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# Evolution of the unfolded protein response ☆

Julie Hollien *

*Department of Biology and the Center for Cell and Genome Science, University of Utah, Salt Lake City, UT 84112, USA*

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ABSTRACT

The unfolded protein response (UPR) is a network of signaling pathways that responds to stress in the endoplasmic reticulum (ER). The general output of the UPR is to upregulate genes involved in ER function, thus restoring and/or increasing the capacity of the ER to fold and process proteins. In parallel, many organisms have mechanisms for limiting the load on the ER by attenuating translation or degrading ER-targeted mRNAs. Despite broad conservation of these signaling pathways across eukaryotes, interesting variations demonstrate a variety of mechanisms for managing ER stress. How do early-diverging protozoa respond to stress when they lack traditional transcriptional regulation? What is the role of the ER stress sensor Ire1 in fungal species that are missing its main target? Here I describe how diverse species have optimized the UPR to fit their needs. This article is part of a Special Issue entitled: Functional and structural diversity of endoplasmic reticulum.



## 1. Introduction

Maintenance of homeostasis in the endoplasmic reticulum relies on a collection of signaling pathways known as the unfolded protein response (UPR). These pathways sense disturbances in protein folding in the ER through transmembrane proteins that then initiate signaling pathways affecting many aspects of gene expression. Together they decrease the load of proteins entering the ER and increase the capacity of the ER to fold and process these proteins. In mammals, these pathways are essential for survival not only during infection and disease, but also during normal development, especially during the differentiation of professional secretory cells.

Reviews over the last two years have offered perspectives on many interesting and fundamental facets of the UPR, including its role in ER homeostasis [1,2], apoptosis [3], disease [4,5], inflammation [6], secretory cell function [7], and aging [8]. This abundance of reviews does not seem completely unwarranted; a recent Pubmed search yielded well over 500 research articles pertaining to the UPR in 2012 alone. A special issue focused on the ER would therefore not be complete without some mention of the UPR. Inspired by recent discoveries in plants and fission yeast, and in an effort to offer a non-redundant review of the UPR, this article will highlight similarities across eukaryotes and variations on these pathways that have evolved in organisms other than the well-studied mammalian and budding yeast model systems.

## 2. An overview of UPR signaling pathways in budding yeast and metazoa

Stress in the ER, generally considered to be the result of an imbalance between the protein folding load and the capacity of the ER, occurs in a variety of circumstances. Pathological ER stress can result from infection or diseases linked to the ER, whereas physiological stress is thought to activate the UPR during differentiation and maintenance of secretory cells in metazoans. A classic example of the latter is the activation of certain aspects of the UPR during the differentiation of antibody-secreting plasma cells [9,10]. Because of the central role of the UPR in regulating the capacity of the ER and managing stress, several of the signal transducers are required for normal development and survival in mammals.

One of the main mechanisms governing UPR signaling was originally worked out in *Saccharomyces cerevisiae*, where a single transmembrane protein, Ire1, is responsible for sensing ER stress [11,12] (Fig. 1A). Oligomerization of Ire1 leads to autophosphorylation and activation of an endoribonuclease domain on the cytosolic side of the membrane. This nuclease cleaves at two specific sites in the mRNA encoding Hac1 [13,14], removing a regulatory intron from the message, which is then spliced back together to form the template for the active Hac1 protein. Hac1p, a bZip transcription factor, upregulates many genes associated with the secretory pathway, including the major ER chaperone BiP [15]. This pathway thereby enhances ER function and is conserved in most eukaryotes, with the known exceptions discussed below.

The metazoan UPR is decidedly more complex that that seen in budding yeast. Mammals possess two copies of Ire1; Ire1α is expressed ubiquitously [16] and is essential for embryonic development [17,18], whereas Ire1β is expressed specifically in intestinal epithelial cells and its deletion sensitizes mice to colitis [19]. Both isoforms of Ire1 can

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* Tel.: +1 801 587 7783; fax: +1 801 581 2174.
*E-mail address:* hollien@biology.utah.edu.

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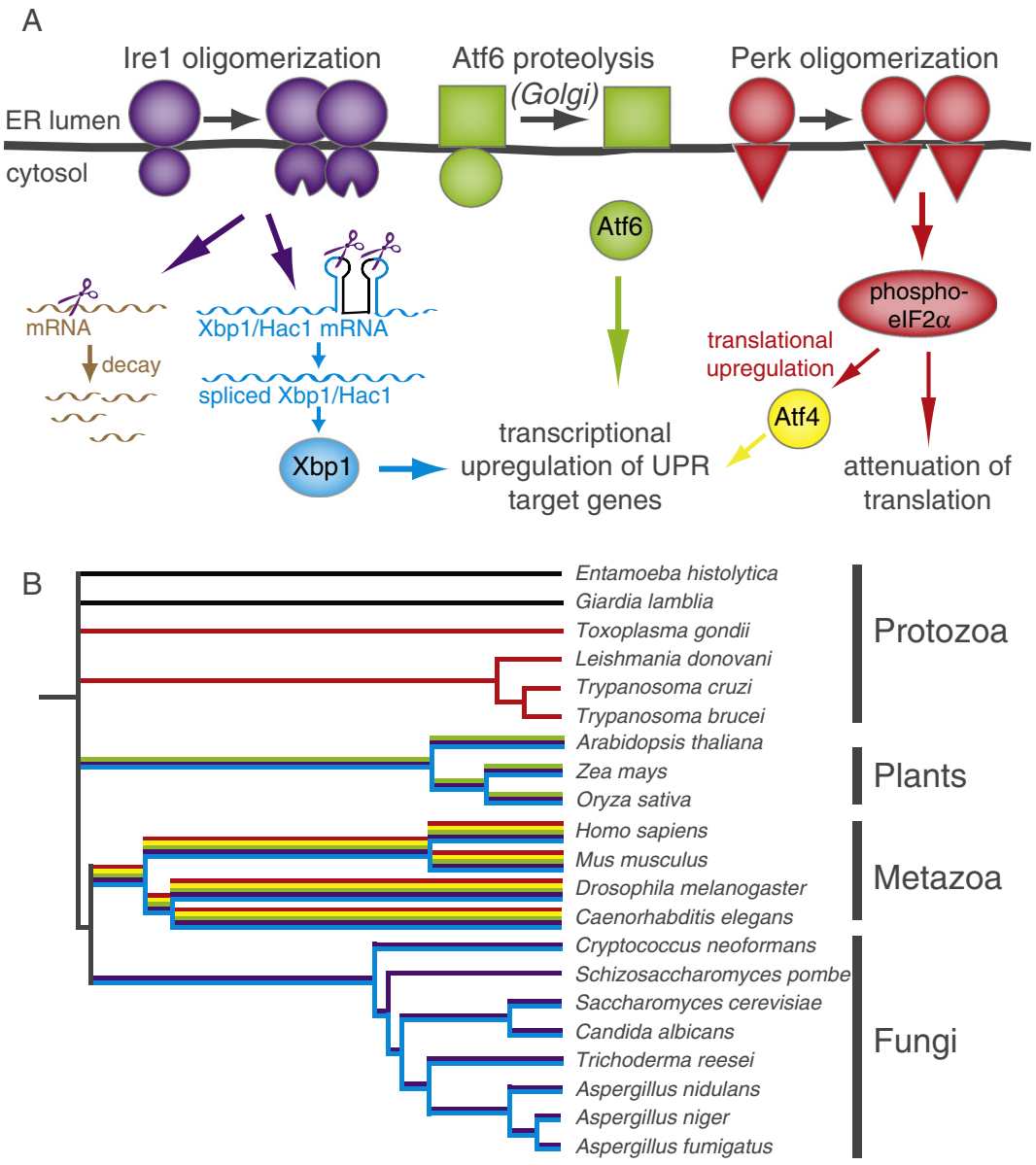


**Fig. 1.** A. An overview of the signaling mechanisms of the unfolded protein response. During ER stress, Ire1 oligomerizes, which activates its cytosolic kinase and nuclease. The outputs of Ire1 include cleavage of the mRNA encoding Xbp1 (Hac1 in yeast) and degradation of mRNAs. Atf6 travels to the Golgi apparatus during ER stress, where its cytosolic domain is released by proteolysis. Perk oligomerizes and phosphorylates eIF2alpha, leading to translational attenuation in general, and translational activation of certain proteins, including Atf4. Xbp1, Atf6, and Atf4 then coordinate a broad transcriptional response to ER stress. B. A tree diagram of the species mentioned in this review. Branches are color coded (same colors as in A) according to whether these UPR pathways exist in these organisms. Note that for some protozoa the evidence for Perk is not clear (see text). Black indicates that there is evidence against a functional UPR in these organisms. The tree was constructed using the online tool iTOL [99].

initiate the splicing of a Hac1-like bZip transcription factor, X-box binding protein (Xbp1) [20–22], but there is some degree of specialization, as the metazoan Ire1 has been shown to regulate other functions in addition to splicing. For example, in mammals and flies, Ire1 mediates the degradation of many other mRNAs through a pathway referred to as regulated Ire1-dependent decay, or RIDD [23,24]. Comparisons of Ire1α and β in mammals suggest that Ire1α is more effective in Xbp1 splicing whereas Ire1β is more promiscuous [25].

In addition to Ire1, metazoans express two other main sensors of ER stress, Perk and Atf6 (Fig. 1A). Atf6 is a transcription factor that travels from the ER to the Golgi during stress, where it is activated by intramembrane proteolysis, mediated by Site-1 and Site-2 proteases (S1P and S2P) [26,27]. The cytosolic domain released by this cleavage is an active bZip transcription factor, capable of inducing UPR target gene expression on its own and of heterodimerizing with Xbp1 [28]. As with Ire1, there are two isoforms of Atf6 in mammals, and deletion of both results in embryonic lethality in mice [28]. Perk, the third main branch of the UPR in metazoans, is an ER transmembrane kinase that phosphorylates eukaryotic initiation factor 2alpha (eIF2α) in response to ER stress [29,30]. This leads to a general translational attenuation, thought to limit the protein folding load on the ER and conserve resources. Conversely, specific mRNAs that harbor short open reading frames in their 5′ UTRs can be upregulated translationally by eIF2α phosphorylation. Examples of such mRNAs include those encoding Atf4 [31], a third bZip transcription factor that regulates UPR target genes important for stress recovery, and Gadd34 [32], which serves as a negative feedback regulator by dephosphorylating eIF2α [33,34].

The basic features of the UPR appear to be well conserved throughout metazoa. Most species have homologs of the three main signaling