

Targeting Endoplasmic Reticulum Stress as a Promising Strategy Against Aging

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Abstract

The endoplasmic reticulum (ER) is a vital organelle in eukaryotic cells that plays a key role in processes such as protein folding, post-translational modifications, and the regulation of intracellular calcium storage. Disruptions in ER function as organisms age can lead to endoplasmic reticulum stress (ERS), which activates the unfolded protein response (UPR). The UPR aims to restore ER homeostasis by modulating protein synthesis, facilitating the degradation of misfolded proteins and increasing the expression of molecular chaperones. However, sustained or severe ERS can trigger apoptosis, and has been associated with various age-related pathologies, such as neurodegenerative diseases, metabolic syndrome, and cardiovascular disorders. In this review, we systematically explore the pathophysiological mechanisms of ERS and the UPR, with a particular focus on structural and functional alterations during aging. Furthermore, we have summarized the significant roles of ERS and the UPR in various age-related diseases, review recent advances in anti-aging therapies targeting these pathways, and discuss potential future intervention strategies.

Keywords: aging; endoplasmic reticulum stress; unfolded protein response; molecular chaperones; apoptosis

1. Introduction

Population aging has become a universal trend in global demographic development [1]. As individuals age, the structure of our tissues and organs undergoes gradual alterations, accompanied by a progressive decline in function, leading to an overall deterioration of health and the onset of various age-related diseases [2]. Aging is a natural process characterized by a series of biological changes, including cellular senescence, metabolic dysfunction, and chronic inflammation [3]. At the molecular level, the process of aging is characterized by the interplay of numerous mechanisms, including genomic instability, telomere shortening, epigenetic changes, and proteostasis imbalance [4,5,6,7,8]. Among these, the disruption of proteostasis is considered a hallmark of aging [9].

Loss of proteostasis and disabled autophagy among aging biomarkers are closely associated with the endoplasmic reticulum (ER): as the core site for protein folding and quality control, ER dysfunction directly triggers the accumulation of misfolded proteins, while autophagy activation can eliminate abnormal proteins by enhancing the synergy between the ER and autophagy, thereby improving aging-related phenotypes such as loss of proteostasis, and this association further impacts the aging process by exacerbating other aging hallmarks including chronic inflammation and mitochondrial dysfunction [10].

The endoplasmic reticulum (ER) serves as a central site for protein synthesis, folding, and secretion, and the maintenance of its homeostasis is crucial for cell survival [11]. The maintenance of ER homeostasis is subject to continuous challenge from a number of factors, including physiological demands and pathological conditions. These factors affect the multifunctional roles of the ER as a Ca^{2+} storage compartment, a center for protein folding and assembly, a site for lipid and sterol biosynthesis, and a platform for signal transduction and inter-organelle communication [12,13]. Increased protein secretion or impaired protein folding leads to the accumulation of unfolded or misfolded proteins within the ER lumen, a condition referred to as “endoplasmic reticulum stress (ERS)” [14]. In response to ERS, eukaryotic cells have evolved an ER-to-nucleus signaling system, commonly known as the unfolded protein response (UPR), which functions to alleviate stress or initiate programmed cell death [15,16,17]. The surveillance of ER proteostasis is primarily mediated by the UPR, a signal transduction pathway that senses the status of protein folding in the ER lumen [18]. In conditions of mild to moderate ERS the UPR is activated to clear unfolded and misfolded proteins, thereby restoring ER homeostasis. This form of response is referred to as the “adaptive/cytoprotective UPR” (Fig. 1). Nevertheless, in circumstances of severe or protracted ERS, the UPR becomes hyperactivated and switches to triggering intrinsic apoptotic pathways [19].



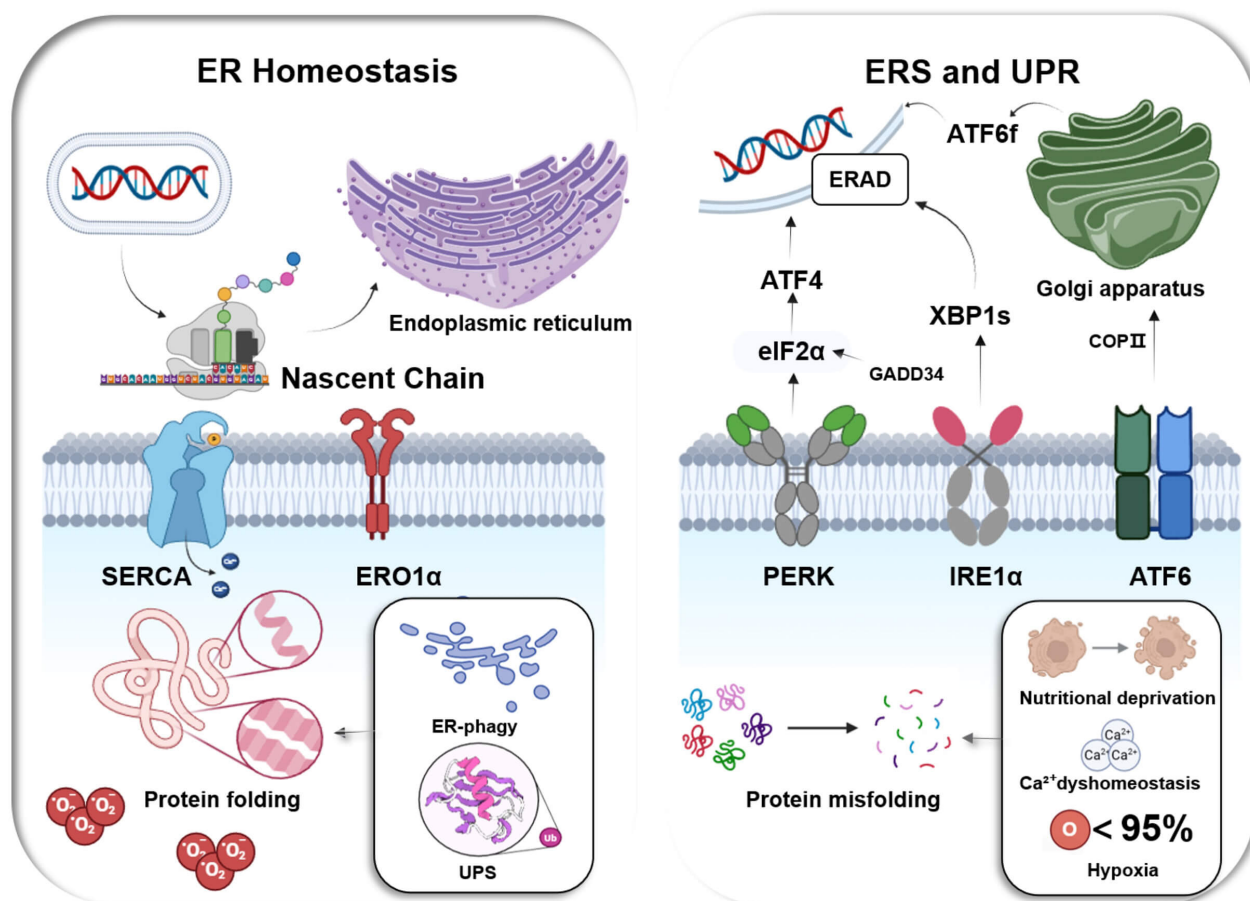


Fig. 1. Two key states of the endoplasmic reticulum (ER): ER homeostasis (left panel) and ERS with activated unfolded protein response (UPR, right panel). In the left panel, the ER maintains balance: nascent protein chains (translated from DNA-encoded mRNA) undergo proper folding (aided by endoplasmic reticulum oxidoreductase 1 alpha (ERO1α), which generates reactive oxygen species (ROS)), sarco/endoplasmic reticulum Ca²⁺-ATPase (SERCA) regulates calcium transport, and unneeded ER components are cleared via ER-phagy or the ubiquitin-proteasome system (UPS). In the right panel, stressors (e.g., nutritional deprivation, calcium dyshomeostasis, hypoxia) cause protein misfolding, triggering endoplasmic reticulum stress (ERS) and the UPR: protein kinase R-like endoplasmic reticulum kinase (PERK) activates eukaryotic initiation factor 2α (eIF2α) (slowing protein synthesis) and activating transcription factor 4 (ATF4) (inducing stress genes, with growth arrest and to DNA damage-inducible transcript 34 (GADD34) reversing eIF2α activity); inositol-requiring enzyme 1α (IRE1α) splices X-box binding protein 1 (XBP1) mRNA into active XBP1s (driving ER-associated degradation (ERAD) to remove misfolded proteins); and activating transcription factor 6 (ATF6) is transported to the Golgi (via COPII vesicles) to form active ATF6f, which enters the nucleus to upregulate endoplasmic reticulum-associated degradation (ERAD)/UPR genes. The figure illustrates the ER's balanced homeostatic state versus its stress-induced adaptive UPR, which works to restore function. Created in BioRender. Hu, L. (2026) <https://BioRender.com/4b4x11f>.

In recent years, a significant body of research has demonstrated a close association between ERS and the UPR with the aging process. Aberrant activation or dysregulation of these genes has been linked to the development of various age-related diseases, including neurodegenerative disorders, metabolic syndrome, and cardiovascular diseases [20]. Conversely, age-associated oxidative stress, metabolic dysfunction, and the accumulation of misfolded proteins can also induce endoplasmic reticulum stress, thereby activating the UPR [21,22]. In light of this, the present review provides a detailed description of the molecular mechanisms underlying ERS and the UPR, and summarizes the characteristics of ERS and UPR in aging

cells. Furthermore, we highlight potential therapeutic interventions targeting ERS that may be employed to delay the aging process.

2. Endoplasmic Reticulum Homeostasis and Stress

2.1 Protein Synthesis and Folding Under Endoplasmic Reticulum Homeostasis

In the context of physiological conditions, the process of acquiring functional conformation necessitates the traversal of a series of folding and post-translational modification steps within the ER by nascent proteins [23]. The

process of signal sequence recognition by the signal recognition particle (SRP) is pivotal in targeting the ribosome in conjunction with the nascent chain to the endoplasmic reticulum membrane via the action of its cognate receptor for the purpose of subsequent processing [24]. Structural and functional studies have revealed that the nascent polypeptide-associated complex (NAC) suppresses non-specific interactions between ribosome-nascent chain complexes and the ER translocon, thereby enhancing the fidelity of protein targeting to the ER [25]. Efficient protein folding within the ER, particularly the formation of disulfide bonds, necessitates an oxidising environment [26]. This process is orchestrated by an array of ER-resident proteins, including protein disulfide isomerase (PDI), ER oxidoreductin-1 (ERO1), peptidyl-prolyl cis-trans isomerases, and multiple molecular chaperones. Collectively, these proteins catalyse and monitor the correct formation of disulfide linkages to ensure productive folding [27,28,29]. In addition to the formation of disulfide bonds, the ER plays a pivotal role in the orchestration of a multifarious array of post-translational modifications. These include N-linked and O-linked glycosylation, acylation, and hydroxylation which are indispensable for the maturation and functionality of proteins [30,31,32].

In addition to its role in protein synthesis, processing, and modification, the ER functions as the largest intracellular Ca^{2+} reservoir and contributes to both signal transduction and translational control [33]. The sarco/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) establishes and maintains a $>10^3$ -fold Ca^{2+} concentration gradient between the cytosol (low nanomolar) and the ER lumen (high micromolar) through ATP-dependent transport, thereby driving Ca^{2+} accumulation within the ER [34]. The ER membrane plays a pivotal role in the sequestration and regulation of intracellular Ca^{2+} by expressing at least three distinct classes of proteins. The process of Ca^{2+} transportation within the cell is initiated by Ca^{2+} pumps, which facilitate the movement of Ca^{2+} from the cytosol to the lumen. Subsequent to these pumps are luminal Ca^{2+} -binding proteins, which function as Ca^{2+} storage buffers. The third component of this process is Ca^{2+} channels, which regulate the release of Ca^{2+} along its electrochemical gradient into the cytosol [35]. In circumstances where the luminal Ca^{2+} load surpasses the buffering capacity, the activity of SERCA is known to indirectly trigger the opening of ryanodine receptors (RyRs) and inositol 1,4,5-trisphosphate receptors (InsP₃Rs). The process described herein results in the release of excess Ca^{2+} from the ER lumen into the cytosol [36].

In the context of environmental stress, genetic variation, the process of aging, or other insults, the architecture and function of the ER are subject to stringent regulation by the cell. Consequently, the morphology and composition of the ER undergo dynamic remodeling in response to metabolic status and developmental stage. Consequently, ER quality control (ERQC) is indispensable for preserving ER homeostasis [37]. The execution of ERQC is primarily

facilitated by two complementary pathways: the ubiquitin-proteasome system (UPS) and ER-phagy [38]. The UPS is an ATP-dependent proteolytic machinery that degrades substrates conjugated to ubiquitin polymers by the enzymatic cascade of E1-E2-E3 enzymes, a process termed ubiquitination [39]. The process of ubiquitination plays a pivotal role in regulating the fate or activity of proteins. The specific function of ubiquitination is determined by the length and topology of the attached ubiquitin (Ub) chains. Proteins bearing Lys48 (K48)-linked poly-Ub chains are typically directed towards the 26S proteasome for degradation, whereas alternative linkages, such as K63-linked chains, have been shown to modulate non-proteolytic functions [40]. The autophagy-lysosome pathway, incorporating selective ER-phagy, can be mobilized as required to eliminate damaged ER domains and terminally misfolded ER proteins, thereby ensuring the maintenance of cellular homeostasis [41]. In summary, ERQC systems recognize correctly folded proteins and forward them to the Golgi apparatus, whereas aberrantly folded or unassembled polypeptides are retained within the ER lumen for either refolding or ultimate disposal.

2.2 Endoplasmic Reticulum Stress (ERS) and Unfolded Protein Response (UPR)

When cells are subjected to conditions of hypoxia, nutrient deprivation, Ca^{2+} dyshomeostasis, or genetic mutations, the accumulation of unfolded or misfolded proteins within the ER is provoked, thus inducing the UPR [42]. This stress instigates an adaptive program termed the UPR, which either restores cellular homeostasis or, when damage is irreparable, drives cells towards apoptosis [43]. The UPR is governed by three evolutionarily conserved sensor proteins (Fig. 2): protein kinase R-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 α (IRE1 α), and activating transcription factor 6 (ATF6) [44].

2.2.1 PERK Signaling Pathway

PERK is a type-I transmembrane protein kinase embedded in the ER membrane. It comprises an ER-lumen-oriented stress-sensing domain, a single transmembrane helix, and a cytosolic kinase domain [45]. Upon ERS, PERK dissociates from its inhibitory chaperone immunoglobulin heavy chain binding protein (BiP) (immunoglobulin heavy-chain-binding protein), undergoes oligomerization and autophosphorylation, and subsequently phosphorylates eukaryotic initiation factor 2 α (eIF2 α) at serine 51 [46]. Phosphorylated eIF2 α has been demonstrated to have increased affinity for eIF2B, thereby sequestering eukaryotic initiation factor 2B (eIF2B) and preventing the guanine-nucleotide-exchange reaction that converts eIF2-GDP to eIF2-GTP [47]. Consequently, the initiation of global translation is attenuated, thereby reducing the influx of nascent polypeptides into the ER and providing the cell with a critical window to refold or degrade accumulated unfolded proteins. This, in turn, ultimately results in the restoration

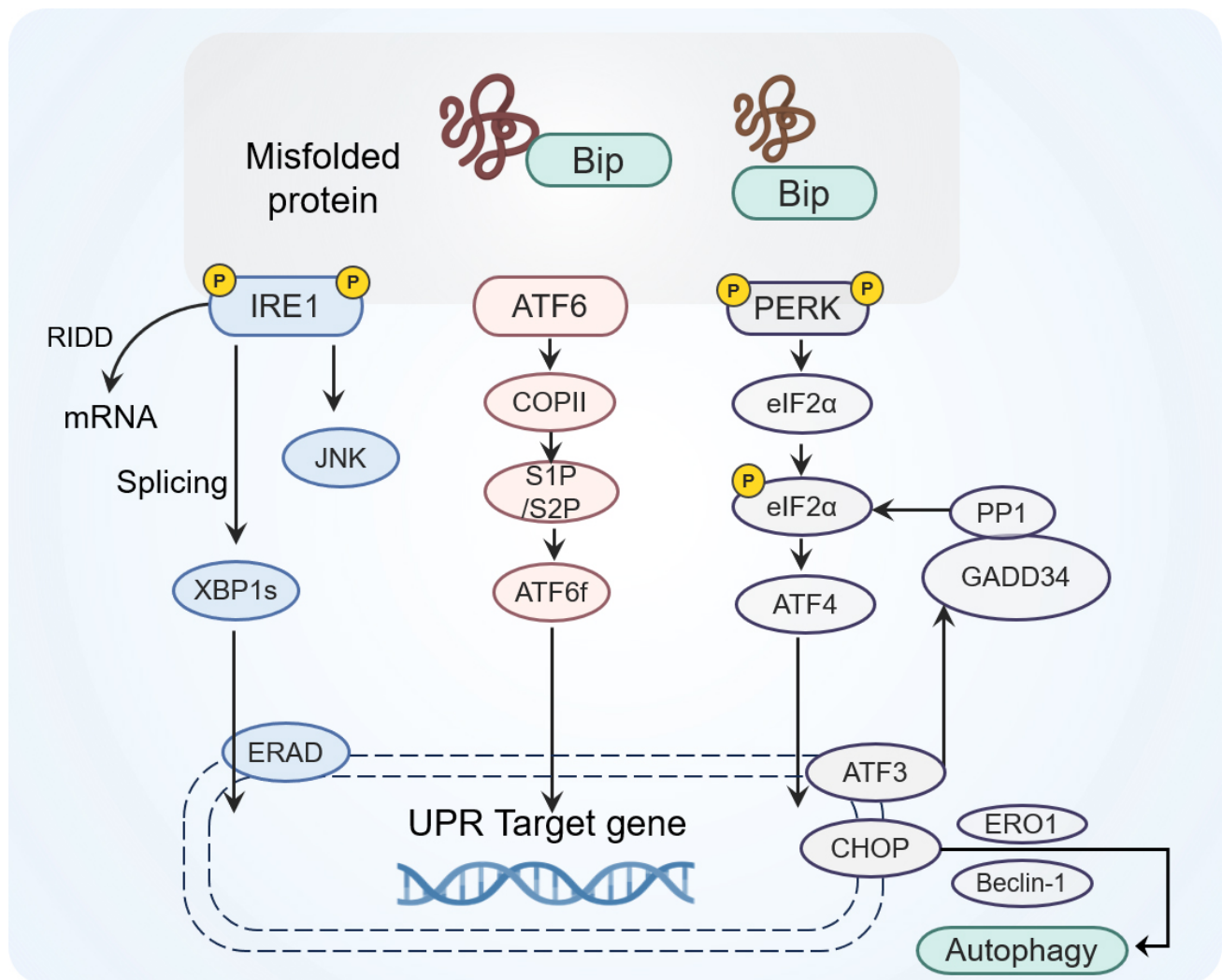


Fig. 2. The unfolded protein response (UPR) is responsible for sensing and counteracting protein misfolding in the endoplasmic reticulum (ER) via three evolutionarily conserved signaling branches: PERK, IRE1, and ATF6. The image illustrates the Unfolded Protein Response (UPR), a cellular mechanism triggered by the accumulation of misfolded proteins in the endoplasmic reticulum (ER). This stress response is mediated by three key sensors—IRE1, PERK, and ATF6—which are normally kept inactive by the chaperone BiP. When misfolded proteins accumulate, BiP is sequestered, activating these pathways. IRE1 autophosphorylates, initiating mRNA splicing and degradation via Regulated IRE1-Dependent Decay (RIDD), while also activating c-Jun N-terminal kinase (JNK). PERK phosphorylates eIF2 α , reducing protein synthesis but promoting translation of *ATF4*. ATF6 translocates to the Golgi, where it is cleaved by site-1 protease (S1P)/site-2 protease (S2P) proteases to release its active form, ATF6f. Together, these pathways induce transcription factors (ATF4, ATF3, CHOP, ATF6f) that upregulate genes involved in protein folding, ERAD, autophagy, and redox balance. The goal is to restore ER homeostasis; however, prolonged stress leads to apoptosis via CHOP and JNK. Recovery is facilitated by negative feedback, such as protein phosphatase 1 (PP1)/GADD34-mediated dephosphorylation of eIF2 α . Created in BioRender. Hu, L. (2026) <https://BioRender.com/5uhhply>.

of ER homeostasis [48]. Concomitantly, this phosphorylation event triggers the selective translational up-regulation of activating transcription factor 4 (ATF4), a member of the bZIP (basic leucine zipper) family [49,50]. Following nuclear translocation, the evidence suggests that ATF4 induces the expression of antioxidant genes, amino-acid metabolic genes, and select molecular chaperones. This process has been demonstrated to enhance the cell's antioxidant capacity and ER protein-folding competence [51]. As

demonstrated, the functions of PERK and other eIF2 α kinases in regulating cognition and the response to neuronal injury have been the subject of extensive characterization [52].

The PERK branch of the UPR has been demonstrated to either alleviate ERS or drive cell death, depending on the intensity and duration of activation and the cellular microenvironment [53]. During the initial phase of ERS, PERK signaling predominantly exhibits a cytoprotective ef-

fect [54]. However, when stress persists, PERK-via ATF4-induces the transcription of activating transcription factor 3 (ATF3) and C/EBP-homologous protein (CHOP), thus tipping the balance towards apoptosis [55]. ATF3 has been observed to bind to promoter regions associated with growth arrest and to DNA-damage-inducible transcript 34 (*GADD34*, also termed PPP1R15A) [56]. As a regulatory subunit of protein phosphatase 1 (PP1), *GADD34* has been demonstrated to recruit PP1, thereby selectively dephosphorylating eIF2 α and restoring global protein synthesis. This, in turn, imposes a negative-feedback loop on the PERK-eIF2 α -ATF4 axis [57]. However, under sustained ERS, this translational rebound increases nascent polypeptide load, amplifies ERS, and creates a vicious cycle that ultimately promotes apoptosis. CHOP further accelerates this process by activating autophagy programs and up-regulating ER oxidoreductin-1 α (ERO1 α), which hyperoxidizes the ER lumen and culminates in Caspase-12/3-mediated apoptosis [58]. Rouschop et al. [59] demonstrated that in models of chronic hypoxia-induced ERS, CHOP binds to the CHOP-response element (CHOP-RE) in the Beclin-1 promoter, markedly elevating Beclin-1 expression, enhancing autophagy, and hastening tumor-cell death.

2.2.2 IRE1 Signaling Pathway

IRE1 is a multifunctional serine/threonine kinase and endoribonuclease embedded in the ER membrane and constitutes a principal regulator of the UPR [60]. Upon ERS, the RNase activity of IRE1 is unleashed and catalyzes an unconventional splicing event in X-box binding protein 1 (XBP1) mRNA, specifically the precise excision of a 26-nucleotide intron, which generates the transcriptionally active splice variant *XBPIs* [61]. *XBPI* is a bZIP transcription factor whose activity is subject to tight modulation by ERS and UPR signaling [62]. Following nuclear translocation, *XBPIs* up-regulates a diverse set of ER-associated genes, including the molecular chaperone p58IPK (58 kDa inhibitor of the interferon-induced, double-stranded RNA-activated protein kinase) and protein disulfide isomerases, thereby enhancing the ER's protein-folding capacity [63]. A clinical cohort study confirmed that peripheral-blood mononuclear cells from rheumatoid-arthritis patients exhibit markedly elevated IRE1 α endoribonuclease activity and increased *XBPI* splicing, both of which correlate positively with disease activity [64]. In addition, *XBPIs* has been shown to drive the expression of key components of ER-associated degradation (ERAD) and ancillary chaperones [65]. ERAD is an essential quality-control mechanism that selectively eliminates misfolded or unassembled proteins. By fine-tuning substrate protein levels and preserving ER homeostasis, ERAD establishes an environment conducive to accurate protein folding [66].

When ER homeostasis cannot be restored during prolonged stress, IRE1 α exerts its endoribonuclease activity to cleave a subset of ER-localized mRNAs in a process termed Regulated IRE1-Dependent Decay (RIDD) [67].

RIDD activity has been observed to increase in proportion to the intensity of ERS, and this has been shown to result in a transient reduction in ER protein load. Concurrently, an observed modulation of inflammatory, metabolic, and inflammasome signaling pathways has been documented. In 2024, Xu et al. [68] demonstrated that IRE1 α -mediated RIDD silences taxane-induced double-stranded RNA (dsRNA), thereby averting NLRP3 inflammasome-dependent pyroptotic cell death. Further studies have revealed that tumor cells under chronic ERS exploit the IRE1 α -RIDD axis to remodel lipid metabolism by degrading mRNAs encoding lipogenic enzymes, thereby underscoring the breadth and physiological significance of RIDD substrates [69]. Should stress persist, the cytosolic domain of activated IRE1 recruits tumor-necrosis-factor-receptor-associated factor 2 (TRAF2), which complexes with apoptosis signal-regulating kinase 1 (ASK1). The activation of the c-Jun N-terminal kinase (JNK) pathway is initiated by this signaling relay, which subsequently induces the expression of CHOP and, in turn, drives the process of apoptosis [70,71]. Therefore, IRE1 functions as a molecular switch whose activation level dynamically regulates the downstream transition from adaptive and protective to apoptotic outputs, serving as a pivotal hub determining cellular survival or death under ERS.

2.2.3 ATF6 Signaling Pathway

ATF6 is a precursor transcription factor tethered to the ER membrane and exists as two isoforms, ATF6 α and ATF6 β [72]. Unlike IRE1 α and PERK, ATF6 activation is phosphorylation-independent. Upon exposure to ERS, BiP dissociates from ATF6 dimers, thus enabling the protein to be packaged into coat protein II (COPII) vesicles and trafficked to the Golgi apparatus. Within the Golgi, the sequential cleavage of ATF6 is catalyzed by site-1 protease (S1P) and site-2 protease (S2P), resulting in the liberation of its cytosolic domain [73]. Recent studies have demonstrated that ERS leads to the generation of the active fragments p50ATF6 α and p60ATF6 β , which, in conjunction with the heterotrimeric transcription factor NF-Y (comprising NF-YA, NF-YB, and NF-YC), bind to ER stress-response elements (ERSEs) [74]. These fragments subsequently translocate to the nucleus, where they up-regulate the expression of molecular chaperones (e.g., GRP78, GRP94, calreticulin) and ERAD-related genes. This process facilitates the clearance of misfolded proteins and thereby restores ER homeostasis. However, under conditions of severe or protracted ERS, the ATF6 pathway has been observed to trigger apoptosis by means of the up-regulation of pro-apoptotic genes, most notably CHOP [75,76]. In the context of mouse embryonic muscle development, a transient CHOP induction, concomitant with caspase-12 activation, has been observed, without significant activation of the IRE1 or PERK branches. This finding indicates that ATF6 possesses the capacity to induce CHOP-mediated apoptosis in an autonomous manner [77].

3. Characteristics of ERS and the UPR in Senescent Cells

3.1 Structural Remodeling

Cross-species studies reveal a highly conserved and quantifiable structural remodeling of the endoplasmic reticulum during aging. In *Caenorhabditis elegans*, the total ER mass in all tissues of aged animals (>7 days) significantly decreased compared to young adults (day 1), with a 30–40% reduction in fluorescence intensity of ER-resident marker proteins [78]. Similar ER structural remodeling has been confirmed in rat sciatic nerves, mouse brains, and human dermal fibroblasts, indicating that ER contraction is a universal feature of organismal aging [79,80].

At the ultrastructural level, the ER in aged cells exhibits characteristic morphological abnormalities, including vesicularization, focal dilation, and abnormal accumulation of unfolded proteins within the lumen [81]. Transmission electron microscopy reveals expanded ER pools, disrupted membrane architecture, and markedly increased ribosome detachment from rough ER in neurons and hepatocytes of aged mice. In sciatic nerves of aged rats, Schwann cell ER exhibits lamellar expansion and vacuolation, accompanied by myelin structural abnormalities [81].

These structural alterations are accompanied by profound reshaping of molecular composition and redox homeostasis. In aged articular cartilage, Ero1- α and other molecular chaperones are significantly downregulated, compromising ER oxidative protein folding capacity. This dysfunction induces ER stress and facilitates chondrocyte apoptosis [82]. Concurrently, NADPH oxidase 4 (NOX4) translocates to the ER membrane in aged hepatocytes, further exacerbating local oxidative stress [83]. Persistent ROS assault induces oxidative modification and functional inactivation of molecular chaperones like BiP, severely impairing their capacity to activate core UPR sensors such as PERK, IRE1, and ATF6. Consequently, aging impairs the adaptive UPR, blunting the inducible activation of its downstream effectors XBP1s and ATF4 [84,85,86]. Consequently, unfolded proteins accumulate extensively within the ER lumen. In aged mouse brains, ubiquitinated protein accumulate with aging, accompanied by CHOP upregulation and caspase-12 activation, ultimately driving cellular dysfunction and death [87,88].

Notably, heterogeneous ER structural remodeling occurs across different species and tissue types. In the naked mole-rat, an extreme longevity model, hepatocytes exhibit compensatory ER hypertrophy and mitochondrial spatial rearrangement, suggesting potential aging delay through enhanced ER functional reserve. In contrast, human dermal fibroblasts primarily display ER fragmentation and reduced rough ER during aging, reflecting diminished secretory function [89].

In summary, ER structural remodeling during aging exhibits cross-species conservation, characterized by: ER mass atrophy, membrane system disorganization, heightened oxidative stress, molecular chaperone inactivation,

and protein aggregate accumulation. These structural alterations not only constitute the morphological basis for ER functional decline but also serve as key drivers of the collapse of aging-related protein homeostasis.

3.2 Functional Decline

In senescent cells, the burden of misfolded or unfolded proteins within the ER rises markedly. This drives a chronically elevated level of ERS [90]. Persistent stress can be triggered by oxidative stress, inflammatory signaling, disturbed Ca^{2+} homeostasis, or defects in N-glycosylation [91]. Although aged cells remain capable of sensing ERS, the three canonical branches—PERK, IRE1 α , and ATF6—are transcriptionally reprogrammed towards a pro-apoptotic output, while protective chaperones such as BiP/GRP78 and PDI are insufficient to re-establish proteostasis, leading to “adaptive failure” [92,93,94]. Young cells exposed to mild accumulation of misfolded proteins typically exhibit low-level ERS, robust chaperone efficiency and high stress tolerance. They resolve the insult via an adaptive unfolded protein response. In contrast, senescent cells accumulate misfolded proteins more readily and display a marked, age-dependent decline in stress resistance, often becoming trapped in an irreversible state of ERS. This loss of tolerance, coupled with a relative amplification of pro-apoptotic UPR signals, drives cells towards death [95].

At the molecular level, the translation of ATF4 is reduced in senescence, its expression fails to increase effectively even under acute stress, which severely compromises adaptive capacity [96]. Both the IRE1 α and PERK pathways deteriorate with age, preventing full downstream gene activation [97]. In pathological contexts (such as neurodegenerative diseases), excessive PERK-P/eIF2 α -P signaling induces a sustained global translational repression, which leads to synaptic failure and neuronal loss [98].

In addition, aging is associated with a decline in ER Ca^{2+} storage resulting from diminished SERCA activity, exaggerated IP₃R/RyR leak, or NOX-driven oxidative stress [99]. Chaperones including BiP, calnexin and PDI, require luminal Ca^{2+} concentrations of within a specific range for optimal function. When Ca^{2+} falls below a critical threshold, their ATPase activity and peptide-binding capacity decrease, thereby promoting the build-up of unfolded proteins [100].

Metabolic dysfunction further accelerates ER decline. In replicative-senescent human alveolar type II epithelial cells, the activities of mitochondrial respiratory complexes I and IV decrease, and ATP levels fall significantly [101]. Because chaperones such as BiP and PDI require ATP molecules per folding cycle, this energy deficit reduces overall folding efficiency, thereby perpetuating the accumulation of unfolded proteins [102]. Collectively, these alterations emphasize the progressive dysfunction of the ER and the UPR during aging and underscore their central roles in the pathogenesis of age-related diseases (as shown in Table 1).

Table 1. Different manifestations of endoplasmic reticulum stress in young and senescent cells.

Characteristic	Younger cells (acute ERS)	Senescent cells (chronic ERS)
State	Temporary, acute	Sustained, low
UPR objective	Restore homeostasis (adaptive)	Maintains life, but dysfunctional
PERK	Inhibit translation and transient activation of ATF4/CHOP	PERK signaling deteriorates; ATF4 activation is impaired and fails to increase under stress; excessive eIF2 α -P in pathology causes sustained translational repression (pro-apoptotic)
IRE1 α	Cutting <i>XBPI</i> (repair), transient RIDD	<i>XBPI</i> splicing is reduced and RIDD is enhanced to activate JNK/NF-KB (pro-inflammatory)
ATF6	Fully activate and upregulate the partner protein	Activation is reduced and repair capacity is reduced
Final outcome	Restore homeostasis or apoptosis	Senescence-Associated Secretory Phenotype (SASP), apoptosis resistance, protein homeostasis collapse

3.3 ER Remodelling in Immunosenescence and Stem Cell Aging

The UPR has long been considered the primary mechanism by which ER stress influences aging. However, emerging evidence indicates that the ER itself undergoes profound structural and functional remodelling during aging, a process that is intimately linked to the UPR but extends beyond canonical stress signalling. In particular, the age-dependent decline in ER volume, the shift from rough sheet-like to tubular ER morphology, and the associated proteomic reprogramming from protein synthesis toward lipid metabolism have emerged as conserved features of aging across species, from yeast to mammals. This remodelling is actively driven by selective autophagy of the ER—termed ER-phagy—which requires core autophagy components such as Atg8 and ULK1, as well as tissue-specific regulators including the previously uncharacterised ER-phagy receptor TMEM-131 and the IRE-1–XBP-1 branch of the UPR [103,104].

These findings provide a new framework for understanding ERS in the context of immunosenescence and inflammaging. The IRE-1–XBP-1 axis, which we identified as a key promoter of ER turnover in the *C. elegans* intestine, is also a well-established modulator of immune cell function and inflammatory cytokine production. During aging, the progressive activation of ER-phagy may initially serve as an adaptive response to reduce ER burden and maintain homeostasis. However, when this process becomes dysregulated—as suggested by the chronic UPR activation observed in aged tissues—it could tip the balance toward maladaptive inflammation. The proteomic shift toward lipid metabolism within the aged ER may further influence the production of lipid mediators that regulate inflammation resolution, thereby contributing to the low-grade, sterile inflammation characteristic of inflammaging.

In parallel, ER remodelling has direct implications for stem cell aging. Stem cells rely heavily on ER function to sustain high secretory demands, such as the production of extracellular matrix (ECM) components that maintain the niche. The age-associated decline in ER mass and rough

ER content observed in multiple *C. elegans* tissues raises the possibility that stem cells undergo similar remodelling, compromising their capacity for ECM production and self-renewal. The identification of TMEM-131 as an ER-phagy regulator that couples collagen secretion to ER turnover is particularly relevant in this context. TMEM-131 contains a luminal domain involved in procollagen processing and a cytoplasmic LIR motif that binds Atg8/GABARAP, linking ER-phagy to the secretory load. Knockdown of “*tmem-131*” restores youthful ER morphology in aged hypodermal cells and reduces ER delivery to lysosomes, suggesting that it normally promotes ER turnover when collagen output declines. This mechanism may represent a conserved strategy for adapting ER capacity to changing secretory demands in stem cells and their niches, and its failure could contribute to stem cell exhaustion.

Importantly, the requirement for both IRE-1–XBP-1 and TMEM-131 in mTOR-dependent longevity underscores the physiological relevance of ER-phagy in lifespan regulation. These tissue-specific pathways illustrate how the core UPR and ER-phagy machinery are co-opted to meet the distinct functional demands of different cell types during aging. Future studies should investigate whether analogous mechanisms operate in mammalian immune cells and adult stem cells, and whether their modulation can mitigate immunosenescence and preserve stem cell function [104].

4. ERS and the UPR in Age-Related Diseases

4.1 Neurodegenerative Diseases

Emerging evidence tightly links ERS to both aging and neurodegenerative diseases [105]. In Alzheimer’s disease (AD), aberrant accumulation of β -amyloid (A β) peptides constitutes the central pathological hallmark [106]. Research confirms that endoplasmic reticulum stress promotes A β production [107,108]. PERK phosphorylation activates beta-secretase 1 (BACE1) transcription, increasing A β production by 2.5-fold [109]. In aged amyloid precursor protein (APP)/ Presenilin-1 (PS1) mice, the integrated stress response inhibitor (ISRIB) reverses ERS

by correcting eIF2 α -dependent translational repression, reduces mean A β plaque size, and restores hippocampal synaptic plasticity and spatial memory [110]. Conversely, A β activates oxidative-stress pathways such as the NOX4–ERO1 α axis, triggering proteasomal degradation of the ERAD core components Derlin-1 and HMG-CoA reductase degradation 1 protein (HRD1) [111]. Consequently, misfolded APP accumulates within the ER lumen, establishing a positive-feedback loop that perpetuates ERS. Super-resolution imaging further reveals that A β down-regulates the ER-phagy receptor FAM134B, preventing clearance of damaged ER membranes [112]. In parallel, A β oligomers insert into the ER membrane, activate IP $_3$ R and ryanodine receptor (RyR) Ca $^{2+}$ channels, and provoke excessive Ca $^{2+}$ efflux from the ER store, ultimately driving cytosolic Ca $^{2+}$ overload [113].

This pathogenic paradigm—wherein misfolded protein aggregates both trigger and are exacerbated by ERS—is not unique to Alzheimer’s disease. Across the spectrum of age-related neurodegenerative disorders, diverse disease-associated proteins converge on the ER as a common target, initiating similar cascades of proteotoxic stress and UPR dysregulation. Notably, while the upstream aggregating proteins differ, the downstream effector pathways (particularly the IRE1 α –JNK–CHOP axis) exhibit striking mechanistic conservation.

In Parkinson’s disease (PD), α -synuclein (α -Syn) aggregates within substantia nigra dopaminergic neurons elicit chronic ERS [114]. α -Syn physically associates with the ER membrane, activating the IRE1 α kinase and consequent JNK phosphorylation, CHOP up-regulation, and caspase-3 activation [115]. Consistent with this mechanism, the IRE1 α inhibitor 4 μ 8C blocks JNK activation and reduces cell death [116]. Similarly, in elderly patients with primary open-angle glaucoma (POAG), mutant myocilin accumulates in trabecular meshwork cells, generating sustained ERS that engages the ATF4–CHOP–caspase-3 axis and triggers apoptosis of retinal ganglion cells (RGCs) [117].

4.2 Cardiovascular Diseases

During myocardial ischemia–reperfusion (I/R), a burst of ROS and Ca $^{2+}$ overload rapidly triggers ERS [118]. In a mouse model of myocardial ischemia/reperfusion (I/R), AAV9 mediated cardiac-specific overexpression of the active ATF6 transcription factor, protecting the heart from I/R injury and restoring the contractile function of ATF6-deficient hearts toward wild-type levels [119]. Single-cell RNA-seq further revealed co-expression of *XBPIs* and Natriuretic peptide B (*Nppb*) in border-zone cardiomyocytes, indicating that the UPR is synchronously activated with pathological remodeling [120]. In transverse aortic constriction (TAC) mice, both the PERK–CHOP and ATF6–Rheb–mTORC1 axes are simultaneously engaged, leading to increased protein synthesis, cardiomyocyte hypertrophy, and eventual decompensation [121]. In

2021, cardiomyocyte-restricted suppressor of cytokine signaling 3 (SOCS3) overexpression in TAC mice suppressed the GRP78–PERK/eIF2 α –ATF4–CHOP module and attenuated cardiac hypertrophy [122]. Retrospective analyses of left-atrial tissue from atrial fibrillation patients (2019–2021) demonstrated a positive correlation between CHOP expression and the extent of interstitial fibrosis [123].

4.3 Metabolic Diseases

ERS profoundly alters insulin synthesis, folding, and secretion within pancreatic β -cells [124]. Comparing non-diabetic control pancreata with those from patients with type 2 diabetes mellitus (T2DM), Marchetti et al. [125] documented increased ER volume density and elevated β -cell apoptosis in the latter [126]. In human T2DM islets, sustained activation of the PERK–eIF2 α –ATF4 axis leads to attenuated proinsulin translation, as previously reviewed [127]. Evidence from a 2025 study suggested that chronic ERS may directly repress insulin transcription, putatively via down-regulation of NK6 Homeobox 1 (*NKX6.1*) and MAF bZIP transcription factor A (*MAFA*) in the investigated cellular models; further studies are needed to validate this mechanism [128]. Treatment with the IRE1 α RNase inhibitor STF-083010 markedly increased pancreatic insulin content and attenuated β -cell apoptosis in Akita (MIDY) mice. Misfolded proinsulin forms disulfide-linked oligomers that entrap wild-type proinsulin in the ER lumen, eliciting an augmented UPR [129]. In post-mortem human islets, CHOP (a marker of ER stress) is markedly up-regulated in β cells of type 2 diabetic donors [126]. In β -cell-specific Chop/Ddit3 knockout mice, loss of CHOP alleviates ER stress and delays rather than enhances glucose-stimulated insulin secretion [130]. Beyond β -cells, ERS in peripheral tissues—liver, skeletal muscle, and adipose—impairs insulin signal transduction, thereby promoting systemic insulin resistance [131,132,133].

In obesity, adipose-tissue expansion and adipocyte hypertrophy trigger ERS and the UPR. In individuals with concurrent hypercholesterolemia, hepatic ER-stress markers (CHOP, XBPIs) correlate positively with Low-Density Lipoprotein Cholesterol (LDL-C) levels, indicating that lipid overload directly induces ERS [134]. Compared with lean controls, subjects with BMI ≥ 30 kg m $^{-2}$ show increases in BiP, CHOP, and XBPIs protein expression [135]. After 16 weeks of high-fat feeding, mouse adipose tissue shows marked up-regulation of ER-stress markers (BiP, CHOP) and inflammatory mediators (TNF- α) at the mRNA level [136]. Dysregulation of the ER and UPR disrupts lipid-metabolic proteins in adipocytes, skewing lipogenesis versus lipolysis and aggravating obesity [137,138,139]. In 3T3-L1 adipocytes, excessive activation of the ATF6 and IRE1-XBP1 branches suppresses Peroxisome proliferator-activated receptor γ (PPAR γ) while paradoxically enhancing triglyceride synthesis, leading to lipid-homeostasis collapse [140]. Systemic oxidative stress and inflammation generated by obesity, in turn, intensify ERS, establish-

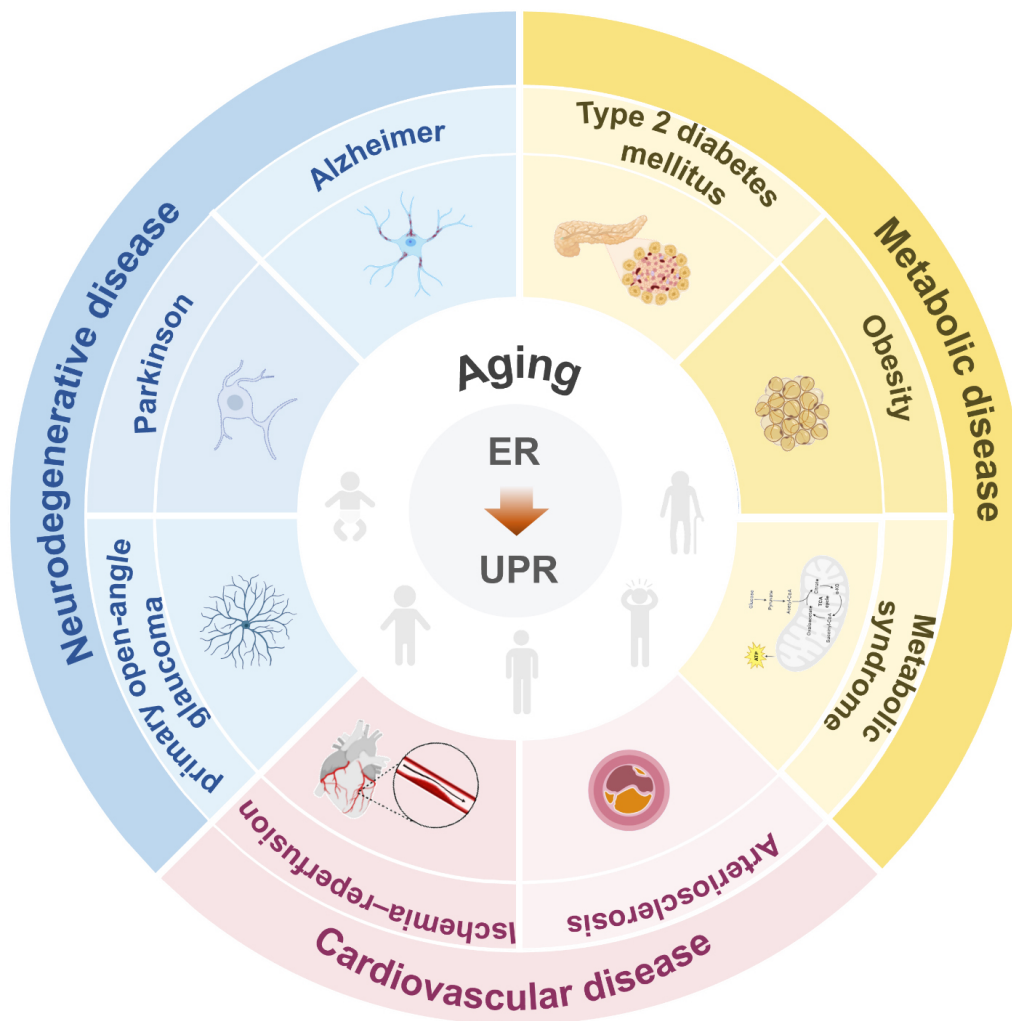


Fig. 3. Endoplasmic reticulum stress and dysregulation of the unfolded protein response in age-related diseases. Multiple major diseases closely associated with aging share a common pathological pathway characterized by persistent endoplasmic reticulum stress and dysregulation of the unfolded protein response. While these diseases appear distinct, they share an upstream, shared molecular hub—the imbalance of the endoplasmic reticulum stress-unfolded protein response axis. This interconnectedness reveals that targeting this pathway represents a promising therapeutic approach for multiple age-related diseases. Created in BioRender. Hu, L. (2026) <https://BioRender.com/vbm3a3m>.

ing a vicious cycle that elevates the risk of obesity-related metabolic syndrome [138].

5. Potential Anti-Aging Strategies Targeting ERS and the UPR

ERS can be mitigated through: chemical chaperones that stabilize proteins; UPR pathway modulators that tune stress signaling; gene therapies that edit or deliver protective genes; and lifestyle interventions like diet, exercise, and sleep that naturally support proteostasis. These approaches collectively aim to restore ER balance and delay aging (Fig. 3).

5.1 Chemical Chaperones

Chemical chaperones are small-molecule compounds that bind to proteins, facilitate their correct folding, and

prevent the accumulation of unfolded species [141]. The prototypical chemical chaperone 4-phenylbutyrate (4-PBA) directly augments ER folding capacity, facilitating the refolding or disposal of misfolded proteins, thereby suppressing CHOP-mediated pro-apoptotic signaling and re-establishing ER proteostasis [142]. 4-PBA, an FDA-approved chemical chaperone, engages exposed hydrophobic residues on misfolded polypeptides, thereby suppressing aggregation [143,144]. As a short-chain fatty acid, 4-PBA also subtly alters ER membrane fluidity, promoting refolding of the Ca^{2+} pump SERCA2b and restoring ER Ca^{2+} stores [145]. In naturally aged mice, 4-PBA administration reduced phospho-eIF2 α and CHOP levels, re-establishes proteostasis, and ameliorates age-associated sleep fragmentation and cognitive decline [146]. A 2016 unilateral ureteral obstruction study demonstrated that 4-

PBA attenuates ER-stress-mediated tubular apoptosis and renal fibrosis [147]. Recent data reveal that 4-PBA diffuses efficiently into cartilage explants and dose-dependently alleviates excessive ERS triggered either by ERp57 deletion or by thapsigargin treatment [148]. Moreover, 4-PBA up-regulates endogenous chaperones such as BiP/GRP78 and ORP150, establishing a positive-feedback loop that reinforces ER homeostasis [149]. Metformin is a first-line drug widely used clinically in treating type 2 diabetes [150]. Furthermore, it has been shown to have anti-inflammatory and anti-aging effects [151]. Hence, a study using ob/ob mice and HFD-induced obese mouse model and administered metformin treatment to investigate whether metformin could alleviate hypothalamic aging [152]. SA- β -gal staining was reduced in the metformin-treated group relative to the hypothalamus of both ob/ob mice and HFD-fed mice. In addition, RT-PCR was performed to detect the expression of cellular senescence-related marker p16. The results indicate that p16 expression levels were increased in the hypothalamus of both ob/ob mice and HFD-fed mice and returned to normal levels following metformin treatment. Importantly, the administration of metformin significantly downregulated the expression of both P16 and γ -H2AX, indicating its potential to mitigate neuronal senescence. Based on these results, obesity induces the aging of neurons in the ARC region of the hypothalamus, whereas metformin has an inhibitory effect on aging.

5.2 Signal Pathway Modulator

A growing arsenal of small molecules and peptides targeting the three canonical branches of the unfolded protein response—PERK, IRE1, and ATF6—has advanced to pre-clinical or early-phase clinical evaluation [153]. GSK2606414, an ATP-competitive PERK inhibitor, blocks PERK autophosphorylation and the downstream eIF2 α -ATF4-CHOP cascade, mitigating ERS and prolonging survival without inducing apoptosis [154]. Phase I safety studies have been completed, prolonged dosing produces reversible hyperglycaemia [155]. A study published in 2024 examined a mouse model of acute lung injury and reported that the IRE1 α RNase inhibitor 4 μ 8C reduced XBP1s levels and attenuated downstream inflammatory/apoptotic signaling. While these results point to a potential therapeutic relevance of IRE1 α , they represent a single-team report and require independent replication [156]. Ceapin-A7, the most advanced ATF6 α -selective antagonist, sequesters ATF6 α on the ER membrane, preventing its COPII-mediated transport and almost completely abolishing formation of the nuclear p50 fragment [157]. Administered intraperitoneally at 5 mg kg⁻¹, Ceapin-A7 suppresses CHOP and F4/80-positive inflammation in models of acute lung injury, renal ischaemia-reperfusion, and obese adipose tissue, restoring tissue function [158,159]. Conversely, the ATF6 agonist AA147 selectively stabilizes ATF6, up-regulates BiP/GRP78, and represses CHOP, rapidly re-establishing ER proteostasis in the livers of aged

mice [160,161]. Collectively, these pathway-specific modulators represent promising agents for delaying aging and treating age-associated diseases.

5.3 Gene Therapy

Gene-editing or gene-delivery technologies now allow precise modulation of ERS and the UPR [162]. Gene editing technologies, particularly the CRISPR-Cas9 system, offer significant advantages in efficiency and cost. However, their safety and ethical challenges cannot be overlooked. We must seriously address potential risks such as off-target effects, genomic instability, and ethical and legal issues. Efforts should focus on enhancing the precision of these technologies and establishing robust regulatory frameworks to ensure their safe, effective, and responsible application in the future [163]. In the field of gene delivery, adeno-associated virus (AAV) vectors have emerged as a prominent tool due to their high transduction efficiency and favorable safety profile. Studies have demonstrated that AAV-mediated overexpression of key UPR components—such as BiP, XBP1s, or glucose-regulated protein 78 (GRP78)—can reverse senescent phenotypes in multiple organs, including the retina and brain [164,165,166,167]. In gene editing and regulation, CRISPR-based systems allow for more targeted interventions. Researchers have utilized CRISPR-mediated knock-in to introduce CHOP-suppressive microRNAs (e.g., *miR-211*, *miR-106b*) into the genome, significantly reducing ERS-induced apoptosis. Furthermore, single-base editing holds promise for correcting pathogenic point mutations in *ATF6*, restoring its transcriptional competence and functionality, thereby repairing UPR signaling defects at the genetic level [168]. These cutting-edge approaches highlight the potential of genetic strategies to modulate ERS pathways. For instance, using an ER-targeted, genetically encoded redox biosensor, researchers from the Chinese Academy of Sciences revealed that age-associated S-nitrosylation of Ero1 α at Cys166 and Cys131 attenuates its oxidase activity, shifting the ER toward reductive stress. Pharmacological inhibition of inducible nitric oxide synthase (iNOS) was shown to reverse this modification, restore ER redox homeostasis, and delay cellular aging [169]. Although these gene-based therapies hold considerable promise, they still face challenges such as delivery efficiency, tissue specificity, off-target effects, and long-term safety, which require further investigation and refinement.

5.4 Lifestyle Intervention

A healthy diet and caloric restriction (CR) re-establish endoplasmic reticulum (ER) proteostasis without triggering excessive apoptosis, thereby extending healthspan [170]. Epidemiological and pre-clinical studies show that dietary phytochemicals—sulforaphane from cruciferous vegetables (broccoli, kale), Riceberry™ protein hydrolysates from pigmented rice, and polyphenol-rich red grapes/blueberries—attenuate oxidative stress and lower

ER-stress markers [171,172,173]. Concurrently, moderate protein intake avoids overloading the ER folding machinery, further preserving ER homeostasis [174,175]. In yeast, *C. elegans*, mice, and non-human primates, CR alleviates ERS and re-establishes proteostasis by dampening insulin/insulin-like growth Factor-1 (IGF-1) signaling and activating the adenosine 5'-monophosphate (AMP)-activated protein kinase/sirtuin 1/peroxisome proliferators-activated receptor γ coactivator α (AMPK/SIRT1–PGC-1 α) axis, thereby diminishing ER load and ROS generation [176]. The 2022 Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) randomized controlled trial provided the first human evidence that a 25% reduction in caloric intake sustained for two years decelerates DunedinPACE pace-of-aging estimate by 2–3% and lowers all-cause mortality risk by 10–15% — an effect size comparable to smoking cessation interventions [177].

Exercise training enhances cellular antioxidant capacity and metabolic flexibility [178]. Regular exercise remodels the UPR in a beneficial manner, restoring ER function in aged skeletal and cardiac muscle [179]. Post-exercise, plasma exosomal *miR*-27b down-regulates CHOP expression and thereby improves endothelial function [180]. Both aerobic and resistance training improve mitochondrial performance, decrease ROS, and restore proteostasis [181,182]. Twelve weeks of moderate-intensity treadmill running reverses high-fat-diet-induced mitochondrial dysfunction and lowers CHOP and GRP78 in skeletal muscle, while chronic resistance training increases the Microtubule-associated protein light chain 3-II/ Microtubule-associated protein light chain 3-I (LC3-II/LC3-I) ratio and decreases p62, thereby improving mitochondria–ER communication and mitigating ERS [183,184]. These adaptations are associated with better cognitive and cardiovascular outcomes in older adults [185,186].

Furthermore, 7–8 h of high-quality sleep maintains circadian levels of basic helix-loop-helix ARNT like 1/cryptochrome 1 (BMAL1/CRY1), thereby reversing age-related cognitive decline [187]. In *Caenorhabditis elegans* (*C. elegans*) experiments, mild cold exposure (15–18 °C, 30 min daily) transiently activates ATF6, enlarges ER lumen volume, and enhances folding capacity, extending *C. elegans* lifespan by 15% [188]. Collectively, these data demonstrate that structured lifestyle interventions—diet, exercise, sleep and mild cold stress—can durably optimize ER protein homeostasis without triggering excessive apoptosis [189].

6. Conclusion

Endoplasmic reticulum stress and the unfolded protein response play pivotal roles in the aging process, with their abnormal activation and dysregulation closely linked to the onset and progression of various age-related diseases [190]. Research in 2023 established “protein homeostasis imbalance” as a novel hallmark of aging [4], with the endoplasmic reticulum stress-unfolded protein response (ERS-UPR)

emerging as a core mechanism. Therefore, elucidating the molecular mechanisms of ERS-UPR and its manifestations in senescent cells is crucial for understanding aging mechanisms and developing anti-aging strategies [84].

Despite significant progress, several critical challenges remain. First, the UPR exhibits remarkable temporal dynamics—its three branches (PERK, IRE1, ATF6) shift from adaptive to maladaptive signaling depending on stress intensity and duration. Future research must prioritize temporal control of UPR modulation, moving beyond static inhibition or activation toward strategies that restore the physiological rhythm and context-dependent flexibility of UPR signaling [62,162]. Second, while lifestyle interventions such as caloric restriction, exercise, and sleep optimization have demonstrated efficacy in alleviating ERS, their effects vary substantially across individuals. Developing personalized lifestyle intervention protocols—tailored to genetic background, metabolic status, and age—will be essential to maximize benefits and minimize variability. Third, the clinical translation of gene therapies targeting ERS pathways demands breakthroughs in novel delivery systems [191]. Advances in tissue-specific AAV serotypes, non-viral vectors, and CRISPR-based precision editing technologies offer promising avenues to enhance targeting specificity, reduce off-target effects, and ensure long-term safety.

Although numerous drugs and interventions are currently under investigation or in clinical use, several challenges persist: evaluating drug efficacy and safety based on the temporal dynamics and pathogenic thresholds of the UPR's triple pathways (PERK/IRE1/ATF6) during aging, enhancing the tissue/cell/signaling pathway specificity of gene therapies, overcoming technical hurdles related to the circadian sensitivity of the UPR, and addressing individual variability in lifestyle interventions [192,193,194].

Looking ahead, with ongoing technological advancements and deepening multidisciplinary collaboration, we are confident in further elucidating the mechanisms by which endoplasmic reticulum stress and the unfolded protein response influence the aging process. This will pave the way for developing more efficient and safer anti-aging strategies, providing a solid foundation for human health and longevity.

Abbreviations

ER, endoplasmic reticulum; ERS, endoplasmic reticulum stress; UPR, unfolded protein response; SRP, signal recognition particle; NAC, nascent polypeptide-associated complex; PDI, protein disulfide isomerase; ERO1 α , endoplasmic reticulum oxidoreductase 1 alpha; SERCA, sarco/endoplasmic reticulum Ca²⁺-ATPase; RyRs, ryanodine receptors; InsP₃Rs, inositol 1,4,5-trisphosphate receptors; ERQC, endoplasmic reticulum quality control; UPS, Ubiquitin-proteasome system; PERK, protein kinase R-like endoplasmic reticulum kinase; IRE1 α , inositol-requiring enzyme 1 α ; ATF6, activating transcription fac-

tor 6; BiP, immunoglobulin heavy chain binding protein; eIF2 α , eukaryotic initiation factor 2 α ; eIF2B, eukaryotic initiation factor 2B; GDP, guanosine diphosphate; GTP, guanosine triphosphate; ATF4, activating transcription factor 4; bZIP, basic leucine zipper; ATF3, activating transcription factor 3; CHOP, C/EBP-homologous protein; DNA, deoxyribonucleic acid; CHOP-RE, CHOP-response element; XBP1, X-box binding protein 1; p58IPK, 58 kDa inhibitor of the interferon-induced, double-stranded RNA-activated protein kinase (PKR); ERAD, endoplasmic reticulum-associated degradation; RIDD, Regulated IRE1-Dependent Decay; dsRNA, double-stranded RNA; TRAF2, tumor-necrosis-factor-receptor-associated factor 2; ASK1, apoptosis signal-regulating kinase 1; JNK, c-Jun N-terminal kinase; COPII, coat protein II; S1P, site-1 protease; S2P, site-2 protease; NF, nuclear factor; ERSEs, endoplasmic reticulum stress-response elements; ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; NOX4, nicotinamide adenine dinucleotide phosphate hydrogen oxidase 4; IP3R, inositol trisphosphate receptor; RyR, ryanodine receptor; AD, Alzheimer's disease; A β , β -amyloid; BACE1, beta-secretase 1; ISRIB, Integrated stress response Inhibitor reverses; APP, amyloid precursor protein; PS1, Presenilin-1; HRD1, HMG-CoA reductase degradation 1 protein; PD, Parkinson's disease; α -Syn, α -synuclein; POAG, primary open-angle glaucoma; RGCs, retinal ganglion cells; I/R, ischemia-reperfusion; AAV, adeno-associated virus; ATF6f, ATF6 fragment; *Nppb*, natriuretic peptide B; TAC, transverse aortic constriction; SOCS3, suppressor of cytokine signaling 3; ox-LDL, oxidized low-density lipoprotein; AGEs, advanced glycation end-products; NET, neutrophil extracellular trap; T2DM, type 2 diabetes mellitus; *NKX6.1*, NK6 Homeobox 1; *MAFA*, MAF bZIP transcription factor A; GSIS, glucose-stimulated insulin secretion; LDL-C, low-density lipoprotein cholesterol; PPAR, peroxisome proliferator-activated receptor; 4-PBA, 4-phenylbutyrate; iNOS, inducible nitric oxide synthase; CRISPR, clustered regularly interspaced short palindromic repeats; GRP78, glucose regulated protein 78kD; CR, caloric restriction; IGF-1, insulin-like growth factor-1; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; SIRT1, sirtuin 1; PGC-1 α , peroxisome proliferator-activated receptor γ coactivator 1 alpha; CALERIE, comprehensive assessment of long-term effects of reducing intake of energy; LC3, microtubule-associated protein light chain 3; BMAL1, basic helix-loop-helix ARNT like 1; CRY1, cryptochrome 1.

Author Contributions

LH: Conceptualization, Investigation, Supervision, Writing original draft, Writing – review & editing. HL: Conceptualization, Investigation, Supervision Writing – review & editing. DA: Supervision, Search References, Writing. MT: Supervision, Methodology, Writing. HW: Conceptualization, Writing – review & editing. QL: Conceptu-

alization, Writing – review & editing. WS: Conceptualization, Writing – review & editing. XZ: Conceptualization, Writing – review & editing. ZF: Conceptualization, Funding acquisition, Writing – review & editing. LC: Conceptualization, Funding acquisition, Writing – review & editing. All authors read and approved the final version and are responsible for the published content. All authors participated fully in the work and agreed to take responsibility for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflicts of interest.

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