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Review article

ER stress in cardiovascular disease

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ABSTRACT

The endoplasmic reticulum (ER) is an organelle involved in protein folding, calcium homeostasis, and lipid biosynthesis. Various factors that interfere with ER function lead to accumulation of unfolded proteins, including oxidative stress, ischemia, disturbance of calcium homeostasis, and overexpression of normal and/or incorrectly folded proteins. The resulting ER stress triggers the unfolded protein response (UPR) that induces signal transduction events to reduce the accumulation of unfolded proteins by increasing ER resident chaperones, inhibiting protein translation, and accelerating the degradation of unfolded proteins. However, if stress is severe and/or prolonged, the ER also initiates apoptotic signaling that includes induction of the pro-apoptotic transcriptional factor C/EBP homologous protein, activation of c-Jun amino-terminal kinase, and cleavage of caspase-12. These ER-initiated events lead to cell death via mitochondria-dependent and -independent apoptotic pathways. Furthermore, the B cell lymphoma 2 family of proteins expressed on the ER and mitochondria are also involved in regulating cell death due to ER stress. Thus, the ER is now recognized as a vitally important organelle that can decide cell survival or death. Recent animal and human studies have revealed that the UPR and ER-initiated apoptosis are implicated in the pathophysiology of various cardiovascular diseases, including heart failure, ischemic heart disease, the development of atherosclerosis, and plaque rupture. Improved understanding of the molecular mechanisms underlying UPR activation and ER-initiated apoptosis in cardiovascular disease will provide us with new targets for drug discovery and therapeutic intervention.

Contents

1. Introduction

The endoplasmic reticulum (ER) is an organelle that has an essential role in multiple cellular processes, such as the folding of secretory and membrane proteins, calcium homeostasis, and lipid biosynthesis [1,2]. A variety of insults can interfere with ER function, leading to the accumulation of unfolded and misfolded proteins in the ER. When ER transmembrane sensors detect the accumulation of unfolded proteins, the unfolded protein response (UPR) is initiated to cope with the resulting ER stress. If ER stress is prolonged or overwhelming, however, it can induce cell death. Recent studies have suggested that the UPR and ER-initiated apoptosis are implicated in the pathophysiology of various human

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diseases, including cardiovascular disease, neurodegenerative disease, diabetes mellitus, and liver disease [1-3]. This review summarizes (1) the molecular mechanisms of the UPR and ER-initiated apoptosis and (2) their involvement in the pathophysiology of cardiovascular disease.

2. The endoplasmic reticulum

The ER is recognized as the organelle involved in the synthesis and folding of secreted and membrane-bound proteins and thus is the first part of the secretory pathway [1-3]. The ER supports the biosynthesis of approximately one third of all cellular proteins in a typical eukaryotic cell [4]. To achieve the proper folding of proteins, the lumen of the ER is a special environment [1,2], e.g., the ER has the highest calcium concentration within the cell. Both protein folding reactions and the functioning of various calcium-dependent ER resident chaperones require a high level of calcium. Furthermore, an oxidizing environment inside the ER is crucial for the formation of disulfide bonds that is required for the proper folding of proteins. As a consequence of these special requirements, ER function is highly sensitive to stresses that disturb calcium homeostasis or alter the intraluminal redox status.

3. UPR signaling

When ER stress occurs, three ER transmembrane sensors are activated to initiate adaptive responses [1-3]. These sensors include protein kinase-like ER kinase (PERK), inositol-requiring kinase 1 (IRE1), and the transcriptional factor activating transcription factor 6 (ATF6). These UPR sensors are located with their N-terminus inside the lumen of the ER and their C-terminus in the cytosol, thereby connecting the ER with the cytosol. All three sensors are maintained in an inactive state through the interaction of their N-terminus with glucose-regulated protein 78 kDa (GRP78) [5]. When unfolded proteins accumulate in the ER, GRP78 releases these sensors to allow their oligomerization and thereby initiates the UPR [5] (Fig. 1).

PERK is a serine threonine kinase that phosphorylates eukaryotic translation initiation factor 2α (eIF2α) after the onset of ER stress to shut off mRNA translation and reduce the protein load on the ER. Paradoxically, however, several mRNAs require the phosphorylation of eIF2α for their translation, including the transcriptional factor ATF4 that induces UPR-related genes to reduce the level of unfolded proteins in the ER.

IRE1α is the most fundamental ER stress sensor and is conserved in all eukaryotic cells. Interestingly, activation of IRE1 elicits endoribonelease activity that specifically cleaves the mRNA encoding the transcriptional factor X-box binding protein 1 (XBP1). This unconventional splicing reaction is required for the translation of transcriptionally active XBP1. Active (spliced) XBP1 binds to ER stress response elements I and II (ERSE-I: CCAAT(N9)CCACG; ERSE-II: ATTGG(N1)CCACG) and to the mammalian UPR element (mUPRE: TGACGTGG/A) to regulate a variety of UPR-related genes [6]. Recent studies showed that XBP1 controls diverse cell type- and condition-specific transcriptional regulatory networks, although it has not been well identified how XBP1 regulates genes in cardiomyocytes [7].

ATF6 is a basic ZIP family transcriptional factor that binds to ERSEs in the promoter region of UPR-related genes. ER stress induces the release of GRP78 from ATF6 and thus permits the translocation of ATF6 from the ER to the Golgi apparatus, where S1P- and S2P-mediated proteolytic cleavage produces a transcriptionally active cytosolic fragment. ATF6 activates a subset of UPR-related genes, including XBP1. The three arms of the UPR (including ATF4, XBP1, and ATF6) coordinately regulate the transcription of various genes encoding ER chaperones and protein folding enzymes in order to reduce the accumulation of unfolded proteins.

4. ER-associated degradation

Another mechanism that reduces the level of misfolded and unfolded proteins in the ER is degradation via the ER-associated protein degradation (ERAD) pathway [1,2]. Most ERAD substrates are ubiquitinated before undergoing degradation by proteasomes. The ERAD mediates retro-translocation of unfolded proteins into the cytosol where these proteins are degraded by the ubiquitin-proteasome machinery.

5. ER-initiated apoptotic signaling

When the UPR fails to control the level of unfolded and misfolded proteins in the ER, ER-initiated apoptotic signaling is induced. Interestingly, all of the ER sensor proteins are responsible for apoptotic signaling as well as for the UPR, but it remains unclear how the cell makes a decision between survival and death (Fig. 2).

IRE1α-dependent apoptotic signaling occurs via diverse pathways. IRE1α interacts with the adaptor protein TNF receptor-associated factor (TRAF) 2. IRE1α and TRAF2 then interact with a mitogen-activated protein kinase kinase kinase, ASK1, which subsequently phosphorylates JNK [8,9].

C/EBP homologous protein (CHOP) is the one of most thoroughly investigated molecules among those involved in ER-initiated apoptotic signaling. CHOP is a pro-apoptotic bZIP transcriptional factor that is mainly regulated by ATF4- and ATF6-dependent pathways [1,2].

Table 1
ER stress and cardiovascular disease.

Diseases	Role of ER stress	Target protein	Refs.
Hypeterophic heart	• Pressure-overload to heart induces UPR	• GRP78	[22]
Failing heart	• ER stress is induced in human failing hearts	• GRP78	[22,23]
	• Pressure-overload to heart finally leads to cardiac apoptosis associated with CHOP induction	• CHOP	[22]
	• Impairment of a retrieval receptor for ER chaperones causes heart failure and CHOP induction	• KDEL/CHOP	[24]
Autoimmune cardiomyopathy	• Autoimmune cardiomyopathy induced by beta-adrenergic receptor peptide is associated with ER stress	• p38/CaMKII • ATF6/GRP78/CHOP	[25]
Alcoholic cardiomyopathy	• Alcohol induces myocardial ER stress	• GRP78/CHOP	[26]
Ischemic heart	• PDI is induced in cardiomyocytes near myocardial infarction in humans	• PDI	[45]
	• GRP94 plays cardioprotective role against hypoxic insult	• GRP94	[46]
	• ATF6 protects the myocardium from ischemic/reperfused myocardium	• ATF6/GRP78/GRP94	[47]
	• Hypoxia induces CHOP and caspase 12 activation, which is inhibited by AMP-activated kinase	• ATF6/GRP78/GRP94	[51]
	• PUMA inhibits cardiomyocyte cell death by ER stress	• PUMA	[52,53]
Cardiotoxicity of anti-cancer drug	• Imatinib induces cardiomyocyte cell death associated with ER stress and JNK activation	• JNK	[31]
	• Proteasome inhibition induces cardiomyocyte cell death via CHOP	• CHOP	[35]
Atherosclerosis	• Oxidative stress causes macrophage apoptosis via CHOP	• CHOP	[39]
	• UPR and ER-initiated apoptosis in macrophage in atherosclerotic lesions		[39,40]
	• Increased CHOP induction in ruptured atherosclerotic plaques	• CHOP	[39,43]