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Review

The role of endoplasmic reticulum in amyloid precursor protein processing and trafficking: Implication's for Alzheimer's disease

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ABSTRACT

The endoplasmic reticulum (ER) is the principal organelle responsible for the proper folding/processing of nascent proteins and perturbed ER function leads to a state known as ER stress. Mammalian cells try to overcome ER stress through a set of protein signaling pathways and transcription factors termed the unfolded protein response (UPR). However, under unresolvable ER stress conditions, the UPR is hyperactivated inducing cell dysfunction and death. The accumulation of misfolded proteins in the brain of Alzheimer's disease (AD) patients suggests that alterations in ER homeostasis might be implicated in the neurodegenerative events that characterize this disorder. This review discusses the involvement of ER stress in the pathogenesis of AD, focusing the processing and trafficking of the AD-related amyloid precursor protein (APP) during disease development. The potential role of ER as a therapeutic target in AD will also be debated.

1. Endoplasmic reticulum stress

The endoplasmic reticulum (ER) was first described in 1945 as an extensive network of interconnected membrane tubules that spread throughout the cytosol [1]. A large number of studies showed that the ER can be divided into three domains according to its structure and function: 1) the nuclear envelope, which controls the flow of information between the cytoplasm and the nucleus, 2) the sheet-like cisternae, also denominated rough ER due to the high content in ribosomes, and 3) the polygonal array of tubules, also called smooth ER [1,2]. This highly dynamic and multifunctional organelle is implicated in protein quality control along the secretory pathway being responsible for protein folding, assembly and post-translational modifications (e.g. glycosylation, disulfide bond formation), among other functions.

1.1. The unfolded protein response and its role in cell survival and apoptosis

Perturbations of ER homeostasis, triggered by several factors including ER Ca^{2+} depletion, oxidative stress and mutated proteins that traffic through the secretory pathway can be responsible for the accumulation of misfolded/malfolded proteins in its lumen leading to ER stress. To re-establish homeostasis, the ER activates the unfolded protein response (UPR) [3,4], which prevents the aggregation and facilitates the folding of damaged proteins, decreases translation to prevent overload of ER lumen with newly synthesized proteins, increases ER biogenesis and volume through the stimulation of lipid synthesis and activates protein degradation via the ER-associated protein degradation (ERAD) pathway [5–7].

In mammals, the mechanisms implicated in the ER stress response are poorly understood. The most accepted hypothesis defends that the

Abbreviations: ER, endoplasmic reticulum; UPR, unfolded protein response; AD, Alzheimer disease; APP, amyloid precursor protein; GRP78/BiP, chaperone glucose-regulated protein 78; PERK, protein kinase RNA (PKR)-like ER kinase; ATF6, activating transcription factor 6; IRE1α, inositol-requiring enzyme-1alpha; XBP1, Xbox binding protein-1; ERAD, ER-associated degradation; ERdj4, DnaJ homolog 4; $p58^{IPK}$, protein kinase inhibitor of 58kDa; EDEM, ER degradation-enhancing α-mannosidase-like protein; RAMP-4, ribosome-associated membrane protein 4; PDI-P5, protein disulfide isomerase P5; JNK, c-Jun NH(2)-terminal kinase; ASK1, apoptosis signal-regulating kinase 1; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; Bcl-2, B-cell lymphoma 2; PUMA, p53 up-regulated modulator of apoptosis; BIM, B-cell lymphoma 2 interacting mediator of cell death; Aβ, amyloid beta; PSN, presenilin; CNS, central nervous system; GTP, guanosine triphosphate; DR6, death receptor 6; BACE, beta-secretase; TGN, trans-Golgi network; PDI, protein disulfide isomerase; PBA, 4-phenylbutyric acid; TUDCA, tauroursodeoxycholic acid; TMAO, trimethylamine oxide; Salubrinal, (3-phenyl-*N*-[2,2,2-trichloro-1-[[(8-quinolinylamino) thioxomethyl] amino]ethyl]-2-propen amide); BIX, BiP inducer X; DBM derivatives, dibenzoylmethane; (NAC), *N*-acetyl cysteine

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ER chaperone glucose-regulated protein 78 (GRP78/BiP) binds the ER stress sensors protein kinase RNA (PKR)-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring enzyme-1alpha (IRE1α) [4]. Under ER stress, GRP78/BiP dissociates from these sensors and promotes their activation, inducing phosphorylation and oligomerization of PERK and IRE1α and the translocation of ATF6 to the Golgi where it is cleaved [4]. Once activated, the ER stress sensors increase several transcription factors and control the expression of chaperones and other modulators of protein quality control within the secretory pathway [4]. After the onset of ER stress, the activation of the three branches of the UPR occurs in a time-dependent manner (Fig. 1) [8,9].

Upon activation, PERK phosphorylates eIF2α on the serine 51 of its α subunit, which leads to the inhibition of delivery of the initiator methionyl-tRNA to the ribosome, resulting in general inhibition of protein translation [9,10]. Paradoxically, eIF2α phosphorylation also promotes the translation of selective mRNAs that contain the internal entry ribosomal site (IRES), leading to the translation of genes associated with UPR, namely the transcription factor gene 4 (ATF4) [10,11]. This transcription factor is responsible for the up-regulation of genes associated with redox homeostasis, energy metabolism and protein folding [3,4].

The activation of IRE1α triggers the selective degradation of mRNAs encoding for proteins with abnormal folding, induces the unconventional splicing of the mRNA encoding the transcription factor Xbox binding protein-1 (XBP1), which shifts the coding reading frame and leads to the expression of a more stable and active transcription factor, XBP1s. XBP1s is responsible for the regulation of a subset of UPR target genes related with protein folding, ER/Golgi biogenesis and ERAD, namely endoplasmic reticulum DnaJ homolog 4 (ERdj4), protein kinase inhibitor of 58kDa ($p58^{IPK}$), ER degradation-enhancing α-mannosidase-like protein (EDEM), ribosome-associated membrane protein 4 (RAMP-4), protein disulfide isomerase P5 (PDI-P5) and HEDJ [12]. In addition, IRE1α interacts with several adaptor proteins, such as c-Jun NH(2)-terminal kinase (JNK), apoptosis signal-regulating kinase 1 (ASK1), the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), and can thus trigger autophagy, apoptosis and/or an inflammatory response [4].

ATF6 is a membrane-spanning protein that after dissociation from GRP78/BiP translocates to the Golgi where it is activated through proteolytic processing. In the nucleus, active ATF6 induces the expression of genes associated with protein quality control mechanisms [13]. This transcription factor can act synergistically with XBP1s [3].

Although the UPR is activated in order to restore organelle and cellular homeostasis, prolonged UPR activation can trigger apoptosis (Fig. 2) [4,14]. Besides the pro-survival effect discussed above, the IRE1α/XBP1 pathway has an important role in apoptosis. Indeed, the phosphorylation of IRE1α by the c-Jun-N-terminal inhibitory kinase

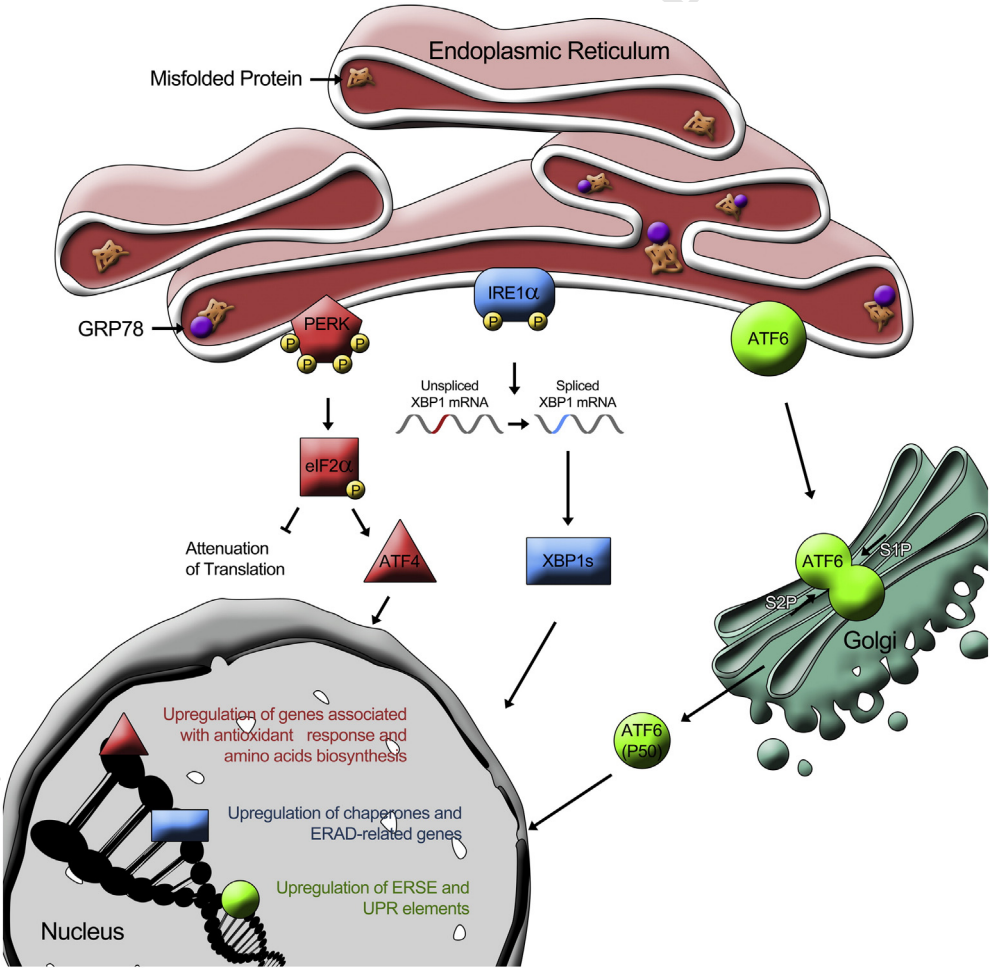

Fig. 1. The unfolded protein response (UPR). Perturbation of endoplasmic reticulum (ER) homeostasis triggers adaptive signaling cascades associated to the ER stress sensors Xbox binding protein-1 (XBP1), protein kinase RNA (PKR)-like ER kinase (PERK) and inositol-requiring enzyme-1alpha (IRE1α). These ER sensors are inactivated through the interaction with the 78 kDa glucose-regulated protein (GRP78/BIP). However, the accumulation of incorrectly folded proteins in the ER lumen detaches GRP78/BIP from these transmembrane proteins, which become activated. Active PERK phosphorylates the eukaryotic initiation factor-2alpha (eIF2α) at serine 51 reducing protein synthesis and, consequently, protein overload in the ER. eIF2α also activates the transcription factor ATF4, which up-regulates UPR target genes encoding factors involved in amino-acid biosynthesis, the antioxidant stress response. The activation of IRE1α leads to non-canonical XBP1 splicing. This spliced form of XBP1 (sXBP1), alone or synergistically with activating transcription factor 6 (ATF6), activates the transcription of UPR target genes. Activated ATF6 migrates to the nucleus to stimulate the expression of genes containing the ER stress response element (ERSE) and the UPR elements.

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