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GRP78 as a Target for Prevention of Age-related Cataract By Regulation of Reticulum Endoplasmic Stress

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ABSTRACT: Cataract is the most common causes of blindness worldwide. The most common kind of cataract is age-related cataract. Measures to prevent the development of cataracts are urgently needed. Significant data suggests that increased endoplasmic reticulum stress is a significant role in cataract development.
The goal of this review is to investigate the involvement of endoplasmic reticulum as a factor in cataracts caused by the buildup of unfolded proteins from lens epithelial cells.
GRP78 is one of the key signs of endoplasmic reticulum stress, and it promotes the UPR to limit the increase in unfolded protein levels. The significance of GRP78 signaling in cataract prevention is discussed in this paper.

KEYWORDS: Cataracts, reticulum endoplasmic stress, GRP78, UPR

INTRODUCTION

Cataracts are caused by a decrease of transparency in the crystalline lens, which impairs vision.[1]
Cataracts are the leading cause of blindness, accounting for more than half of all cases globally.[2] According to the WHO, 314 million people have visual issues, 45 million of them are blind, with developing nations accounting for more than 90% of cases. Cataracts are the most common cause of blindness and impaired vision worldwide. The WHO assessed it to be over 17 million (47.8%) in 2002.[3]
Surgery is the only available and effective way to treat cataracts, but it costs a lot of money and requires highly trained personnel. Unfortunately, maximum cataract patients stay in growing international locations wherein get admission to to surgical operation is limited. Therefore it is necessary to think about how to prevent it, namely by developing a non-surgical approach. These strategies not only improve the quality of life, but also reduce the burden on public health.[4]
The pathophysiology of senile cataracts is complex, with oxidative stress being the primary initiator of cataract development. Oxidative stress causes endoplasmic reticulum stress in lens epithelial cells. Endoplasmic reticulum stress occurs when there is a protein imbalance between unfolded and folded proteins.[5] Endoplasmic reticulum stress that is not resolved immediately will affect the folding process of the protein, causing defective proteins that are not folded or misfolded (missfolding or unfolding). The accumulation of proteins that fail to fold will lead to aggregation into large aggregate particles resulting in cataracts.[6]
To overcome failed or misfolded proteins, the endoplasmic reticulum releases heavy-chain binding immunoglobulin Binding immunoglobulin Protein (BiP) / Glucose Regulated Protein (GRP78) by digesting failed proteins via the Endoplasmic Reticulum Associated Degradation (ERAD) pathway. If the misfolded protein remains in the endoplasmic reticulum, GRP78 functions as an initiator to trigger the Unfolding Protein Response (UPR). The UPR regulates endoplasmic reticulum stress by activating three transducers: Inositol-requiring kinase 1 (IREI), protein-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6. (ATF6). These three transducers are dormant under normal conditions and are strictly guarded by GRP78. They are only released when the endoplasmic reticulum is under stress to detect and bind to proteins that fail to fold. [6,7]
Although scientific evidence suggests a functional link between oxidative stress and endoplasmic reticulum stress, the mechanisms behind this correlation remain unknown. Future research will look at the pathophysiology of cellular changes in the protein folding process that result in the synthesis of unfoldable proteins, as well as the pathways involved in the exact mechanism of interaction between oxidative stress and endoplasmic reticulum stress. The goal is to get a thorough grasp of. These findings contribute significantly to the development of cataract treatment methods including oxidative stress and endoplasmic reticulum stress.[8,9]

METHODS

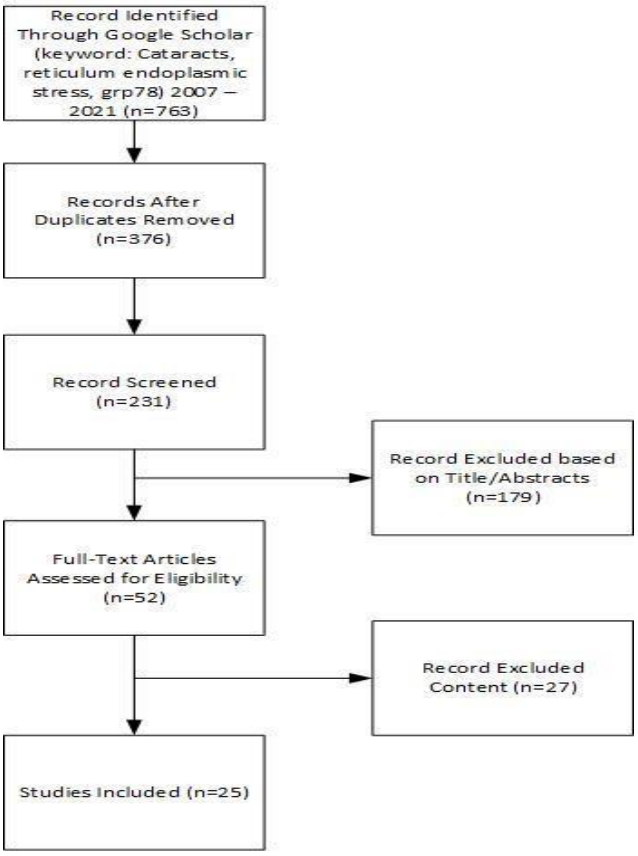

Figure 1. Method of Literature Search

From systematic searches to decisive approaches, we collected 763 articles from Google Scholar. After filtering, duplicate searches excluded 397 articles. 189 articles had no title or abstract and were neither full-text nor in English. 154 articles were irrelevant content. Only 23 articles met the requirements of this study.

RESULTS

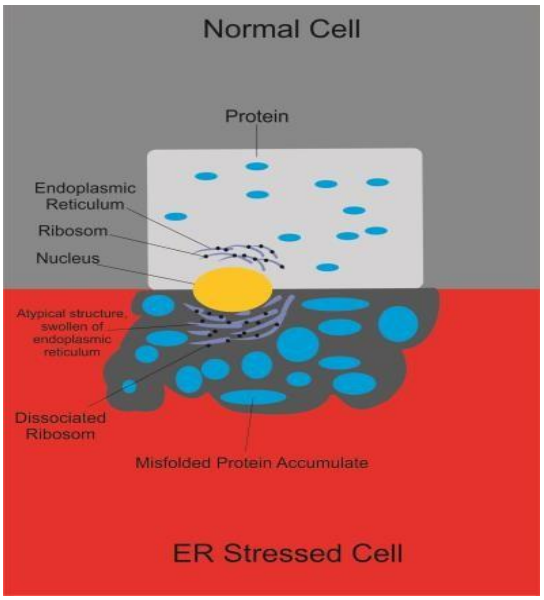

Figure 2. Comparison between normal cells and cells with stressed endoplasmic reticulum

Description: Compared to normal cells, stressed endoplasmic reticulum cells show significant differences in the structure of the endoplasmic reticulum, including luminal swelling and ribosome breakdown.

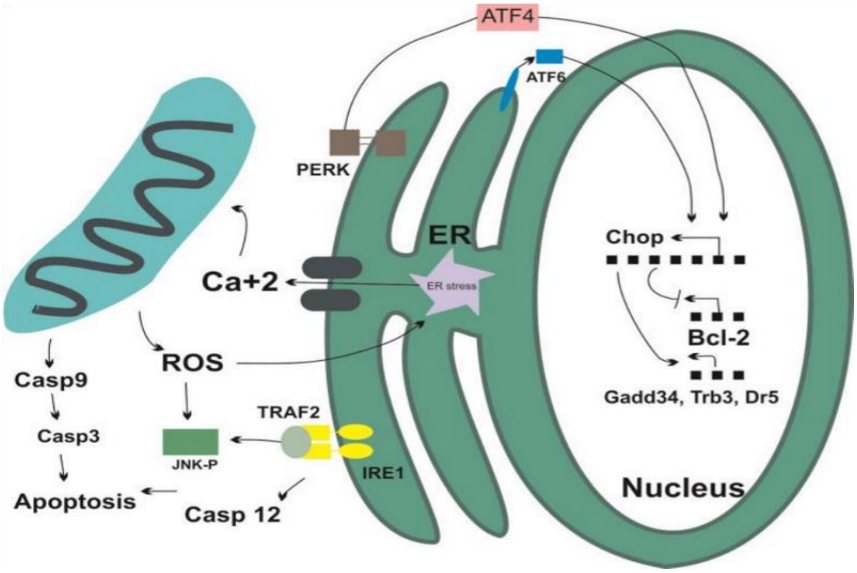

Figure 3. ER stress-induced apoptotic pathways

Endoplasmic reticulum stress activates many redundant caspase activation mechanisms, including mitochondrial and independent routes. TRAF2 was recruited for JNK phosphorylation and activation by activated IRE1. Caspase-12 is the caspase-activation cascade's proximal effector, leading procaspase-9 to cleave procaspase-3, a crucial cell death enforcer. The transcriptional activation of genes encoding proapoptotic activity mediates a second cell death signaling pathway triggered by endoplasmic reticulum stress. Apoptotic transcriptional CHOP activation is caused by PERK, ATF6, and maybe IRE1 activation by upregulating the genes Gadd34, Dr5, and Trb3 or decreasing the expression of the anti-apoptotic gene Bcl2. Endoplasmic reticulum stress-induced Ca + 2 release and mitochondrial inner membrane depolarization create mitochondrial ROS. Oxidative stress thus leads to multiple cell death pathways with unresolved ER-stress interactions.

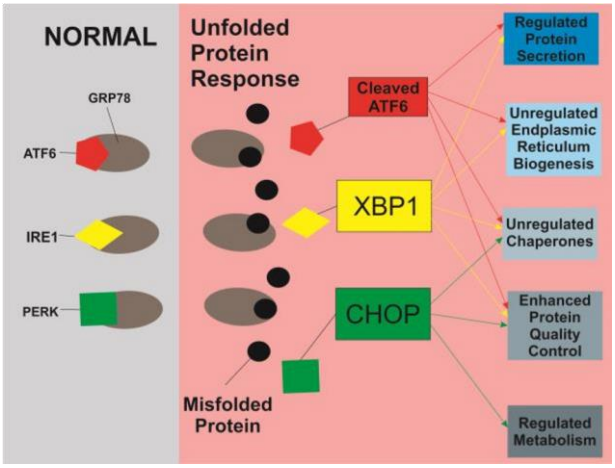

Figure 4. UPR downstream signaling pathways.

Description: GPR78 is the starter of the UPR process and is also involved in protein biosynthetic quality control, including protein synthesis, folding, and assembly.[10] The UPR was found to be initiated by three local endoplasmic reticulum-transmembrane signal converters. These converters are called IRE1, PERK, and ATF. It is constitutively produced in cells, but its expression is tightly regulated by GRP78, making it inactive under normal conditions.[11,12] Can bind to misfolded proteins. This triggers the converter and initiates the UPR downstream signaling cascade. After activation, ATF6 localizes to the nucleus and acts as a transcription factor to increase gene expression of several endoplasmic reticulum proteins involved in protein folding, secretion, modification, and ERAD activities. Basic Leucine Zipper is abbreviated as bZIP. eIF2 is an abbreviation for Eukaryotic Initiation Factor 2. ERAD is an abbreviation for endoplasmic reticulum-associated degradation. S1P is an abbreviation for sphingosine-1-phosphate, whereas S2P is an abbreviation for sphingosine-2phosphate.

DISCUSSION

Reticulum Endoplasmic Stress

The folding technique of proteins withinside the Endoplasmic Reticulum may be very crucial and really touchy to intracellular and extracellular stimuli, including endoplasmic reticulum calcium ions, power garage as well as redox homeostasis, accelerated translation of mRNA, cytotoxicity, and inflammation.[13,14] Several proteins that fail to fold are usually observed withinside the endoplasmic reticulum.[15] A variety of studies have shown that any disruption in protein biosynthesis, such as an unexpected increase in protein production, blockage of disulfide bond formation, depletion of metabolic capacity, and interference with N-glycosylation, can result in the generation of failed proteins.[15,16] Misfolding of the most important proteins is related to the complexity and quantity of protein produced. Because goblet cells produce a significant number of complicated proteins, they produce more misfolded proteins and are more prone to the buildup of failed folding proteins than other cells. Under ordinary conditions, the endoplasmic reticulum has state-of-the-art protein great manage mechanisms to multiply and remove misfolded proteins. However, endoplasmic reticulum equilibrium can be jeopardized if the level of protein misfolding surpasses the normal refolding threshold, resulting in a buildup of failed folding proteins and an unusual condition known as endoplasmic reticulum stress.[17]

Endoplasmic reticulum stress has far-reaching consequences for all cellular activities. It has been shown to be capable of reversing functioning transcription and translation processes, as well as intra- and extracellular signaling pathways. The result is it can cause a variety of ailments. [18,19]

Unfolded Protein Response (UPR)

To reduce endoplasmic reticulum stress, cells create the UPR, a network of parallel and distinct multifactorial transcriptional and signaling pathways. The endoplasmic reticulum stress response is made up of several transcription factors and enzymes that have been found and investigated throughout the years.[20, 21] The endoplasmic reticulum's refolding ability is enhanced, and ERAD reduces the buildup of collapsed proteins. When the stress is too great, the apoptotic signaling system is triggered, or when the UPR is disturbed and the UPR fails. (Fig. 2)[22]

GPR78 initiates the UPR process and is also in charge of controlling protein biosynthesis quality, including protein synthesis, folding, and assembly.[10] It has been discovered that UPR is initiated by three local-endoplasmic reticulum transmembrane signal transducers. These transducers are referred to as IRE1, PERK, and ATF. It is constitutively produced in cells, but its expression is strictly regulated by GRP78, making it inactive under normal.[11,12] When a misfolded protein forms in the endoplasmic reticulum, GRP78 unbinds and releases this transducer, allowing it to identify and bind to the misfolded protein. This triggers the transducer and initiates a UPR downstream signaling cascade,[23] as depicted in Figure 3.

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DECLARATIONS

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