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Regulation of Innate Immunity by signaling pathways emerging from the endoplasmic reticulum

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Abstract

The innate immune system has evolved the capacity to detect specific pathogens and to interrogate cell and tissue integrity in order to mount an appropriate immune response. Loss of homeostasis in the endoplasmic reticulum (ER) triggers the ER-stress response, a hallmark of many inflammatory and infectious diseases. The IRE1/XBP1 branch of the ER-stress signaling pathway has been recently shown to regulate and be regulated by innate immune signaling pathways in both the presence and absence of ER-stress. In contrast, innate immune pathways negatively affect the activation of two other branches of the ER-stress response as evidenced by reduced expression of the pro-apoptotic transcription factor CHOP. Here we will discuss how innate immune pathways and ER-signaling intersect to regulate the intensity and duration of innate immune responses.

Keywords

ER-stress; IRE1; XBP1; TLR; innate immunity

Introduction

The endoplasmic reticulum (ER) is a subcellular compartment involved in the biosynthesis of cellular molecules, including membrane-bound and soluble proteins that are destined for intracellular organelles or the cell surface. Newly translated proteins in the ER undergo post-translational modifications such as glycosylation or disulfide bond formation. These modifications are key for proteins exposed to the extracellular space to withstand a harsh extracellular environment. Beyond its scaffolding role in organizing the synthesis of key extracellular proteins involved in cell-cell communication, the ER harbors a crucial sensing network of signaling pathways that integrates protein synthesis, folding, export and degradation with the physiology of the cell, the tissue and the organism. When the process of protein synthesis and protein folding is out of balance, the ER responds by inducing a transcriptional program, known as the unfolded protein response (UPR), that leads to the

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elevated expression of ER-chaperones and genes involved in ER expansion as well as molecules affecting ER and cellular functions. The activation of the UPR generally reflects a loss of ER-homeostasis, a condition referred to as ER-stress [1].

Background: The Unfolded Protein Response

The UPR relies on a highly coordinated response involving three parallel signaling branches using the transmembrane proteins ATF6, PERK and IRE1 as proximal sensors localized at the ER (Figure 1) [2]. Upon activation, ATF6 is relocated to the Golgi where it is cleaved by S1P and S2P proteases. Cleavage of ATF6 releases a fragment that translocates to the nucleus to promote gene expression. PERK is a kinase that undergoes oligomerization and autophosphorylation upon activation leading to the translational activation of the transcription factor ATF4 while causing attenuation of global mRNA translation by phosphorylating the α-subunit of the regulating initiator of the translation machinery, eIF2. The most conserved signaling branch relies on IRE1, an ER anchored kinase and ribonuclease that functions by promoting post transcriptional maturation of *XBP1* mRNA. Upon activation, IRE1 initiates the unconventional processing of the *XBP1* mRNA. In mammalian cells, a 26 nucleotide intron-like portion of *XBP1* mRNA is spliced out leading to a shift in the codon reading frame. Translation of this new mRNA results in the conversion of XBP1 from an inactive 267 amino acid long protein to an active form of 371 amino acids. Both forms of XBP1 have a DNA binding domain, but only the active (spliced) form of XBP1 harbors a functional transactivation domain at the C-terminus [3–5]. While the three branches cooperate to drive UPR-responsive gene expression, IRE1 activation is rapidly attenuated despite the persistence of stress, while PERK activity is sustained [6]. These observations suggest that the kinetics of activation and deactivation of the individual ER-signaling branches may promote time-regulated specific outputs influencing the cell's ultimate fate in response to ER stress.

Many physiological and pathological conditions that affect protein folding, calcium flux, oxidative stress, glycosylation, can instigate features of ER-stress. A role for the ER-stress pathway in immunology was first recognized when XBP1 was identified as an essential transcription factor involved in the differentiation of plasma B cells [7]. Secretory cells including plasma cells that are specialized to produce high amounts of secreted immunoglobulins, and Paneth cells or exocrine acinar cells that secrete antimicrobial molecules and digestive enzymes respectively, depend on the UPR for survival and maintenance of an expanded and highly active ER [8,9]. More recently, the UPR has also been shown to be essential for the survival and development of dendritic cells (DCs) [10]. Beyond its role in the development of functional secretory cells, there is growing evidence that ER-signaling pathways can affect the functions and cellular physiology of fully differentiated cells such as hepatocytes and macrophages [11,12]. Interestingly, some of the functions associated with the activation of IRE1 and XBP1 operate independently of the engagement of the other ER-stress pathways and the engagement of a classic UPR. This has been shown for example in hepatocytes where XBP1 is essential in the regulation of cholesterol and triglyceride levels through its control of hepatic lipogenesis, [12].

Here we will discuss findings highlighting the role of ER-signaling pathways in the regulation of innate immunity and inflammation focusing on the recently identified role of IRE1 and XBP1 in fully differentiated immune cells. We will also discuss similarities between and cross-talk among ER-signaling pathways and innate immune pathways.

Innate immunity and ER signaling pathways share common signaling modules

Similarities in signaling pathways stemming from innate immune pathways and ER stress signaling components have been noted [13]. Both IRE1 and TLRs trigger the production of

ROS and acute phase proteins and both engage NEMO and TRAF adaptors to trigger inflammatory signaling components such as NF-κB, the mitogen-activated protein kinase (MAPK), and c-Jun N-terminal kinase (JNK) [14–16]. Moreover, IRE1 and PERK are evolutionarily related to proteins involved in innate immunity (Figure 2). Animal, plant and yeast IRE1 cytosolic domains encoding for the kinase and RNase domains are more than 40% similar to human RNaseL, suggesting that RNaseL evolved from an IRE1 ancestor sequence. RNaseL is a cytosolic kinase that senses viral infection. Upon activation, RNaseL promotes the degradation of viral RNA: these degradation products lead to the activation of type 1 interferon and innate immune pathways including RIG-I/CARDIF pathways [17]. Similarly, mammalian PERK is related to mammalian antiviral effectors including GCN2, HRI and PKR [18]. GCN2 is conserved in yeast and phosphorylates the alpha-subunit of yeast translation initiation factor eIF2 (Sui2p) in response to starvation. In mice, GCN2 is implicated in mounting innate immunity to RNA viruses [19]. Haem-regulated eIF2alpha kinase (HRI) is essential for the regulation of globin gene translation and the survival of erythroid precursors in iron/haem deficiency and plays an essential protective role in anemias of iron deficiency, erythroid protoporphyria, and beta-thalassemia. It has also been reported that HRI protein is present in murine macrophages, and that HRI-deficient mice exhibit impaired macrophage maturation and a weaker inflammatory response with reduced cytokine production upon LPS challenge, suggesting that HRI may regulate immune responses [20]. Finally, PKR is a well characterized antiviral protein found in most human cells that senses double stranded RNA and mediates type I interferon responses [21]. The similarities between IRE1 and PERK with known innate immune regulators suggest that some signaling modules used by innate immune sensors and ER-signaling pathways may have co-evolved to respond to specific stresses and insults. The cross-talk recently identified between these pathways supports this hypothesis [22–24].

Infected and Inflamed tissues display features of ER-stress

To establish their niche and replicate, intracellular pathogens have evolved to interact with specific intracellular organelles including the ER. Viruses for example, depend on ER membranes for budding and can produce large numbers of infectious viral particles that may overload the ER. It is therefore not surprising that viruses trigger significant ER-stress as measured by the induction of UPR markers [25]. ER-stress has also been suggested to be involved in the inflammatory component of chronic diseases [26]. Diseases such as atherosclerosis, cystic fibrosis, inflammatory bowel disease and type 2 diabetes, display features characteristic of ER-stress and inflammation, including the induction of classic UPR markers, neutrophil and macrophage infiltration and increased acute phase proteins [26]. Moreover, XBP1 has been demonstrated to have a role in inflammatory bowel disease [8] and type 2 diabetes [27]. While inflammation may contribute to the induction of ER-stress markers in affected tissues, recent evidence suggests that ER-stress, by triggering specific ER-signaling pathways might promote inflammation *per se* [13].

ER-stress boosts innate immunity and inflammatory responses

Low levels of stress are physiological and can transmit essential survival or adaptive signals. At higher levels, however, the responses become maladaptive and cause damage. Intracellular stress signals such as DNA damage and oxidative stress have been shown to regulate aspects of the inflammatory response [28,29]. Similarly the ER-stress observed in inflammatory pathologies was postulated to be involved in determining the size, nature and longevity of the immune response [30–32]. Several *in vitro* and *in vivo* studies recently suggested that ER-stress might increase inflammatory responses.. In human aortic endothelial cells, oxidized phospholipids lead to endoplasmic reticulum stress and activation of the unfolded protein response (UPR) that is required for maximal inflammatory gene expression [33]. Similarly, HLA-B27 misfolding and UPR activation in macrophages can

result in enhanced induction of the pro-Th17-inducing cytokine IL-23 [34] and increased production of type I interferon [35], upon challenge with LPS. HLA-B27 misfolding is characteristic of increased susceptibility to spondyloarthritides, a group of heterogeneous immune-mediated autoinflammatory diseases. While this remains to be demonstrated *in vivo*, it is tempting to speculate that ER-stress could be directly linked to the development of autoinflammatory syndromes. Consistently, *in vitro* experiments have also demonstrated that macrophages treated with pharmacological agents triggering ER-stress display a dramatically enhanced response to TLR4 and TLR2 activation [22,35]. Using XBP1 deficient macrophages we showed that XBP1 was required for the maximal induction by membrane TLRs of a subset of genes including IL-6, especially under conditions of ER stress.[22]. Similar findings were observed in macrophages infected with the intracellular bacteria, *Francisella tularensis*, further demonstrating the propensity of ER-stress to enhance innate immune responses.

ER-signaling components involved in innate immunity

A possible explanation for the observed enhancement of innate immune responses upon ER-stress came from the discovery that components of ER-signaling pathways are directly involved downstream of innate immune receptors. The over-activation of these pathways during ER-stress may therefore contribute to the observed increase in innate immune responses. We have reported that, in the absence of detectable ER-stress, TLR4 and TLR2 specifically promote the phosphorylation of the ER-signaling kinase IRE1 and activation of its downstream target XBP1 [22]. Intriguingly, IRE1 activation by pathogens and TLRs does not promote activation of the other ER-signaling pathways and therefore does not induce ER-stress target genes. Instead, TLR-activated XBP1 is required for optimal and sustained production of proinflammatory cytokines in macrophages [22] (Figure 3). This specificity in output likely reveals the influence of other transcriptional regulators specific to TLR responses or the ER-signaling pathways that modulate XBP1 activity. The role of XBP1 in unstressed macrophages was also highlighted by studies utilizing XBP1 deficient mice. XBP1 deficiency markedly increased bacterial burden in animals infected with the TLR2-activating pathogen *Francisella tularensis*. These observations uncover an unsuspected critical new function for the XBP1 transcription factor in mammalian host defenses and demonstrate that specific branches of the ER-signaling pathways are directly used by innate immune pathways in the absence of ER-stress.

XBP1 and ATF6 are also activated in *Caenorhabditis elegans* upon infection with pore-forming toxin-harboring bacteria and are required for proper defense against these pathogens [36]. How ER-signaling protects the worms is unclear. It is unknown whether XBP1 and ATF6 act by enhancing an inflammatory response or by promoting a protective ER-stress response. In a different model, *C. elegans* infected with *Pseudomonas aeruginosa*, activation of the innate immune kinase PMK-1 triggers IRE1 and XBP1 [37]. Interestingly, XBP1 loss of function decreases the viability of infected worms, possibly due to increased activation of PMK-1, an effect observed even in the absence of pathogen [37]. This suggests that XBP1 may function to suppress the detrimental effects of PMK-1 activation during the immune response. In plants, the ATF6-like protein ZIP60 [38] (an important component of the plant ER-stress response) is also induced upon infection with a bacterial pathogen. Tobacco leaves infected with *Pseudomonas cichorri* upregulate the expression of ZIP60, and silencing of ZIP60 allows higher multiplication of *P. cichorri* compared to control plants [39], further suggesting that ER-signaling pathway involvement in host defenses against pathogens is evolutionarily conserved.

Regulation of ER signaling pathways by innate immune receptors

Recent evidence suggests that infections and innate immune pathways redirect the ER-stress response to enhance ER-signaling pathways that drive inflammation while down-regulating other pathways. It is striking, for example, that livers from patients with untreated hepatitis C exhibit hepatocyte ER-stress and activation of the three ER-stress sensors (IRE1, ATF6 and PERK) without apparent induction of UPR-responsive genes. In contrast, genes involved in liver proliferation, inflammation, and apoptosis are significantly induced in these samples [40]. This lack of UPR-gene induction may be explained by the inhibiting action of Hepatitis C downstream of IRE1 [41] or by the capacity of the innate immune system to actively inhibit specific branches of the ER-stress response to redirect the response toward inflammation. The same phenomenon may explain why bacteria and parasites that trigger the activation of ER-signaling pathways such as IRE1, activate only a few classic UPR markers. In line with this hypothesis, it has been shown that the ATF4-CHOP branch of the UPR can be specifically inhibited by TLR signaling [23]. Moreover, it was reported in macrophages that TLR signaling could inhibit ATF6 and PERK activity [22] (Figure 3). While the mechanisms involved in the dampening of specific ER-signaling pathways and their functions *in vivo* are still unclear, these observations clearly demonstrate that innate immunity has the capacity to coordinate ER-signaling responses in the presence of TLR-activating pathogens.

Innate immune sensors may also positively regulate the physiological changes triggered by ER-stress. Recently, the anti-viral protein PKR has been shown to respond to ER-stress and nutrient signals to regulate insulin action and metabolism and is required for optimal JNK activation upon ER-stress [24], further demonstrating that ER-signaling and innate immune pathways are significantly interconnected and can regulate each other.

Closing remarks

The ER-stress response is a fundamental sensing pathway common to virtually all eukaryotes. We suggest that portions of this pathway may represent an ancestral innate immune recognition mechanism that detected and responded to cellular injury inflicted by replicating pathogens such as viruses. However, the role for ER-signaling pathways in innate immunity is an emerging concept that is only recently supported by experimental evidence. Many questions remain unsolved. While a picture is emerging where ER-signaling pathways such as IRE1 and XBP1 do not *per se* promote immunity or inflammation but modify immune responses by increasing the duration and intensity of specific inflammatory cytokines, future studies will be required to fully assess the physiological relevance of this “adjuvantic” role of IRE1 and XBP1. It will also be important to interrogate whether engagement of ER-signaling pathways by innate immune recognition is specific to membrane-bound TLR receptors or whether other pathways such as PKR and Rnase, for example, intersect with ER-signaling. Finally, little is known about the mechanisms used by TLRs and possibly other innate immune receptors to regulate ER-stress responses. It will be particularly important to address the significance and physiological relevance for this regulatory loop for the evolution of innate and inflammatory response *in vivo*. These studies will undoubtedly shed some new light on the role of cellular stress pathways in regulating health and susceptibility to infection and autoinflammatory diseases.

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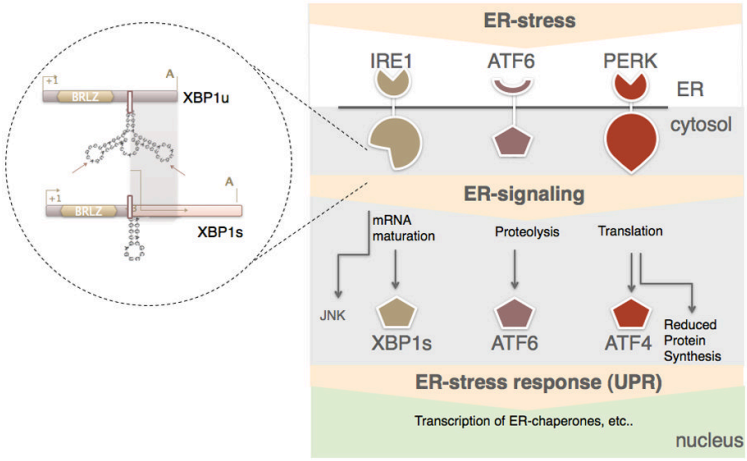

Figure 1. ER-signaling pathways involved in the ER-stress response

Accumulation of unfolded proteins or injury in the ER triggers a stress response that activates ER-signaling pathways including IRE1, ATF6 and PERK. Active IRE1 triggers an unconventional splicing of the transcription factor XBP1 (left enlarged panel) leading to the removal of 26 nucleotides and the translation of an active transcription factor. IRE1 can also activate additional signaling components such as JNK and TRAF2. The transcriptionally active form of ATF6 is produced by proteolysis. PERK activation triggers translation of the transcription factor ATF4 and inhibits the translation initiator factor alF2a. When these pathways are activated simultaneously they trigger the ER-stress or unfolded protein response (UPR) characterized by the transcription of genes that increase the folding capacity of the ER, decrease the synthesis of proteins involved in ER-overload and sensitize the cells to apoptosis, autophagy, and inflammatory responses.

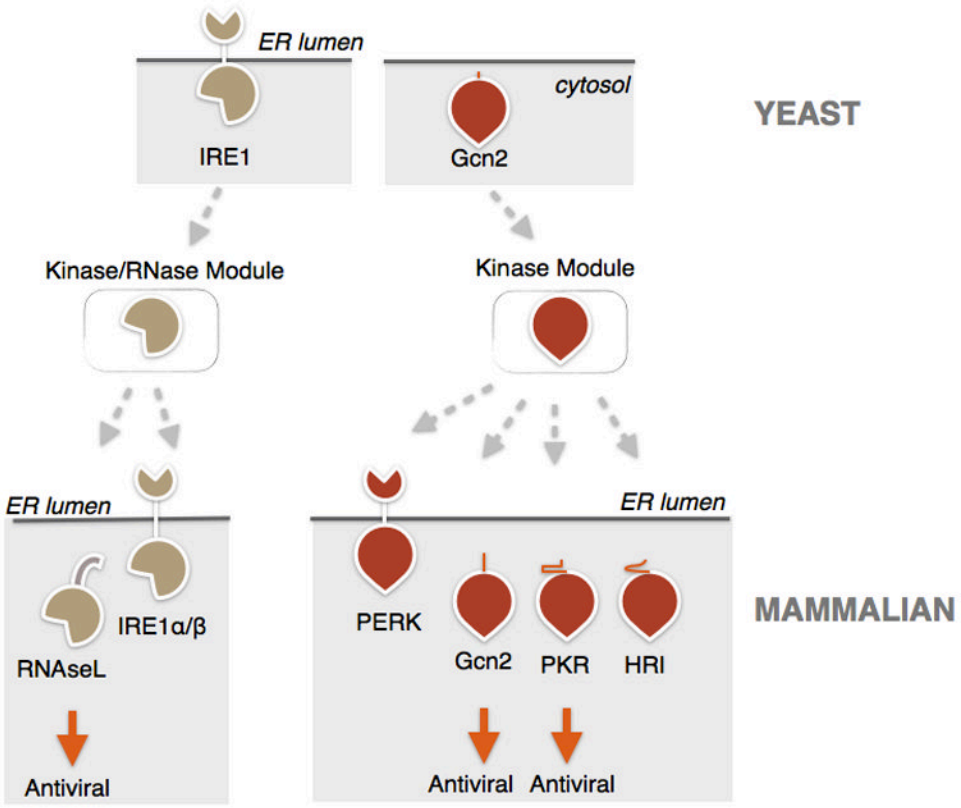

Figure 2. Similarities between ER-signaling and innate immune pathways

Evidence suggests that some innate immune sensors evolved from ancestral stress sensing pathways. Both IRE1 and PERK kinases are evolutionarily related to innate immune sensors. The cytosolic (effector) domain of yeast IRE1 containing the kinase and RNase domain of IRE1 is highly similar to mammalian IRE1α and β as well as to the effector region of the cytosolic viral sensor RNaseL. Similarly, the yeast kinase module of GCN2 is related to the kinase region of mammalian PERK as well as to mammalian kinases GCN2, HRI and PKR. Studies in mice have shown roles for GCN2 and PKR in sensing viruses, while defects in TLR responses have been reported in HRI deficient mice.

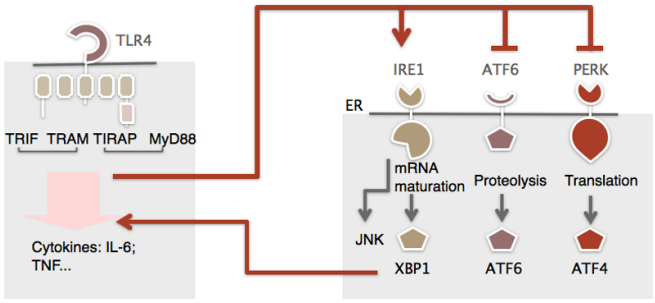

Figure 3. Regulatory loops connecting TLR and ER-signaling

TLR4 and TLR2 activate the transcription factor XBP1 by selectively activating the IRE1 kinase while suppressing the other branches of the ER-stress pathway. Because of the absence of the other ER-signaling pathways, the activation of IRE1 and XBP1 does not contribute to an ER-stress response. However, activated XBP1 amplifies TLR signaling by enhancing cytokine production.