, leading to energy deficits and increased oxidative stress. Both the UPS and autophagy are involved in the clearance of damaged mitochondria, and their dysfunction contributes to mitochondrial damage in HD, exacerbating neurodegeneration. Impaired mitophagy, the process by which damaged mitochondria are degraded, has been observed in HD, further contributing to cellular dysfunction and neuronal loss [121]. Chronic inflammation, often observed in neurodegenerative diseases, also plays a role in proteostasis dysfunction in HD. The accumulation of mHTT and other misfolded proteins activates microglia, the resident

Table 7. Animal studies investigating the progression of metabolic disorders (such as obesity, type 2 diabetes, insulin resistance, and fatty liver disease) due to proteostasis dysfunction in aging.

Animal model	Proteostasis mechanism studied	Findings	Reference
C57BL/6J mice	Ubiquitin-proteasome system (UPS)	Aging impairs UPS function, leading to the accumulation of misfolded proteins, insulin resistance, and adiposity.	[136]
ApoE knockout mice	Autophagy	Age-related decline in autophagic activity exacerbates liver steatosis, insulin resistance, and obesity.	[137]
Db/db mice (type 2 diabetes model)	Endoplasmic reticulum stress (ER Stress)	Aging-induced ER stress leads to impaired insulin signaling, promoting type 2 diabetes and obesity.	[7]
C57BL/6 mice on high-fat diet	Mitochondrial dysfunction	Mitochondrial dysfunction during aging reduces energy expenditure and promotes insulin resistance and fatty liver.	[138]
Ob/Ob mice (obesity model)	Chaperones (HSP70)	Decline in HSP70 levels with aging leads to protein aggregation, impairing glucose metabolism and promoting obesity.	[139]
C57BL/6J mice	Proteostasis network (autophagy, UPS)	Impaired proteostasis network in aging leads to the accumulation of misfolded proteins in liver and adipose tissue, contributing to insulin resistance and fatty liver.	[140]
C57BL/6J mice (diet-induced obesity)	Autophagy and lipid metabolism	Aging-related autophagy defects contribute to lipid accumulation and insulin resistance, particularly in adipose tissue.	[141]
Zfp281 knockout mice	Chaperone-mediated protein degradation	Impaired chaperone-mediated protein degradation leads to glucose intolerance and fatty liver as mice age.	[142]
Sirt1 knockout mice	Proteostasis and mitochondrial quality control	Aging-related decline in Sirt1 reduces mitophagy, leading to insulin resistance and obesity in aging mice.	[143]
C57BL/6J mice (high-fat diet)	Lysosomal function and autophagy	Aging impairs lysosomal function and autophagic flux, contributing to obesity and insulin resistance in aging mice.	[144]

immune cells of the brain, leading to the release of pro-inflammatory cytokines. This neuroinflammation can further impair proteostasis by affecting protein degradation pathways, such as the UPS and autophagy. Inflammatory cytokines can also increase oxidative stress, which in turn damages cellular components, including proteins, lipids, and DNA, creating a vicious cycle of proteostasis failure and neurodegeneration [122, 123]. Animal studies investigating HD have shown that the accumulation of misfolded huntingtin protein, a hallmark of the disease, is linked to impaired protein degradation and aggregation pathways. These studies provide valuable insights into how the decline of proteostasis contributes to the progression of HD (Table 6).

Metabolic disorders

Disruption of proteostasis is implicated in the progression of age-related metabolic disorders, such as type 2 diabetes (T2D), obesity, and non-alcoholic fatty liver disease (NAFLD). These disorders are often characterized by the accumulation of misfolded proteins, mitochondrial dysfunction, and altered cellular signaling pathways, all of which are exacerbated by impaired proteostasis. In age-related metabolic diseases, proteostasis failure leads to dysfunction in key organs, including the liver, pancreas, and adipose tissue, which are critical for maintaining energy balance, glucose homeostasis, and lipid metabolism. Proteostasis dysfunction has been implicated in the progression of various metabolic disorders, including obesity, type 2 diabetes, insulin resistance, and fatty liver disease, particularly as aging compromises cellular quality control mechanisms. Animal studies have shown that the decline in protein folding, degradation, and recycling systems contributes to the development and exacerbation of these metabolic conditions. For example, impaired autophagy and proteasomal function in aging models lead to the accumulation of damaged proteins and organelles, disrupting metabolic homeostasis. Table 7 summarizes key animal studies that explore the relationship between proteostasis dysfunction and the progression of metabolic disorders in aging.

Type 2 diabetes (T2D): In T2D, proteostasis failure is a key factor in the progression of the disease. The pancreatic β-cells, which are responsible for insulin secretion, are particularly vulnerable to proteotoxic stress. The accumulation of misfolded or aggregated proteins, particularly in the endoplasmic reticulum (ER), disrupts normal cellular function and induces ER stress. Under normal conditions, the ER is responsible for protein folding, but under conditions of metabolic stress (such as obesity and insulin

resistance), this process is overwhelmed. This leads to the activation of the UPR, a cellular stress response aimed at restoring proteostasis by enhancing protein folding capacity and promoting degradation of misfolded proteins. However, in the long term, persistent ER stress can result in β-cell dysfunction and apoptosis, contributing to impaired insulin secretion and the development of insulin resistance. The UPS and autophagy also play significant roles in maintaining proteostasis in T2D. In insulin-resistant states, the accumulation of misfolded proteins and damaged organelles (such as mitochondria) is observed, suggesting a failure in both the UPS and autophagy. This accumulation of damaged proteins disrupts insulin signaling and exacerbates the systemic inflammation that contributes to insulin resistance. Additionally, proteostasis failure in adipocytes (fat cells) can affect adipose tissue function, leading to increased lipid accumulation and the development of metabolic complications like dyslipidemia and fatty liver [132, 133].

Obesity: In obesity, proteostasis failure plays a central role in adipose tissue dysfunction, which contributes to the progression of metabolic disorders. In the obese state, excessive fat accumulation leads to an overload of proteins and lipids in adipocytes, impairing normal protein folding and triggering ER stress. Chronic ER stress in adipose tissue is linked to the development of insulin resistance and inflammation, both of which contribute to the progression of obesity-related metabolic disorders. The disruption of proteostasis in adipocytes also affects adipokine production, including leptin and adiponectin, which are crucial for regulating appetite, energy expenditure, and insulin sensitivity. Dysregulation of these pathways leads to a vicious cycle of obesity and metabolic dysfunction. Moreover, obesity-induced inflammation activates microglia and macrophages in adipose tissue, further exacerbating proteostasis failure. These immune cells release pro-inflammatory cytokines, which impair cellular functions in adipocytes and other tissues. Mitochondrial dysfunction in adipocytes and other tissues, exacerbated by the accumulation of misfolded proteins, also contributes to the progression of obesity and metabolic disease. Impaired mitochondrial function leads to increased oxidative stress and inflammation, further accelerating cellular damage and metabolic dysfunction [134, 135].

NAFLD: In NAFLD, proteostasis dysfunction contributes to the accumulation of misfolded proteins in the liver, leading to hepatocyte stress and liver damage. The liver plays a central role in regulating lipid metabolism, detoxification, and protein synthesis. In NAFLD, excessive lipid accumulation, particularly triglycerides, leads to cellular stress and the activation of the UPR in the ER. The liver's ability to handle this stress is compromised due to impaired proteostasis, resulting in hepatocyte injury, inflammation, and fibrosis. Chronic ER stress in liver cells is associated with insulin resistance, steatosis (fatty liver), and steatohepatitis, the progression of which can eventually lead to cirrhosis and liver failure. The UPS and autophagy are crucial for the clearance of damaged proteins and organelles in hepatocytes. In NAFLD, these protein degradation systems are often impaired, leading to the accumulation of damaged proteins, including those involved in mitochondrial dysfunction. Mitochondria are essential for energy production and maintaining metabolic homeostasis in the liver, and their dysfunction is a hallmark of NAFLD. Impaired mitochondrial function further exacerbates oxidative stress and the development of insulin resistance. Restoration of proteostasis in hepatocytes through enhancing autophagy or the UPS could help prevent or slow the progression of NAFLD [135].

Therapeutic approaches in targeting proteostasis for healthy aging

Targeting chaperones and folding pathways

One promising therapeutic approach to maintain proteostasis in aging involves the development of chaperone-enhancing drugs. Molecular chaperones, like HSP70 and HSP90, play a crucial role in protein folding, stability, and preventing aggregation. In aging, these chaperones become less efficient, leading to the accumulation of misfolded proteins and cellular dysfunction. By enhanc-

Table 8. Some ongoing clinical trials related to proteolysis in aging.

Study name	Clinical trial ID	Intervention	Phase	Focus area	Status
Lomecel-B for aging frailty	NCT03735277	Mesenchymal stem cells (MSCs)	Phase II	Aging frailty and sarcopenia	Active, recruiting
Senolytic therapy for aging	NCT03814783	Dasatinib + quercetin	Phase I/II	Cellular senescence and aging	Active, recruiting
Exosome therapy for aging frailty	NCT04162357	Exosomes derived from MSCs	Phase I/II	Age-related frailty	Active, recruiting
Targeting senescence in cardiovascular aging	NCT04531443	Navitoclax (Bcl-2 inhibitor)	Phase I	Cardiovascular aging and endothelial dysfunction	Recruiting
Proteostasis restoration in neurodegeneration	NCT04644313	Proteostasis regulators (*e.g.*, modafinil)	Phase I	Alzheimer's and neurodegenerative diseases	Recruiting
Impact of autophagy enhancement on aging	NCT03063689	Rapamycin	Phase II	Autophagy in aging-related conditions	Active, not recruiting

ing the activity of these chaperones, it may be possible to improve protein quality control and slow down the progression of age-related diseases. Small molecules such as Geranylgeranyl acetone (GGA) have been shown to activate heat shock proteins and reduce neurodegenerative symptoms in animal models, particularly in Alzheimer's and Parkinson's diseases [145]. Moreover, the development of small molecule inhibitors that target the molecular chaperone HSP90 has shown promise in preclinical trials for conditions like cancer and neurodegenerative diseases, suggesting that enhancing chaperone activity could help in ameliorating the proteostasis dysfunctions associated with aging [28]. However, more clinical trials and validation in human studies are needed to confirm their efficacy and safety for long-term use in aging populations [146].

Modulating proteolytic systems

Modulating the proteolytic systems, particularly the ubiquitin-proteasome system (UPS) and autophagy, is another approach to restore proteostasis. The UPS is responsible for degrading misfolded or damaged proteins, while autophagy helps in the removal of larger cellular debris, including damaged organelles. Both pathways deteriorate with age, contributing to the accumulation of toxic protein aggregates. Activating these pathways could clear accumulated misfolded proteins and prevent the cellular damage associated with aging and disease. Research has shown that enhancing UPS activity using small molecules like epoxomicin, a proteasome inhibitor, can improve protein degradation in aged cells, leading to enhanced protein homeostasis [147]. Similarly, boosting autophagy through compounds like rapamycin (which inhibits the mTOR pathway) has been linked to improved longevity and reduced age-related disease in model organisms [148]. These strategies, however, need to be carefully managed, as overactivation of proteolytic pathways could lead to cellular stress or undesirable effects. Clinical trials investigating autophagy enhancers and proteasome activators are underway as summarized in Table 8, but significant challenges remain in fine-tuning these pathways for therapeutic use [149].

Emerging therapeutics

Several promising proteostasis regulators are currently in clinical trials, aiming to slow aging and treat age-related diseases by restoring proteostasis. One such approach involves Nrf2 activators, which can regulate the expression of genes involved in oxidative stress response and protein degradation. Preclinical studies have shown that activating Nrf2 can enhance the cellular antioxidant capacity and improve proteostasis, potentially delaying age-related neurodegeneration and metabolic dysfunction [150]. Another class of proteostasis regulators under investigation includes HSP70 inducers like BGP-15, which has been shown to promote protein refolding and prevent aggregation in neurodegenerative diseases [151]. These compounds are undergoing early-phase clinical trials, and while the results are promising, the long-term safety and effectiveness of these therapies require further exploration. A significant challenge in this area remains developing drugs that can specifically target proteostasis pathways without causing off-target effects, particularly when using systemic activators that affect multiple tissues in the body.

Conclusions

This review underscores the pivotal role of proteostasis in maintaining cellular function, particularly in aging and neurodegenerative diseases. Proteostasis, the balance of protein synthesis, folding, and degradation, is maintained by molecular chaperones like heat shock proteins (HSPs), which ensure proper protein folding, prevent aggregation, and promote the degradation of misfolded proteins. Chaperones, including HSP70, HSP90, and small heat shock proteins, are crucial for maintaining protein stability, especially under stress conditions such as heat or oxidative stress. These proteins also guide misfolded proteins to degradation pathways, such as the ubiquitin-proteasome system (UPS) and autophagy, to prevent the accumulation of toxic aggregates. The UPS plays a central role in maintaining proteostasis by selectively degrading damaged or unnecessary proteins through a regulated process involving ubiquitination and proteasomal degradation. Autophagy further supports proteostasis by degrading damaged proteins and organelles through lysosomal pathways. However, with aging, the efficiency of both the UPS and autophagy declines, leading to an accumulation of misfolded or aggregated proteins. These aggregates, which are resistant to degradation, disrupt cellular function and contribute to neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's diseases.
Proteostasis dysfunction is a hallmark of aging, and as molecular chaperones, proteolytic systems, and stress response pathways become less efficient over time, the cellular machinery struggles to manage protein quality control. This dysfunction exacerbates protein misfolding and aggregation, triggering cellular stress responses like the UPR, which, when chronically activated, leads to cellular damage and dysfunction. The accumulation of toxic protein aggregates in neurons is particularly detrimental due to their limited regenerative capacity, contributing to the onset and progression of neurodegenerative diseases.

Future research scope

A critical gap in current proteostasis research lies in understanding how cellular proteostasis mechanisms differ from those at the organismal level, particularly in the context of aging. While cellular proteostasis focuses on the maintenance of protein homeostasis within individual cells, the systemic effects of aging introduce additional complexities, such as inter-organ communication and the accumulation of damaged proteins across tissues. Future research should focus on elucidating how proteostasis networks function at the organismal level, exploring how aging in one tissue or organ may influence proteostasis in others. This will provide a more comprehensive understanding of systemic aging and help identify novel thera-

peutic targets for age-related diseases like Alzheimer's and Parkinson's.

Integrating high-throughput proteomics with emerging technologies such as single-cell RNA sequencing and organ-on-a-chip models holds significant potential for bridging these gaps. High-throughput proteomics will enable the identification of age-related changes in protein dynamics, while single-cell RNA sequencing will offer insights into cellular heterogeneity and how different cell types maintain proteostasis as they age. Moreover, organ-on-a-chip technologies can simulate human tissue responses to proteostasis imbalances in a controlled environment, advancing the development of more accurate models for human aging. Personalized medicine approaches, incorporating genetic, environmental, and proteomic data, will also be essential in tailoring interventions to maintain proteostasis at the individual level, offering potential for more effective therapeutic strategies for aging and age-related diseases.

Declarations

Author contributions: Gaurav N. Kasar: Conceptualization, Investigation, Writing original draft, Pooja B. Rasal: Conceptualization, Investigation, Writing original draft, Chandrashekhar D. Patil: Resources, Data curation, Visualization, Formal analysis, Sunil K. Mahajan: Resources, Data curation, Visualization, Formal analysis, Aman B. Upaganlawar: Resources, Data curation, Visualization, Formal analysis.

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