Biochimica et Biophysica Acta xxx (2012) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Endoplasmic reticulum stress as a pro-fibrotic stimulus ☆

Harikrishna Tanjore [a], William E. Lawson [a,d], Timothy S. Blackwell [a,b,c,d,*]

[a] Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA
[b] Department of Cell and Developmental Biology, Vanderbilt University School of Medicine, Nashville, TN, USA
[c] Department of Cancer Biology, Vanderbilt University School of Medicine, Nashville, TN, USA
[d] Department of Veterans Affairs Medical Center, Nashville, TN, USA

ARTICLE INFO

Article history:
Received 30 August 2012
Received in revised form 14 November 2012
Accepted 16 November 2012
Available online xxxx

Keywords:
Unfolded protein response
Fibrosis
Interstitial lung disease
Apoptosis
Epithelial–mesenchymal transition

ABSTRACT

Current evidence suggests a prominent role for endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR) in fibrotic conditions affecting a number of internal organs, including the lungs, liver, GI tract, kidney, and heart. ER stress enhances the susceptibility of structural cells, in most cases the epithelium, to pro-fibrotic stimuli. Studies suggest that ER stress facilitates fibrotic remodeling through activation of pro-apoptotic pathways, induction of epithelial–mesenchymal transition, and promotion of inflammatory responses. While genetic mutations that lead to ER stress underlie some cases of fibrosis, including lung fibrosis secondary to mutations in surfactant protein C (*SFTPC*), a variety of other factors can cause ER stress. These ER stress inducing factors include metabolic abnormalities, oxidative stress, viruses, and environmental exposures. Interestingly, the ability of the ER to maintain homeostasis under stress diminishes with age, potentially contributing to the fact that fibrotic disorders increase in incidence with aging. Taken together, underlying ER stress and UPR pathways are emerging as important determinants of fibrotic remodeling in different forms of tissue fibrosis. Further work is needed to better define the mechanisms by which ER stress facilitates progressive tissue fibrosis. In addition, it remains to be seen whether targeting ER stress and the UPR could have therapeutic benefit. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

1. Introduction

In addition to its role in neurodegenerative diseases and diabetes, endoplasmic reticulum (ER) stress is emerging as a factor in a variety of diseases that result in fibrotic remodeling of internal organs, including liver, gastrointestinal (GI) tract, kidneys, heart, and lungs [1–7]. The ER is an important intracellular organelle whose tasks include facilitating the conversion of nascent proteins to functional forms. Conditions such as calcium depletion, glucose or nutrient deprivation, viral infections, environmental exposures, aging, or expression of mutant proteins can alter the functionality of the ER, resulting in ER stress. To maintain homeostasis, cells rely on protective mechanisms to help them cope with ER stress, pathways referred to collectively as the unfolded protein response (UPR). The UPR encompasses three transmembrane proteins that act as sensors of ER stress with activation of downstream pathways orchestrating a cascade of events that have evolved to protect the cell [1]. Cells with high metabolic activity or with high secretory function rely on the UPR pathways to maintain homeostasis in the setting of ER stress. Perhaps this is best illustrated in the function of plasma cells, which rely on a highly functioning UPR to maintain homeostasis in the setting of immunoglobulin production. However, when ER stress is severe or prolonged, cellular dysfunction can ensue, resulting in injury or death, inflammatory signaling, and/or phenotype transition. This review focuses on structural cells, primarily epithelial cells, where evidence indicates that ER stress can enhance vulnerability to injury and facilitate fibrotic remodeling in a variety of tissues. Although the mechanisms linking ER stress and fibrosis are incompletely understood, we will discuss the current state of knowledge regarding the contribution of ER stress and the UPR to cellular dysfunction and fibrosis.

2. Endoplasmic reticulum stress and the unfolded protein response

The endoplasmic reticulum (ER) is an organelle found in all eukaryotic cells. It is crucially involved in protein folding, lipid synthesis, glycogen production and storage, and calcium metabolism [1]. Under normal physiological conditions, chaperone proteins assist in folding of nascent proteins, thereby preventing aggregation of proteins in the ER. Immunoglobulin heavy-chain-binding protein (BiP), also referred to as glucose regulated protein 78 (GRP78), is an important chaperone that is typically increased when ER stress is encountered. In fact, upregulation of BiP can serve as an indicator of ER stress [8–10]. BiP binds to transmembrane sensor protein PKR-like endoplasmic reticulum Kinase (PERK), activating transcription factor 6

☆ This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

* Corresponding author at: Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, T-1218 MCN, Nashville, TN 37232–2650, USA. Tel.: +1 615 343 4761; fax: +1 615 322 2586.
E-mail address: timothy.blackwell@vanderbilt.edu (T.S. Blackwell).

0925-4439/$ – see front matter © 2012 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.bbadis.2012.11.011

(ATF6), and inositol-requiring enzyme 1 (IRE-1), maintaining each in its inactive state [11]. With protein accumulation in the ER, BiP interacts with these nascent proteins and is released from these transmembrane sensors. Once unbound from BiP, these three transmembrane proteins can then assume their activated state, leading to the cascade of events known as the UPR (Fig. 1). PERK and IRE-1 are activated by phosphorylation while ATF6 is activated by proteases. These UPR proteins then act to maintain homeostasis and normal functioning of the ER and the cell through attenuating protein translation, increasing cytoprotective factors, enhancing production of folding chaperone proteins, and up-regulating expression of pro-degradation factors (Fig. 1) [12,13]. However, when these UPR mechanisms fail or when the UPR is hyperactivated, apoptotic cell death can occur [14].

Activation of PERK occurs by trans auto-phosphorylation and dimerization. Activated PERK phosphorylates the α-subunit of eukaryotic translational initiation factor 2 (peIF2α), which hinders global protein synthesis [15]. The importance of PERK in cell survival in the setting of ER stress was established by studies in which cells with mutant PERK were shown to be unable to phosphorylate eIF2α, leading to increased sensitivity to induction of ER stress and greater cell death [16]. In addition to inhibition of protein translation, peIF2α induces the expression of ATF4, which has been shown to increase expression of protective redox proteins as well as the pro-apoptotic protein CCAAT/enhancer binding protein (EBP) homologous protein (CHOP) [17]. As a result, a delicate balance appears to dictate whether phosphorylated eIF2α dependent mechanisms are pro- or anti-apoptotic [15–17]. Along these lines, cells from ATF4 knockout mice are more sensitive to oxidative damage [16,18].

ATF6 is an important component of the UPR pathways and has been implicated in several diseases. When activated by ER stress, ATF6 translocates to the golgi, where it is cleaved by site1 and site2 proteases into an NH2 terminal domain and a cytosolic domain. The cleaved cytosolic domain is then transported into the nucleus where it activates the transcription of several ER proteins such as BiP, X-box binding protein 1 (XBP1), GRP94, calreticulin, calnexin, protein disulfide isomerase (PDI), and CHOP [10,19–21]. ATF6 has two isoforms — ATF6α and ATF6β. Of the two isoforms, ATF6α has been shown to be most important for cell survival under ER stress. Double knockouts of ATF6α and ATF6β results in embryonic lethality while single gene deletion of ATF6α or ATF6β does not result in an obviously abnormal phenotype. However, when ATF6α knockout mice are challenged with intraperitoneal injection of the ER stress inducing agent tunicamycin, survival of mice is reduced compared to wild type controls [22].

IRE-1 is a transcription factor in the UPR pathway and its importance in the UPR is well established in studies from mammalian cells. It exist in two isoforms — IRE-1α and IRE-1β. When activated, IRE-1 undergoes dimerization, with the RNase domain of IRE-1 cleaving XBP1 into its spliced (and active) form. Spliced XBP1 acts as a transcription factor and promotes the transcription of ER associated degradation (ERAD) target genes such as ER degradation enhancing α-mannosidase-like protein (EDEM) [23,24]. Knockouts of IRE-1 and XBP1 are embryonic lethal with defects in liver development. Intestinal epithelial specific

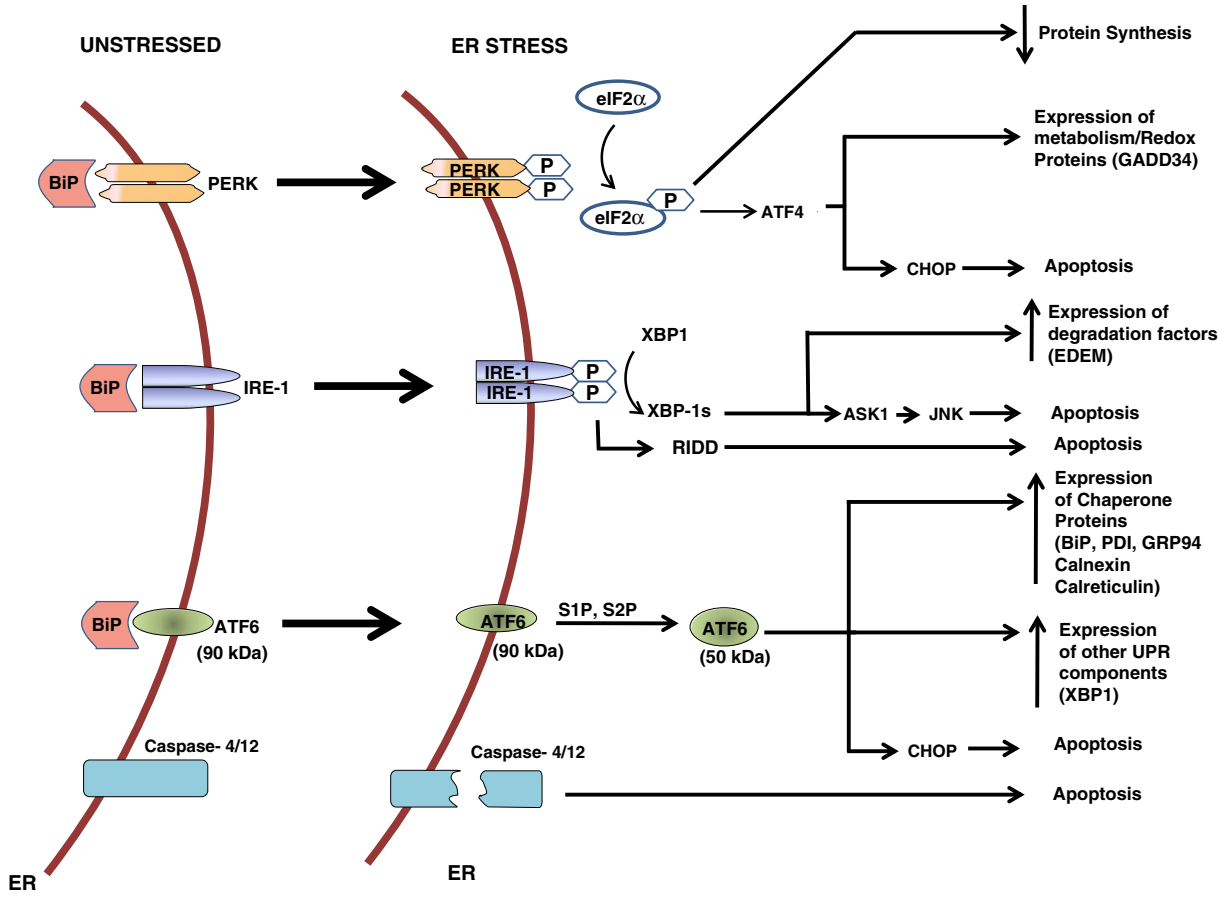

Fig. 1. Schematic illustration of ER stress and the UPR. ATF = activating transcription factor; BiP = immunoglobulin heavy-chain-binding protein; EDEM = ER degradation enhancing α-mannosidase-like protein; eIF2α = eukaryotic initiation factor 2α; ER = endoplasmic reticulum; GADD34 = growth arrest and DNA damage protein 34; IRE = inositol-requiring enzyme 1 (IRE-1); PERK = PKR-like ER kinase; XBP1 = X-box binding protein 1; GADD34 = growth arrest and DNA damage-inducible protein; PDI = protein disulphide isomerase; GRP94 = glucose-regulated protein 98; CHOP = C/enhancer binding protein (EBP) homologous protein; ASK1 = apoptosis signal-regulating kinase 1; JNK = c-Jun N-terminal kinases; S1P = site-1 protease; S2P = site-2 protease; RIDD = regulated IRE1-dependent decay.

Please cite this article as: H. Tanjore, et al., Endoplasmic reticulum stress as a pro-fibrotic stimulus, Biochim. Biophys. Acta (2012), http://dx.doi.org/10.1016/j.bbadis.2012.11.011