The Egyptian Journal of Medical Human Genetics xxx (2017) xxx–xxx

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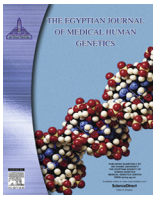
Contents lists available at ScienceDirect

The Egyptian Journal of Medical Human Genetics

journal homepage: www.sciencedirect.com



Review

The endoplasmic reticulum stress response in disease pathogenesis and pathophysiology

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ARTICLE INFO

Article history:
Received 5 June 2017
Accepted 2 July 2017
Available online xxxx

Keywords:
Endoplasmic reticulum
ER stress response
Hormesis
Unfolded protein response
ER overload response

ABSTRACT

The minute experience of disease progression happens in the cell. Whereas recent researches have focused separately on disease, molecular mechanisms reveal the coincidence of pathways that provide guided benefit to biomedicine. Interestingly, taken-for-granted mechanisms like endoplasmic reticulum (ER) quality control or ion exchange and cell polarity indeed play major roles in epidemiologically relevant problems like viral infection, tumorigenesis and other chronic disorders. The ER synthesizes proteins destined for the nucleus and Golgi, as well as cell-surface receptors needed for cell-to-cell communication. This is therefore the target of viral infection in making the cell susceptible to receptor-mediated invasion, and is usually affected in tumor cells to promote cell insensitivity. Any aberrations therefore, such as protein unfolding, are acted upon by molecular chaperones and prevented from leaving the ER. These proteins are essential for cell survival, and intuitively the ER must activate stress responses to evade immediate cell dysfunction as the cell processes lag behind. This review will discuss mainly the ER and its role in the pathogenesis and pathophysiology of epidemiologically-relevant diseases, as well as updates on mechanisms related to the ER stress response.

Contents

1. Introduction

Disease begins and ends with the cell. Cellular homeostasis is of vital importance, and has been shown to progress to senescence and cell death should the protein machinery be consistently perturbed. However, the cell must not be thought of as passive. In the event of cellular stress, genes that promote tolerance and sur-

Peer review under responsibility of Ain Shams University.

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http://dx.doi.org/10.1016/j.ejmhg.2017.07.004
1110-8630/

vival are upregulated, until the cell can no longer compete with such an extremity [1]. Since physiologic functions rely heavily on homeostasis, it is not surprising that other aberrations such as Ca^{2+} dysregulation, chronic inflammation, nutrient deficiency and inappropriate extracellular ionic strength all contribute and possibly induce stress in cells [2–4]. While there are manifold pathways that describe the role of homeostasis in pathogenesis, the endeavour of unifying published concepts to profoundly describe disease is of greater significance. In achieving a comprehensive understanding of a given disorder, it is important to recognize the multi-factorial and multi-faceted nature of cell functions. For instance, considering inflammation in the context of cell regulation would lead to the role of T cells in immunological tolerance at anatomic places where a pool of antigens are expected to be, such as in the digestive tract [5–7]. Likewise, stress-induced inflammation brought by cell necrosis even in the absence of a pathogen may be realized as plausible [8,9]. To this end, the review will highlight cross-talks between Ca^{2+} transport and the ER stress response, which will be related to the pathogenesis and pathophysiology of certain medical conditions.

2. The ER stress response

The endoplasmic reticulum (ER) regulates the flow of macromolecules such as lipids, proteins and carbohydrates needed in maintaining cell function. Accordingly, it is mandatory to maintain homeostasis [10], and in cases where it is not, the organelle initiates several pathways directed toward restoration, some of which are not yet well-elucidated.

In usual cases, the effect of perturbation is aberrant protein folding. Such mechanisms that the ER employs to regulate this unwanted process are both preventive and modulatory in nature. The ER recognizes peptides being newly synthesized through the signal recognition particle (SRP) which causes an arrest in elongation and resumes being directed to the translocon in what is called co-translational translocation [11,12]. Proper protein folding is ensured by chaperones such as calreticulin and membrane-bound calnexin as an orchestrated quality control point in the ER [13]. Inhibitors targeting vital points in the glycoprotein biosynthesis have been used to understand further the underlying mechanisms for ER function, some of which are tunicamycin, an *N*-glycosylation inhibitor; thapsigargin and 2,5-di-*t*-butyl-1,4-benzohydroquinone (BHQ), which inhibit the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), and castanospermine and 1-deoxynojirimycin for glucosidase I and II inhibition, among others [14]. Through these, it was found that persistently unfolded proteins are targeted for either ER-associated (ERAD) or autophagic degradation [15]. Intuitively, misfolding and degradation of proteins must be addressed if the cell is to survive.

3. Unfolded protein response (UPR)

The unfolded protein response is a well-known ER pathway against challenges of stress. In physiologic conditions, the dsRNA-activated protein kinase (PKR)-like ER kinase (PERK) is stabilized by heat shock protein 90 (HSP90) and immunoglobulin heavy chain binding protein (BIP); however, ER stress permits the release, dimerization and autophosphorylation of PERK, which then phosphorylates the eukaryotic initiation factor 2 (eIF2) complex at the Ser51 position leading to a cascade of events to attenuate protein synthesis. Phosphorylated eIF2 has a manifold greater affinity for GDP that would prevent re-initiation of translation due to lack of eIF2B-mediated GTP exchange for reformation of the eIF2-GTP-$tRNA_{met}$ complex [16,17]. In this event, attenuation of mRNA translation occurs with a concomitant upregulation of genes translating anti-stress proteins and amino acid transporters, such as the activating transcription factor 4 (ATF4). This protein interacts with the ER and upregulates ER stress response genes associated with both cell survival and apoptosis, with the matter of time in question (Fig. 1).

In persistent accumulation of errors, ATF4 upregulates the transcription of genes encoding C/EBP homologous protein (CHOP)/GADD153 that activates ER-mediated apoptosis [18,19], probably through repression of the B-cell lymphoma 2 (Bcl2) gene and sensitization of cells to the persistent stress [3,20]. These are followed by the upregulation of Bcl-2-like protein 11 (BIM) [21] that together with BH3-only proteins preferentially activate Bcl-2-associated X protein (BAX) to cause mitochondrial damage [22–24]. As to how ATF4 executes such a time-sensitive response, the PERK-dependent miR-211 inhibit the expression of CHOP until apoptosis is deemed necessary [25]. Further, it is important to acknowledge the short turnover of both CHOP and ATF4 – requiring the presence of chronic ER stress to activate the apoptotic signals [26].

When ER stress is activated, BIP dissociates from the inositol-requiring kinase 1 (IRE1) to permit IRE1 detection of protein misfolding [27,28], although BIP-independent detections have also been proposed [29]. Having both endoribonuclease (ERN) and serine-threonine kinase (STK) activities, the oligomerization at the ER membrane and autophosphorylation at S724 of IRE1 allows the ERN-mediated splicing and expression of X-box binding protein 1 (Xbp1) mRNA [10,30,31]. Xbp1 is a transcription factor that together with nuclear factor Y (NF-Y) upregulate chaperone and protein degradation genes for error fixation [32,33] while also upregulating $P58^{IPK}$ that binds to the kinase domain of PERK. Should the kinase domain of PERK be blocked, PERK activity would decrease – permitting the expectation that the protein load of ER would increase [34]. This downregulation of PERK activity has a duality: in events that stress is relieved this would cease attenuation of protein synthesis and homeostasis is achieved; however, in persistent ER stress, the PERK-dependent miR-211 would cease to attenuate CHOP expression which may eventually lead to further stress and apoptosis [35,36] (Fig. 1). This activity of IRE1 is therefore essential in the later phase of the UPR [34,37]. What is of interest to many diseases is the activity of IRE1α, which is present in every cell, and constitutes the most conserved UPR cascade found in eukaryotes – permitting *in vivo* studies to shed significant light on the ER stress response [10,38].

Definitively, the kinase domain of IRE1 serves pro-apoptotic functions in late-phase UPR. Its interactions with proteins lead to the activation of procaspase-12 and the apoptosis signal regulating kinase 1 (ASK1), eventually leading to c-Jun N-terminal kinase-mediated cell death [39–41]. However, Lin, Walter and Yen proposed that IRE1 also contributes directly to apoptosis by possible downregulation of other mRNAs committed to ensuring survival [10]. Nonetheless, consensus remains elusive.

4. ER overload response (EOR)

Interestingly, EOR is one among others that bridge the gap between the ER stress response and the regulation of Ca^{2+}. For it to occur, Ca^{2+} must be released from the ER followed by ROS production, both of which lead to the activation of the nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) [42]. It is far less studied than the UPR, but its action can apply from acute to chronic disease. In releasing Ca^{2+} stores from the ER lumen to the cytosol, ROS production eventually leads to the activation of NF-κB, which is a sequence-specific transcription factor that is a key point in cell proliferation, inflammation and hence cell survival [43,44] (Fig. 2A). Being a principal calcium storage and signalling