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Review

Endoplasmic reticulum stress and protein quality control in diabetic cardiomyopathy☆

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ABSTRACT

Endoplasmic reticulum (ER) stress, together with the unfolded protein response (UPR), is initially considered an adaptive response aiming at maintenance of ER homeostasis. Nonetheless, ER stress, when in excess, can eventually trigger cell apoptosis and loss of function. UPR is mediated by three major transmembrane proteins, including inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase (PERK), and activating transcription factor (ATF) 6. A unique role has been speculated for ER stress in the pathogenesis of diabetes mellitus (DM) and its complications. Recent studies have shown that ER stress is an early event associated with diabetic cardiomyopathy, and may be triggered by hyperglycemia, free fatty acids (FFAs) and inflammation. In this mini-review, we attempted to discuss the activation machinery for ER stress in response to these triggers en route to disrupted ER function and cellular autophagy or apoptosis, ultimately insulin resistance and development of diabetic cardiomyopathy. This article is part of a Special Issue entitled: Autophagy and protein quality control in cardiometabolic diseases.

1. Introduction

Diabetes mellitus (DM) is a chronic, progressive metabolic disorder characterized by deficiency of insulin secretion, loss of insulin sensitivity or both, resulting in elevated plasma glucose levels. Individuals with DM display an increased risk for macro- and micro-vascular complications [1,2]. These vascular injuries often coexist and contribute to the onset and progression of hypertension, ischemia as well as diastolic/systolic dysfunction [3]. Moreover, cardiovascular complications account for the high morbidity and mortality in diabetic populations. When compared to the age-matched controls, the relative risk of heart failure is 2-fold greater in diabetic males, and 5-fold greater in diabetic females, independent of age, ethnicity, body mass, dyslipidemia and coronary artery disease according to the Framingham Heart Study [4]. Diabetic cardiomyopathy is a distinct myocardial disease in patients with DM, leading to the structural and functional changes in the heart independently of hypertension, coronary artery and valvular heart disease [5]. These changes can eventually result in left ventricular hypertrophy (LVH) and diastolic/systolic dysfunctions [6]. An array of chronic and complex changes have been identified at the molecular level, contributing to the etiology of diabetic cardiomyopathy such as perturbations of intracellular energy metabolism, alterations in intracellular ion homeostasis and oxidative stress [7–9]. More recently, ER stress was suggested to contribute to the onset and progression of diabetic cardiomyopathy [10,11]. Nevertheless, the precise interplay among ER stress, development of cardiac hypertrophy and progression to heart failure still remains elusive.

ER is an organelle with rough and smooth regions. The rough region of membrane forms stacks of flattened cisternae and is composed of a membrane-enclosed lumen. The smooth region of membrane is connected to these membranous cisternae to form a fine network of tubules. Polypeptide chains of secreted, transmembrane and luminal proteins synthesize, fold and mature in the ER lumen [12]. It also serves as a site for lipid biosynthesis and Ca^{2+} storage [13]. Nascent polypeptides are transferred into the ER lumen, undergoing posttranslational modifications and rounds of folding interactions in order to optimize their functions. Correctly folded proteins then move away from the ER to remote intracellular organelles and the extracellular surface, while misfolded proteins are either retained within the ER or subject to degradation by cytoplasmic proteasomes [14].

Efficient ER function relies heavily on numerous quality control factors, such as molecular chaperones, folding enzymes and a Ca^{2+}-rich environment [15]. When ER homeostasis is aberrant under the conditions of radiation, hypoxia, ischemia, oxidation or dysregulation of Ca^{2+}, ER stress response will be triggered to cope with this imbalance,

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which is also termed as the UPR [12]. It was first described by Kozutsumi in 1988 as an adaptive mechanism to increase the protein folding capacity as well as to decrease the unfolded protein load [16]. The UPR aims to restore the ER homeostasis by (1) decreasing the load of proteins in the ER via translational attenuation, (2) increasing the transcription of chaperones and other proteins involved in the folding and maturation of proteins, and (3) inducing the degradation of misfolded proteins via the ER-associated degradation (ERAD) complex [17]. If it fails, ER initiates the death signaling pathways [18].

In this mini-review, we will attempt to discuss the possible mechanisms behind the potential contribution of ER stress and UPR in the pathogenesis of diabetic cardiomyopathy, in an effort to provide some evidence for the potential UPR-targeted therapies for this disease.

2. Protein quality control and signaling pathways of the UPR

Quality control is a complicated mechanism that maintains the protein biosynthesis with properly folded and assembled structures in the ER [19]. It relies on molecular chaperones and folding enzymes to monitor and assist the folding process. These chaperones and enzymes can be classified into three major groups: (1) binding protein/glucose regulated protein (BiP/GRP) 78, GRP94, (2) calnexin (CNX) and calreticulin (CRT), (3) protein disulfide isomerase, such as ER protein (ERp) 57 and ERp72 [15]. GRP78 and GRP94 have the ability to recognize exposed hydrophobic regions, a common feature of nascent misfolded proteins, thus assisting protein folding and assembling [20]. CNX and CRT interact with glycoproteins via their lectin binding ability, allowing folding and interacting with enzymes [21,22]. ERp57 uses the oxidative environment of the ER to generate disulfide linkages, which are directly affected by the primary donor of the energy [23]. If quality control is unable to fold the protein, the UPR will be triggered by the continuous accumulated unfolded/misfolded proteins in three transmembrane protein-mediated signaling pathways, namely inositol-requiring enzyme 1 (IRE1), protein kinase RNA-like ER kinase(PERK) and activating transcription factor (ATF) 6 pathways (Fig. 1) [24]. Under physiological conditions, these sensors are maintained in an inactive state by binding to GRP78, while ER stress increases the binding of BiP to the luminal misfolded proteins, and the resultant sequestration away from IRE1, PERK and ATF6 usually leads to the activation of these ER stress signaling molecules [25].

2.1. IRE1 signaling pathway

IRE1 is consist of an N-terminal luminal sensor domain, a single transmembrane domain and a C-terminal cytosolic effect or region which manifests both kinase and endoribonuclease activity [26]. There are two isoforms of IRE1 namely IRE1α and -1β. The UPR is mainly governed by IRE1α. Upon activation, IRE1α mediates an unconventional cytoplasmic splicing, to remove a 26-nucleotide intron from X-box-binding protein 1 (XBP1) mRNA, yielding a fusion protein XBP1s [27]. XBP1s act as a potent transcription factor for the expression of potential UPR target genes, to upregulate the ER chaperones, components of the ERAD complex and the biosynthesis of phospholipid, and to export and degrade misfolded proteins in an effort to resolve ER stress [28]. IRE1 activates Jun N terminal kinase (JNK) by recruiting the apoptosis signal-regulating kinase 1 (ASK1), caspase-12 and tumor necrosis factor receptor-associated factor 2 (TRAF2), which are pro-apoptotic [29].

Many cell metabolism modulators regulate the IRE1 pathway. IRE1α is phosphorylated by PKA, to control the glucagon-mediated expression of gluconeogenic genes [30]. Both XBP1 splicing and JNK activation are controlled by the mammalian target of rapamycin complex 1 (mTORC1), the major sensor of nutrient and energy in cells [31,32]. P85, a repressive regulatory subunit of PI3K, also interacts with XBP1, increasing its nuclear translocation and transcriptional activity [33].

2.2. PERK signaling pathway

PERK is a type 1 transmembrane protein that possesses a luminal domain similar to that of IRE1, and a cytoplasmic portion that possesses protein serine/threonine kinase activity. It has a PEK-like catalytic

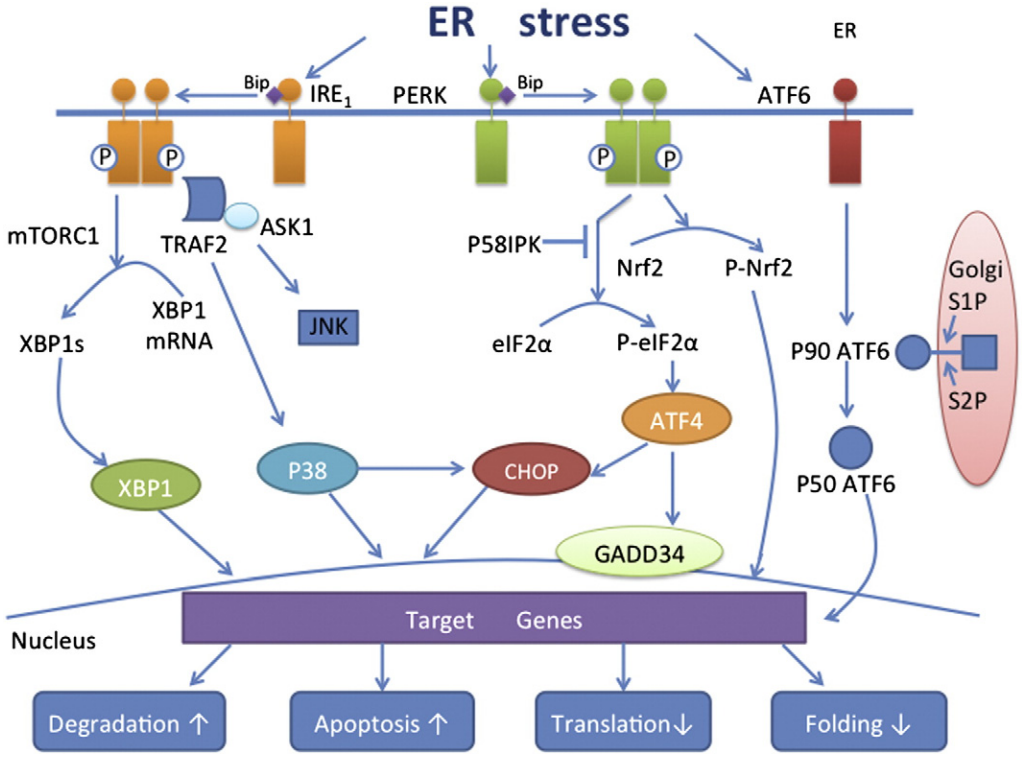

Fig. 1. When ER is unable to fold secretory and membrane proteins, the accumulated unfolded/misfolded proteins trigger the UPR in three transmembrane protein-mediated signaling pathways, as IRE1, PERK and ATF6 pathways.