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Review article

Cytoprotective small molecule modulators of endoplasmic reticulum stress

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ABSTRACT

Cellular health depends on the normal function of the endoplasmic reticulum (ER) to fold, assemble, and modify critical proteins to maintain viability. When the ER cannot process proteins effectively, a condition known as ER stress ensues. When this stress is excessive or prolonged, cell death via apoptotic pathways is triggered. Interestingly, most major diseases have been shown to be intimately linked to ER stress, including diabetes, stroke, neurodegeneration, and many cancers. Thus, controlling ER stress presents a significant strategy for drug development for these diseases. The goal of this review is to present various small molecules that alleviate ER stress with the intention that they may serve as useful starting points for therapeutic agent development.

Contents

1. Introduction

Normal cellular function is highly dependent on the function of individual secreted and membrane proteins. A functional endoplasmic reticulum (ER) is of paramount importance as this

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organelle serves as the quality control center for proteins, ensuring their proper folding, assembly, and post-translational modifications.[1] When the ER cannot process proteins effectively, a condition known as ER stress ensues.[2] When this stress is excessive or prolonged, cell death via apoptotic pathways is triggered. Therefore, it is not surprising that abnormal or dysfunctional ER function is intimately linked to disease pathogenesis. There are multiple recent reviews describing the link between ER stress and many major diseases.[3,4] The goal of this review is to present various small molecules that alleviate ER stress with the intention that they may serve as useful starting points for therapeutic agent development.

2. ER stress pathways

The accumulation of unfolded, mutant, or disease-related toxic proteins (e.g. β-amyloid, α-synuclein) within the ER can trigger ER stress and a series of reactions knows as the unfolded protein response (UPR). This condition can also be initiated by a variety of chemical (thapsigargin, tunicamycin, arsenic trioxide) or environmental (reactive oxygen species, oxidative stress) factors. The UPR is mediated by three distinct ER stress sensors: protein kinase RNA (PKR)-like ER kinase (PERK), activating transcription factor-6 (ATF6), and inositol-requiring protein-1 (IRE1). The three ER stress sensors, PERK, IRE1α, and ATF6, and their respective molecular mechanisms, are detailed in Figure 1. These have the initial goal of re-establishing protein homeostasis in the ER to promote survival, accomplished mainly through regulation of molecular chaperone levels. PERK, a transmembrane protein kinase, phosphorylates eukaryotic translation initiation factor 2A (eIF2 α), effectively turning off translation while increasing ATF4 transcription which in turn increases or restores CHOP expression leading to GADD34 transcription. This, in turn, creates a feedback loop involving eIF2 α dephosphorylation and reinitiation of translation. IRE1 α activates ASK1 via XBP1 mRNA splicing, regulating gene expression. Finally, upon activation, ATF6 is exported to the Golgi complex where it is cleaved to release its transcription factor. These three arms work synergistically to attempt to restore ER protein homeostasis. In non-stressed cells, these sensors are retained in the ER lumen by interactions with Bip/GRP78. During ER stress, Bip releases these three sensors, causing their activation.[5] The goal of UPR activation is to accommodate the accumulated unfolded proteins and rescue the cell. However, if the ER stress is too severe or prolonged, the ER can then initiate apoptotic signaling leading to cell death.[6] The specific UPR proteins responsible for both rescue and apoptosis include PERK and IRE1. The small molecules detailed in this review target various features of the UPR.

3. Individual reports

3.1. Salubrinal and Guanabenz

Boyce and co-workers[7] identified a small molecule known as Salubrinal (Sal) which had been shown to protect rat pheochromocytoma (PC12) cells from ER stress-mediated apoptosis induced by tunicamycin (a protein glycosylation inhibitor) and brefeldin A (inducer of ER stress that acts by blocking ER-to-Golgi vesicle

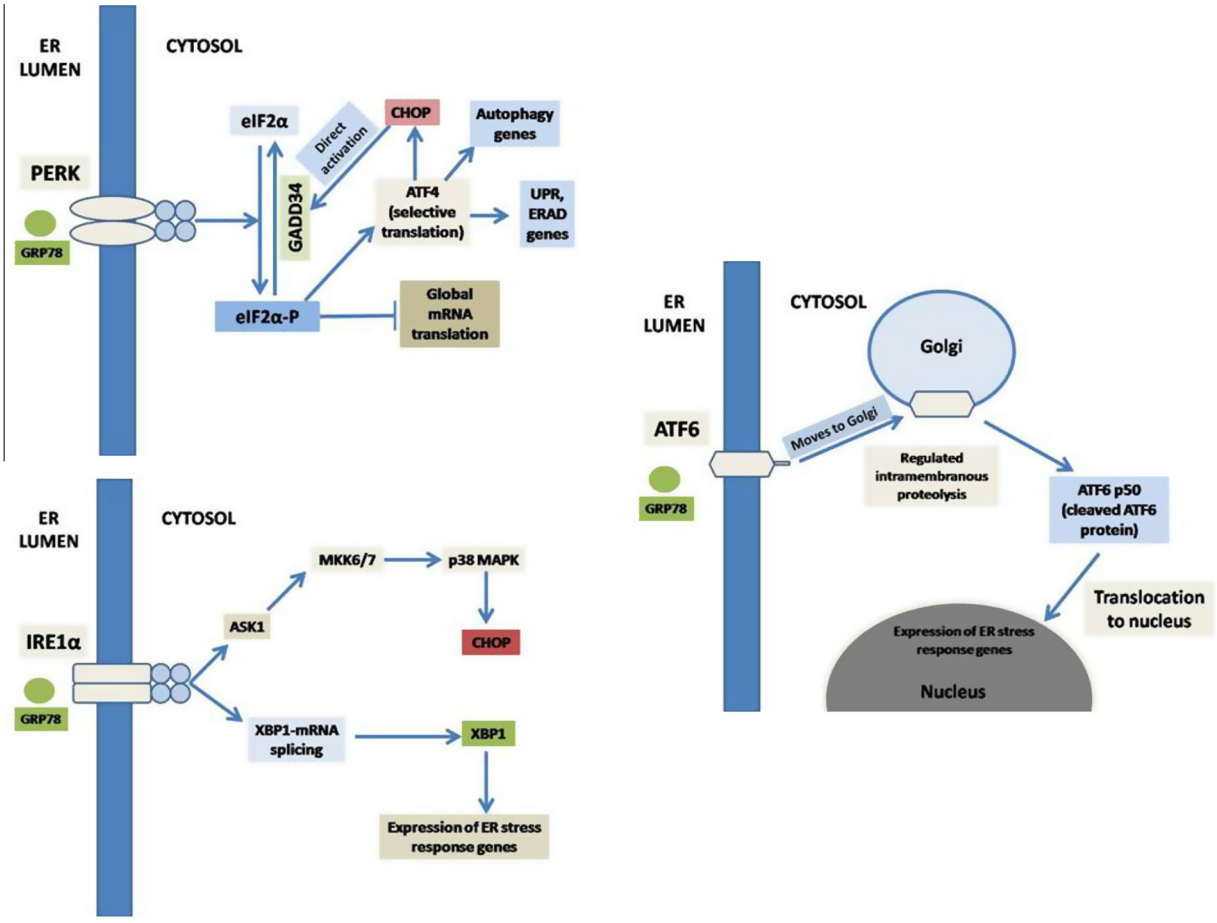

Figure 1. Activation of UPR sensors during ER stress: UPR is mediated by three distinct ER stress sensors: protein kinase RNA (PKR)-like ER kinase (PERK), activating transcription factor-6 (ATF6) and inositol requiring protein-1 (IRE1). In non-stressed cells, these sensors are retained in the ER lumen by interactions with Bip/GRP78. During ER stress, Bip releases these three sensors, causing their activation.