Exploring the Role of Endoplasmic Reticulum Stress in Various Diseases: Implications and Potential Therapeutic Strategies

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Abstract

This study examines prospective therapeutic approaches to modulate Endoplasmic reticulum stress (ER stress) for disease intervention and emphasizes the significant role of ER stress in the pathophysiology of numerous diseases. ER stress is an intracellular stress response when the ER fails to properly fold and repair proteins. This cellular stress response holds crucial relevance in developing many diseases, such as metabolic-related diseases, neurodegenerative diseases, and cardiovascular diseases. This work reviews the underlying mechanisms of ER stress and summarizes its association with various diseases. ER stress can lead to the disordered accumulation of intracellular proteins and the abnormality of cell function, impairing the normal physiological function of cells. These abnormal processes are closely related to disease development.

Furthermore, several potential therapeutic options have been described, aiming to modulate ER stress and alleviate symptoms of associated diseases. These therapeutic options include small molecules, chemical chaperones, modulation of the UPR signaling pathway, gene therapy, and more. By modulating ER stress, researchers can intervene in disease development and provide new ideas and methods for preventing and treating these diseases.

Keywords: ER stress; neurodegenerative diseases; metabolic disorders; cardiovascular diseases; treatment strategies.

1. Introduction

ER stress is a cellular stress response that refers to the disordered state of the endoplasmic reticulum (ER) when confronted with abnormal conditions. The ER is a vital cellular organelle primarily involved in protein synthesis, folding, and post-translational modification processes. When cells face external environmental changes, pathological conditions, or genetic mutations, it may result in ER dysfunction and the accumulation of misfolded or unfolded proteins, which in turn causes ER stress. [1].

ER stress has become an important player in the pathogenesis of many diseases, including cardiovascular diseases, metabolic disorders, and neurodegenerative diseases. Currently, the global population is aging, and the burden of metabolic disorders, obesity, and neurodegenerative diseases is increasing [2]. Alzheimer's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS), and Parkinson's disease are examples of neurodegenerative disorders, and this phenomenon is often associated with the progressive degeneration and loss of neurons in specific areas of the brain. ER stress is observed in these diseases, leading to protein misfolding, aggregation, and neuronal dysfunction [3]. Metabolic conditions cover a variety of disorders, such as obesity, metabolic syndrome, type 2 diabetes, and nonalcoholic fatty liver disease. ER stress is linked to imbalances in glucose and lipid metabolism, malfunction of pancreatic β-cells, and insulin resistance, which are key features of these diseases [4]. Atherosclerosis, heart failure, and myocardial infarction are among the primary reasons for morbidity and mortality globally. ER stress has a pivotal function in endothelial dysfunction, vascular inflammation, oxidative stress, and apoptosis, contributing to the initiation and progression of these cardiovascular diseases [5].

In recent times, numerous research efforts have delved into understanding the influence of ER stress on the onset and advancement of these conditions. ER stress contributes to cellular dysfunction, disrupting vital signaling pathways and important cellular processes. This disruption leads to the accumulation of toxic protein aggregates, activation of inflammatory responses, and disturbances in cellular metabolism. Understanding the involvement of ER stress in these diseases is crucial as it provides insights into underlying mechanisms and potential therapeutic targets. Targeting ER stress and its downstream signaling pathways makes it possible to mitigate the pathological consequences associated with these diseases and develop new therapeutic strategies [6].

This research will delve into ER stress and examine associated molecular mechanisms and their particular importance in neurodegenerative diseases, metabolic disorders, and cardiovascular disease. Emphasis will be

placed on the impact of ER stress on disease initiation and progression, highlighting its potential as a therapeutic target. By elucidating the complex relationship between ER stress and these diseases, the findings significantly enhance the field's knowledge and set the groundwork for upcoming research and potential treatments.

2. Mechanisms of endoplasmic reticulum stress

2.1 Endoplasmic reticulum

The ER is a series of connected membrane tubes and sacs distributed throughout the cytoplasm of eukaryotic cells. It consists of two distinct regions: the rough ER, distinguished by ribosomes on its exterior, and the smooth ER, devoid of ribosomes on its surface. The rough ER is primarily responsible for protein synthesis and folding, while the smooth ER is involved in lipid metabolism, detoxification, and calcium storage [7]. This organelle plays a vital role in maintaining cellular integrity and the normal function of various organs and tissues. When the ER detects protein folding disturbances or cellular stress, it triggers a signaling pathway called the unfolded protein response (UPR) to restore ER stability and ensure cell survival [7].

2.2 Unfolded Protein Response (UPR)

The UPR is a conserved cellular signaling mechanism triggered by ER stress. Its goal is to reestablish ER balance by enhancing the ER's folding ability, degrading misfolded proteins, and attenuating overall protein synthesis [8].
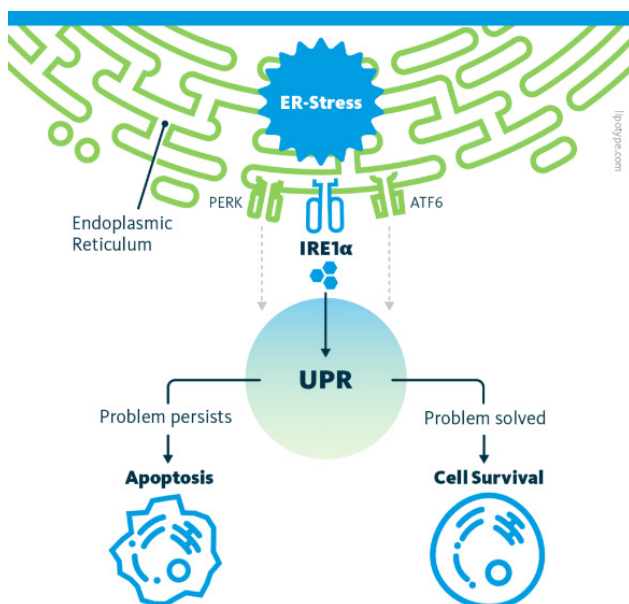

Figure 1. Three major ER transmembrane sensors mediate UPR [9].

Three primary transmembrane sensors in the ER mediate the UPR: Inositol-requiring enzyme 1 (IRE1) is a transmembrane protein in the ER that functions as an endoribonuclease. It has two isoforms, IRE1α and IRE1β, with IRE1α being autophosphorylated and activated upon ER stress [8]. Another sensor is the Protein kinase RNA-like endoplasmic reticulum kinase (PERK), a transmembrane protein in the ER that exhibits protein kinase activity. PERK is activated through autophosphorylation during the ER stress. Once activated, PERK adds a phosphate group to the α-subunit of eukaryotic translation initiation factor 2 (eIF2α), leading to an overall attenuation of protein synthesis. Decreasing protein synthesis helps to relieve ER stress by lowering the influx of unfolded proteins into the ER [8]. Lastly, the third sensor activates transcription factor 6 (ATF6), a type II transmembrane protein on the ER membrane. ATF6 translocates to the Golgi apparatus and is subjected to proteolytic cleavage by site one and site two proteases during ER stress. This cleavage releases the cytoplasmic domain of ATF6, which acts as a transcription factor. ER folding and lipid metabolism-related genes expressed are activated by cleaved ATF6 translocating to the nucleus. ATF6 is crucial in restoring ER homeostasis and enhancing cell viability during ER stress conditions [8, figure 1].

2.3 Causes and Inducers of ER Stress

Various factors can initiate ER stress, such as protein misfolding, oxidative stress, calcium imbalance, and lipid dysregulation. Protein misfolding occurs when newly synthesized proteins fail to fold properly or when mutations in protein-coding genes create misfolded proteins. Reactive oxygen species (ROS) generation and the antioxidant defense mechanisms of the cell are out of balance, causing oxidative stress to disrupt the proper folding of proteins and trigger ER stress [10]. Calcium imbalances (involving impaired ER calcium release or reuptake) disrupt ER homeostasis and trigger UPR. In addition, changes in lipid metabolism, such as abnormal lipid accumulation or changes in membrane composition, can induce ER stress [11].

3. ER stress-related diseases

3.1 Alzheimer's disease

Alzheimer's disease is a neurological condition linked to memory loss and cognitive impairment in old age. ER stress is a significant mechanism in the development of Alzheimer's disease and is closely related to the accumulation of misfolded proteins. In Alzheimer's disease, irregular proteins accumulate to create plaques

within the brain, including Amyloid beta and TAU proteins. Misfolding of these abnormal proteins prevents them from properly folding into a functional conformation and accumulates into toxic aggregates. These protein aggregates disrupt normal cellular function, resulting in neuronal dysfunction and cognitive decline. The buildup of abnormal proteins induces ER stress and triggers the UPR in the ER. UPR aims to reestablish ER balance by increasing chaperone production, reducing protein synthesis, and promoting protein degradation. However, in AD, UPR often fails to resolve ER stress, resulting in the persistent activation of the stress response and further neuronal damage [12].

ER stress and the associated UPR adversely affect neuronal function, leading to cognitive decline. ER stress disrupts synaptic function, impairs axonal transport, and alters calcium homeostasis, all essential for normal neuronal communication and plasticity. Moreover, ER stress in AD affects the processing and clearance of amyloid precursor protein (APP). In typical scenarios, APP is broken down by designated enzymes to produce soluble fragments easily cleared from the brain. However, ER stress alters the activity of these enzymes, leading to increased Aβ production and impaired clearance mechanisms. This further exacerbates the accumulation of Aβ plaques and leads to neurotoxicity and cognitive decline [13].

Currently, ER stress therapy for Alzheimer's disease is still in the research and development stage. In Alzheimer's disease, a new type of treatment, protein folding aids, could hold promise. This auxiliary aids in the correct protein folding, forming a functional conformation. Enhancing the correct folding of proteins can reduce the accumulation of misfolded proteins, thereby reducing the degree of ER stress. Antioxidants and anti-inflammatory agents are also a foreseeable treatment option. Endoplasmic reticulum stress can promote inflammation and oxidative stress, further exacerbating the progression of Alzheimer's disease. Therefore, using antioxidants and anti-inflammatory agents may help attenuate neuronal damage from ER stress. These drugs can reduce the release of inflammatory mediators, inhibit the process of oxidative stress, and attenuate the negative effects of ER stress [11.12].

3.2 Parkinson's disease

Parkinson's disease's characteristic pathological sign is the abnormal aggregation of α-synuclein to form Lewy bodies. Research indicated that ER stress significantly contributes to the aggregation and neurotoxicity of α-synuclein. ER stress leads to the malfunctioning of the ER and abnormal protein folding, leading to aggregation of α-synuclein. Aggregated α-synuclein further activates the ER stress response, forming a vicious cycle. These aggregates can trigger neurotoxicity, interfere with the normal function of nerve cells, and trigger cell death [14]. Parkinson's disease is primarily attributed to the progressive degeneration and death of dopaminergic neurons in the brain, which leads to movement disorders and other symptoms. ER stress can cause disturbances in intracellular calcium ion concentration, leading to mitochondrial dysfunction, oxidative stress, and inhibition of mitophagy. These changes lead to damage and death of dopaminergic neurons, further exacerbating motor dysfunction. In addition, ER stress affects the intracellular protein synthesis, breakdown, and folding machinery, further interfering with dopamine signaling and the normal function of neurons [14].

Researchers are actively exploring ways to modulate ER stress to mitigate its adverse effects on Parkinson's disease. This may include pharmacological interventions targeting the ER stress signaling pathway and treatments that promote mitochondrial function and autophagy. One therapeutic approach that could be investigated is the enhancement of autophagy, the process by which cells clear and recycle unwanted or abnormal proteins and organelles. The study discovered that promoting enhanced autophagy may be a potential strategy to alleviate protein aggregation and ER stress in Parkinson's disease [11]. Several drugs and compounds, such as the antiviral rapamycin and the supplemental enzyme Q10, have been studied to enhance cell autophagy [15].

3.3 Diabetes

In the context of diabetes, ER stress is linked to the development of insulin resistance and β-cell dysfunction. Insulin resistance is when the body's cells don't respond as effectively to insulin's actions. This hormone regulates the uptake of glucose from the blood into the cells. In tissues targeted by insulin, like the muscle, fat tissue, and liver, ER stress activates the UPR and leads to impairment of insulin signaling. Disruption in insulin signaling leads to a decrease in the uptake and utilization of glucose by cells, which in turn leads to elevated blood glucose and insulin resistance. In addition, ER stress can further affect glucose homeostasis by activating inflammatory responses. ER stress induces the release of inflammatory factors, such as cytokines and chemokines, which may interfere with insulin signaling and lead to insulin resistance. In addition, ER stress directly damages β-cells in pancreatic islets, affecting their function and viability, resulting in decreased insulin secretion and disturbance of glucose metabolism [3].

Given the role of ER stress in diabetes, therapeutic

strategies aimed at alleviating ER stress have been explored as potential treatments for the disease. For example, chemical chaperones, some studies have shown that 4-phenylbutyric acid (PBA) and tauroursodeoxycholic acid (TUDCA) can act as chemical chaperones. They can help restore ER homeostasis by promoting proper protein folding, and these chaperones can reduce ER stress and improve insulin sensitivity. Also, targeting the UPR signaling pathway is a new idea, and inhibitors of the PERK pathway have shown promise in improving ER stress-induced insulin resistance [11].

3.4 Obesity

There is a link between ER stress, the development of chronic inflammation, and adipose tissue dysfunction, both of which are strongly associated with obesity. In obesity, expanding adipose tissue may lead to ER stress due to increased protein synthesis and lipid metabolism demands. Endoplasmic reticulum stress in adipocytes leads to adipose tissue dysfunction, inhibits adipocyte differentiation and fatty acid synthesis, and promotes fatty acid release and production of inflammatory factors. This inflammation is known as a chronic low-grade inflammatory state [16]. This inflammation further exacerbates insulin resistance, impairs adipocyte function, and contributes to obesity-related metabolic complications, such as type 2 diabetes and cardiovascular disease [2].

Targeting ER stress in obesity is a potential therapeutic strategy to improve metabolic health. Like diabetes, chemical chaperones such as PBA and TUDCA can relieve ER stress in adipose tissue, and these chaperones may help reduce ER stress-induced inflammation and improve adipose tissue function [11]. A more lifelike treatment option is lifestyle changes, such as diet and exercise, which are crucial in managing obesity-related ER stress. Caloric restriction and weight loss have been shown to reduce indicators of ER stress in fat tissue. In addition, regular exercise can improve ER function and reduce ER stress, thereby attenuating the adverse effects of obesity on adipose tissue.

3.5 Atherosclerosis

ER stress has been linked to the onset and advancement of atherosclerosis, a chronic inflammatory disease characterized by plaque buildup in arteries. ER stress can lead to endothelial dysfunction, a pivotal early occurrence in atherosclerosis, and the formation of foam cells involved in plaque formation. Endothelial dysfunction pertains to the compromised function of endothelial cells that comprise the blood vessels' inner layer. ER stress in endothelial cells results in the production of pro-inflammatory molecules like cytokines and adhesion molecules. These inflammatory factors can promote the recruitment of immune cells like monocytes to endothelial cells, thereby triggering the formation of early atherosclerotic lesions [17]. Foam cells form when immune cells absorb oxidized low-density lipoprotein (LDL) particles within the artery walls. Endoplasmic reticulum stress can enhance the uptake of oxidized LDL by macrophages and promote their transformation into foam cells [17]. Accumulation of foam cells in arterial walls contributes to plaque formation and progression of atherosclerosis [5,17].

ER, stress affects the stability of atherosclerotic plaques and increases the risk of cardiovascular events such as heart attack and stroke. Endoplasmic reticulum stress occurring in advanced plaques triggers the production of matrix metalloproteinases (MMPs). These enzymes break down the extracellular matrix and weaken the fibrous cap that encases the plaque. Vulnerable plaques with a weak fibrous cap are more prone to rupture, which can lead to the formation of blood clots that block arteries and lead to acute cardiovascular events. In addition, ER stress-induced inflammation exacerbates plaque destabilization. Inflammatory mediators released by stressed cells within plaques can promote the recruitment of immune cells, amplify inflammation, and impair the resolution of inflammation. This chronic inflammation further weakens the plaque structure and increases the risk of rupture [17].

Targeting ER stress has emerged as a potential therapeutic strategy to control atherosclerosis and reduce cardiovascular risk. Although research in this area is ongoing, modulation of the UPR signaling pathway is an ongoing research direction. Inhibitors or modulators targeting these pathways, such as PERK or IRE1, have shown promise in preclinical models to reduce ER stress and slow atherosclerosis progression [17]. There is also lipid-lowering therapy, which aims to reduce low-density lipoprotein cholesterol levels in patients, such as statins or other lipid-lowering drugs, which have been proven effective in controlling atherosclerosis. These therapies indirectly affect ER stress by reducing the influx of oxidized LDL into the arterial wall and foam cell formation [11,17].

4. Conclusion

ER stress occurs when the ER is overwhelmed and unable to properly fold and process proteins, resulting in ER activation and the cellular stress response initiation. This stress can disrupt normal cellular function and lead to disease development. This article details the mechanisms involved in ER stress in neurodegenerative,

metabolic-related, and cardiovascular diseases. Regarding therapeutic strategies, it is promising to develop specific effective interventions targeting ER stress components or signaling pathways. These strategies include chemical chaperones, agents that modulate UPR signaling, and agents that decrease ER stress and recover ER homeostasis. Recognizing the significance of ER stress in disease pathogenesis is critical for medical development. Understanding the role of ER stress can identify potential therapeutic targets and develop strategies to alleviate ER stress-associated cellular dysfunction and inflammation. Efforts to better understand ER stress and its effects may lead to discovering new diagnostic markers and therapeutic interventions. Furthermore, it may pave the way for a personalized medicine approach, as the severity and impact of ER stress may vary from person to person.

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