ISSN 2706-6819 Vol.7, Issue 3: 72-78, DOI: 10.25236/IJFM.2025.070310

Understanding the Role of the Endoplasmic Reticulum Stress Sensor IRE1α in Aging

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Abstract: *Aging is a progressive biological process that leads to a decline in multiple organ functions and finally to disease. A key feature of aging is the breakdown of proteostasis, particularly affecting the endoplasmic reticulum (ER). As an adaptation to ER stress, the unfolded protein response (UPR) is activated to maintain ER homeostasis. Among the three arms of the UPR, IRE1α is the most ancient pathway involved in maintaining proteostasis. As such, multiple studies demonstrate IRE1α's significance in ensuring healthy aging. The process of aging can be delayed through various strategies, including genetic modifications, dietary adjustments, and pharmacological interventions, which are correlated with improved ER proteostasis, activation of the UPR and IRE1α. This article reviews the latest progress in understanding the role of the UPR and IRE1α signaling in the aging process and its interconnection with other aging biomarkers, including cellular senescence.*

Keywords: *UPR, ER Proteostasis, Healthy Aging*

1. Introduction

With the aging population increasing around the world, deciphering the molecular pathways and processes that lead to aging is becoming more critical. The inability to give an adequate response to cellular stress is toxic in aging organisms, resulting in accumulated damage to cells and loss of proteostasis. Also, age-dependent unfolded protein accumulation during aging drives aging-related diseases. The ability of organisms to respond to ER stress, also known as the UPR (unfolded protein response), decreases with aging, which is harmful in the face of accumulated unfolded proteins, indicating the importance of the UPR in resolving ER stress (Endoplasmic Reticulum Stress) in aging [1, 2].

The Endoplasmic reticulum (ER) is a membrane-bound organelle that is crucial for protein synthesis, folding, and trafficking within cells. Upon disruption of cellular homeostasis (e.g., hypoxia, aging, physical exercise, infections, glucose or calcium imbalance, etc.), the demand for protein synthesis increases. If newly synthesized peptides cannot be folded properly in a timely manner, the accumulation of unfolded proteins will induce ER stress (Endoplasmic Reticulum Stress), triggering the activation of the UPR (unfolded protein response) [3-5]. There are three ER-resident transmembrane sensors of the UPR: protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) [6]. Among them, IRE1 is the most evolutionarily conserved UPR sensor [7].

IRE1α is a transmembrane protein comprising a luminal domain, a linker region, and a cytoplasmic domain [8]. During the resting state, BiP/glucose-regulated protein 78 (GRP78), an ER-resident chaperone, interacts with the luminal domain of IRE1α to restrain its activity [5]. Loss of ER homeostasis causes BiP to dissociate from IRE1α, leading to the activation of IRE1α. Besides, the binding of unfolded proteins to IRE1α can also induce its activation [9]. Upon activation, IRE1α undergoes autophosphorylation via its kinase activity and oligomerization to induce its RNase activity, which is located in its cytoplasmic tail. RNase activation of IRE1α initiates unconventional splicing of XBP1 mRNA by cleaving out 26 nucleotides, followed by ligation by a tRNA ligase, RTCB, to generate the spliced form of XBP1 (XBP1s). XBP1s then enters the nucleus to induce the expression of UPR-related genes, including those encoding protein chaperones, ERAD (ER-associated degradation) components,

ISSN 2706-6819 Vol.7, Issue 3: 72-78, DOI: 10.25236/IJFM.2025.070310

and genes involved in ER biogenesis, to resolve ER stress [10, 11]. Besides XBP1, the cleavage targets of the RNase activity of IRE1α can include microRNAs [12] and mRNAs, a process termed regulated IRE1α-dependent decay (RIDD) [2, 13, 14]. In addition to its RNase-dependent functions, IRE1α can also participate in the JNK and IKKβ-NF-κB inflammatory signaling pathways via its interaction with TNF-receptor-associated factor 2 (TRAF2) [15, 16].

2. The role of IRE1α in aging

2.1 IRE1α in aging in simple model organisms

The components of the UPR, especially IRE1α, are vital for longevity in simple animal models, including fruit flies, C. elegans and yeast. Yeast cells have a shorter lifespan due to mutations within the IRE1α pathway, which is the only UPR pathway in yeast [17]. IRE1α plays an important role in longevity partly through its splice target, the spliced form of XBP1 (XBP1s). Overexpression of XBP1s in the small intestinal cells of fruit flies can extend their lifespan, while overexpression of XBP1s in the fat body of fruit flies can promote longevity by regulating their metabolic state [18]. Besides, the unspliced form of XBP1 (XBP1u) also plays a role in lifespan extension [18], although the detailed mechanism remains to be elucidated. The protection conferred by XBP1s to fruit flies from Alzheimer's disease decreases with aging, consistent with the decreasing intensity of the UPR observed with aging [19].

C. elegans has been widely used to elucidate mechanisms involved in longevity. The significance of the IRE1/XBP1 pathway in neurons for healthy aging has been established [11, 20-24]. Both overexpression and loss-of-function (lof) mutations of XBP1s can affect the lifespan of C. elegans significantly. Specifically, XBP1s exerts its lifespan extension function by inducing the UPR in the intestine via secreting small clear vesicles [20]. Overexpression of XBP1s in the intestine of C. elegans demonstrated that the induced UPR in the gut regulates genes involved in lipophagy [22], proteostasis [23] and lipid metabolism [24]. Overexpression of XBP1s in different types of neurons exerts different effects on changes in gene expression patterns in peripheral tissues. Whereas the UPR in dopaminergic neurons modulates lipid depletion distally, the UPR in serotoninergic neurons plays a role in promoting adaptive homeostasis throughout the body [25]. Overexpression of XBP1s in glutamatergic neurons enhances protein homeostasis, whereas overexpression of XBP1s in octopaminergic neurons upregulates the antipathogen immune response [26]. Meanwhile, activated UPR in GABAergic neurons has less effect on lipid metabolism homeostasis [26]. It remains unclear why expression of XBP1s in different neuronal types has different effects.

As important components of the nervous system, glial cells, in addition to providing protection, maintain metabolic homeostasis of neurons. Overexpression of XBP1s in the four astrocyte-like glial cells of C. elegans promotes longevity through modulating proteostasis throughout the body [21]. The expression of TFEB, a transcription factor that regulates lysosome biosynthesis, is upregulated when XBP1s is overexpressed in glial cells to regulate lipid metabolism and intestinal autophagy [27]. Induced UPR in neuronal and glial cells can regulate gut and whole-body proteostasis in a cell-nonautonomous manner. When the mitochondrial UPR is activated, astrocyte-like glial cells can also send signals to neurons through small clear vesicles and to peripheral tissues through dense-core vesicles to promote longevity [28].

The Nervous system of C. elegans can sense ER stress to send signals to peripheral tissues to modulate global adaptation and thereby regulate lifespan. In addition to ER stress, the heat shock response has a similar function. Activation of IRE1/XBP1s by volatile pathogen-associated compounds in neuronal cells can promote lifespan [29]. In summary, activation of IRE1/XBP1s to induce cellular adaptation to ER stress can benefit health and extend lifespan.

2.2 IRE1α in aging in mammalian aging

During healthy aging, ER proteostasis is impaired in human tissues. Increased UPR in the eye lens indicates increased ER stress [30], and this increased ER stress is related to functional defects in aging islet β cells [31]. Meanwhile, ER stress in human muscle attenuates with aging, a process that can be improved by physical exercise [32]. Higher levels of ER stress and aging markers were detected in lung fibroblasts derived from older humans than from younger humans [33]. Thus, the intensity of the UPR decreases with aging, impairing its ability to maintain ER proteostasis, which may result in accumulation of misfolded/unfolded proteins and damage to ER proteostasis.

ISSN 2706-6819 Vol.7, Issue 3: 72-78, DOI: 10.25236/IJFM.2025.070310

Mouse models provide a powerful tool for manipulating gene expression to study the UPR in mammalian aging. Overexpression of XBP1s in neurons can delay or even prevent cognitive decline in healthy aging [34]. 70% of the proteomic changes observed in the brain during normal aging can be reversed by overexpression of XBP1s in the hippocampus of mice, accompanied by improved synaptic function [34]. Genes upregulated by overexpression of XBP1s, which are downregulated in the hippocampus with healthy aging in mice, are also downregulated in the hippocampus of aged humans [34].

Conditional knockout of IRE1α in the retina results in decreased outer nuclear layer thickness as animals age [35], indicating the significance of the IRE1/XBP1s pathway in ocular aging.

The IRE1/XBP1s pathway has also been linked to ocular aging. In a model of retinitis pigmentosa, which is related to chronic ER stress, mice were more susceptible to retinal degeneration due to defective UPR [35]. A model with deletion of XBP1s in the retina exhibits dysfunction of photoreceptors [36]. Thus, whether IRE1/XBP1s can regulate lifespan in mammals remains to be determined.

2.3 IRE1α in cell senescence

Although loss of ER proteostasis is a sign of the aging process, UPR signaling can promote other aspects of aging. Cellular senescence is characterized by stable growth arrest, a proinflammatory secretome and other changes [37]. Human senescent cells show enhanced ER stress sensing, but insufficient UPR-related transcriptional induction [38]. The activation of the IRE1/XBP1s pathway is important for cell senescence caused by DNA damage [39].

The UPR activation and enhanced autophagy in senescent cells are involved in the upregulation of SASP (senescence-associated secretory phenotype) secretion [40-42]. DNA damage agent-induced senescence increased ER stress when autophagy was inhibited with quercetin, leading to senolysis [43]. Conditional knockout of ATF6 or IRE1 in β cells of non-obese diabetic (NOD) mice prior to insulitis induces a senescence phenotype in β cells [44]. The IRE1/XBP1s pathway is involved in regulating the number of senescent cells in the brain during aging. Whereas deletion of IRE1α accelerates the accumulation of senescent cells during aging, overexpression of XBP1s reduces the number of senescent cells [34]. IRE1α regulates the response to DNA damage through RIDD, which can lead to a senescent phenotype; conversely, DNA damage can also trigger the oligomerization of IRE1α to catalyze RIDD [45].

Verteporfin treatment, which inhibits the YAP-TEAD pathway, reduces ER biogenesis and induces ER stress [46]. Owing to high protein secretion demand imposed by the SASP, the activated UPR is required to maintain ER proteostasis to sustain cell survival. Consequently, VPF treatment can selectively reduce the viability of senescent cells [46]. Thus, the high demand for protein synthesis and secretion in senescent cells underlies the significance of the UPR in regulating senescence.

2.4 IRE1α as a mediator in aging-modifier approaches

Multiple interventions to extend lifespan act through the IRE1/XBP1s pathway. Under dietary restriction, the IRE1/XBP1s pathway is activated in a metabolic adaptation that promotes enterocyte homeostasis and longevity in Drosophila [47]. The IRE1/XBP1s pathway can also enhance the lifespan of insulin/IGF-1 signaling mutant C. elegans [48]. Interaction between XBP1s and the FOXO transcription factor can promote longevity in a fruit fly model [18]. IRE1/XBP1s is required for the longevity effects of dietary restriction, resulting in increased ER-associated degradation (ERAD) gene expression and degradation of ER proteins [49].

Exposure of C. elegans to Tm (tunicamycin, an ER stress activator) in early development can enhance proteostasis, prevent age-related UPR decline, and extend adult lifespan [49], a phenomenon called ER hormesis. ER preconditioning using genetic manipulation to alter ER homeostasis can also promote longevity [50]. Glucose and vitamin D restriction can also promote longevity of C. elegans via a UPR-dependent pathway [51, 52].

Endurance exercise can promote healthy aging at least partly through inducing metabolic stress and by improving ER proteostasis [53]. Endurance exercise can prevent aging-induced chronic ER stress in muscle [54]. Endurance exercise induces less upregulation of the UPR gene expression program in older humans [32], possibly due to impaired UPR activation. Resistance training and swimming can restrict the expression of ER stress-related proteins in the heart during aging [55, 56]. Resistance training can also induce the UPR program in peripheral blood mononuclear cells from older humans [57].

ISSN 2706-6819 Vol.7, Issue 3: 72-78, DOI: 10.25236/IJFM.2025.070310

Metformin, an AMPK activator, can prevent aging-related hearing loss and reduce the UPR activation [58]. ER stress declines and cognitive function improves in mice after Metformin intake [59]. Although a correlation between the UPR and Metformin has been established, direct evidence is still needed.

3. Discussion

An organism's robustness and the preservation of its health rely on homeostatic mechanisms that respond to molecular changes, orchestrating reactions across organs. It is anticipated that the disruption of proteostasis during aging influences cells, since maintaining the cell-type-specific proteomes is the cornerstone of health maintenance. The molecular mechanism underlying the declined activity of the proteostasis network during aging remains an unresolved question, potentially stemming from a lack of evolutionary pressure to preserve proteome integrity after reproduction. The aging process may encompass increased impairment of ER proteostasis---manifesting as alterations in the secretory pathway, malfunction of the ER folding apparatus, protein aggregation within the ER, among others---or a deficiency in monitoring and repairing damage, such as the oxidative inactivation of UPR stress sensors, which could, in turn, exacerbate the breakdown of proteostasis.

We hypothesize that the ability to detect misfolded proteins becomes compromised with age, potentially leading to the decline of tissue integrity, based on published studies. The brain-gut axis is a dynamic and reciprocal communication system that functionally links different organs. While there is substantial evidence from invertebrate studies indicating a relationship between neuronal UPR and protein homeostasis in the gut, it remains unclear if such a link exists in mammals. This uncertainty poses a significant question for future research. Notably, research has demonstrated that XBP1s in the hypothalamus can induce a cell-nonautonomous activation of the UPR in the liver, influencing energy metabolism [60]. Nonetheless, the role of this pathway in the aging process has yet to be elucidated.

The exposome plays a pivotal role in shaping the aging process in humans. Our sensory perceptions act as the critical link, bridging our body with the external environment. The link between the perception of food, the hypothalamus, and hepatic XBP1s signaling might represent evidence of a sensory-proteostasis nexus in mammals [61]. As previously discussed, in C. elegans, the perception of olfactory cues exerts life-extending influences by modulating the UPR. Similarly, in these organisms, responses to cold stress have been associated with IRE1 signaling [62], a pathway that influences both longevity and health [63]. We conjecture that the nervous system functions as a central hub, collecting diverse information from the exposome and capable of discerning even the slightest deviations in cellular homeostasis. It then sends signals throughout the organism to foster adaptation and promote survival.

Despite the availability of sophisticated genetic tools that allow the manipulation of various UPR signaling pathways in specific tissues [11, 64], evidence connecting UPR signaling to the aging process in mammals remains insufficient, with the majority of research focusing on the nervous system. Enhancing the UPR artificially could potentially delay or even prevent the decline in tissue function associated with aging. We emphasize the potential widespread advantages of boosting UPR activity in the brain---for instance, through gene therapy---not only to enhance brain function but also to regulate proteostasis throughout the entire organism. In recent years, a surge in research has underscored the pivotal role of the UPR in promoting healthy aging, while also revealing numerous challenges. Given that biological age can diverge from chronological age at the level of individual organs and cell types, it remains to be determined whether interventions aimed at the UPR can alter biological age, alongside other key indicators of aging such as cellular senescence and inflammaging.

The decline in ER proteostasis could serve as a prognostic indicator for aging patterns and as a biomarker to evaluate the effectiveness of potential therapeutic interventions. It has been suggested that the evaluation of aging clocks might incorporate the analysis of tissue-specific protein aggregation [65], based on the observation that aging leads to the aggregation of proteins. Proteomic analysis of plasma has revealed that markers of proteostasis undergo changes early in life, providing predictive insights into the likelihood of developing dementia [66], and that age-related changes specific to tissues may be identifiable in blood samples [67]. These insights open the door to testing the effectiveness of drugs targeting the UPR for aging-related interventions, as well as to monitoring biomarkers of aging for personalized medicine through ex vivo cultures. Similar to the approach taken with senolytics, we suggest that interventions aimed at improving ER proteostasis could mitigate a wide range of diseases, potentially due to the UPR's fundamental role in the biology of aging, which is a primary risk factor for the onset of numerous chronic diseases.

ISSN 2706-6819 Vol.7, Issue 3: 72-78, DOI: 10.25236/IJFM.2025.070310

Acknowledgements

We would like to thank all authors whose work is cited in this collection for their contributions. And we thank Leon for critical reading and editing of the manuscript.

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