Introduction: the unfolded protein response's role in disease pathophysiology

Arthur Kaser · Richard S. Blumberg

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Protein function is fundamentally dependent on correct protein folding and post-translational modification. For proteins entering the secretory pathway, this occurs in the endoplasmic reticulum (ER), which is also critically involved in cholesterol and lipid biosynthesis and which is the site of intracellular calcium storage [1–3]. Protein folding is an energy-dependent process that involves a variety of proteins including chaperones, and the occurrence of misfolded proteins imposes stress on the ER. The unfolded protein response (UPR) has evolved to counter this stress by adapting protein folding mechanisms and the cell's protein folding capacity to the level of demand determined by the role and activation state of the individual cell. As secretory cell types are particularly sensitive to ER stress due to their high protein production burden, abnormalities in the UPR are increasingly recognized as an important contributor to disease pathogenesis [4], the topic of the current issue of *Seminars in Immunopathology*.

Three major branches of the UPR have evolved, each of which consists of an ER transmembrane protein that serves as proximal sensor of ER stress in conjunction with an ER resident chaperone, grp78 [1–3]. These three ER transmembrane proteins are inositol-requiring enzyme 1 (IRE1) [5], with its isoforms α and β ; activating transcription factor 6

(ATF6; α and β isoforms) [6] and PKR (double-stranded RNA-dependent protein kinase)-like ER kinase (PERK), which activate specific downstream transcriptional effectors [1]. IRE1 acts as an endoribonuclease, excising a 26nt sequence from the mRNA encoding X-box binding protein 1 (XBP1), which results in a frameshift and translation of the active transcription factor (XBP1s, s for spliced) that transactivates UPR target genes [5, 7]. The IRE1/XBP1 branch is the evolutionarily most conserved branch of the UPR. Upon sensing ER stress, ATF6 is packaged into vesicles, which are released from the ER and traverse to the Golgi, where ATF6 is cleaved by site-1 and site-2 proteases (S1P, S2P) [6, 8], releasing the active transcription factor fragment that enters the nucleus and also transactivates a set of UPR target genes, in part by co-operating with XBP1s. XBP1 and ATF6 transactivate genes that are involved in protein translation, folding and quality control, but also in ER-associated degradation [8], rendering the removal of misfolded proteins via the proteasome an integral part of the UPR. Finally, PERK activation by the occurrence of misfolded proteins in the ER results in phosphorylation and hence inactivation of elongation and initiation factor 2 α (eIF2 α) and consequent inhibition of mRNA transcription [8]. This decreases the global flux of proteins entering the ER. However, certain mRNAs that contain short open reading frames in their 5' untranslated regions are preferentially transcribed under conditions of limiting eIF2 α . Amongst those is activating transcription factor 4, a further UPR transcription factor that, among other target genes, transactivates CHOP (transcription factor C/EBP homologous protein) [8]. CHOP in turn transactivates genes involved in apoptosis induction and thereby connects ER stress that has become unsustainable with cell death.

The UPR serves a critical homeostatic function not only confined to bona fide secretory cells, but almost ubiquitously in the organism. As such, temporal induction of ER stress is

A. Kaser (✉)

Division of Gastroenterology and Hepatology, Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Level 5, Box 157, Cambridge CB2 0QQ, UK
e-mail: ak729@cam.ac.uk

R. S. Blumberg (✉)

Division of Gastroenterology, Hepatology and Endoscopy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Thorn 1419 75 Francis St, Boston, MA 02115, USA
e-mail: RBLUMBERG@PARTNERS.ORG

part of a physiological process, e.g. upon transition from a quiescent to an activated state [2, 8]. The differentiation of activated B cells into immunoglobulin-secreting plasma cells is one example of such a physiological process [7, 9]. In those instances, ER stress is typically temporally confined and resolved when a new equilibrium of protein production and folding is reached. In contrast, persistent ER stress has emerged as a pathological process that is involved in a variety of diseases [8].

ER proteostasis can be affected at multiple levels. A classical example is protein misfolding caused by mutations in genes, which can underlie both monogenic as well as polygenic diseases. Well-known examples are human leukocyte antigen-B27 [10], α_1 -antitrypsin [11, 12] and cystic fibrosis transmembrane conductance regulator [13], where protein misfolding and consequent ER stress play an important role in the pathophysiology. These examples highlight how individual proteins that enter the secretory pathway, when misfolded, do not only cause pathology due to the individual protein's malfunction but, through a persistently activated UPR, have broader implications for cells that go beyond the remit of the individual protein's function.

Genetically encoded alterations that are associated with disease have also been described for proteins that are directly involved in ER-localized protein folding or post-translational modification. Examples for this are mutations in protein disulfide isomerases [14]. Similarly, prolonged ER stress can also be a consequence in genetically encoded impairment of sensors and effectors of the UPR, examples of which are variants in [15]. However, persistent ER stress is clearly not only a consequence of genetic alterations, but is induced by a plethora of host physiological responses to exogenous 'insults'. ER stress arising in the liver and other organs in obesity as a consequence of high calorie intake might serve as a prime example [16]. Another—evolutionary ancient—example is the requirement of the UPR in *Caenorhabditis elegans* to survive an innate immune response upon infection with *Pseudomonas aeruginosa* [17], where the induction of protein production of inflammatory mediators serves as the trigger of ER stress.

Inflammatory mediators in their own right, ranging from cytokines to reactive oxygen species, can induce ER stress [18]. Also, a variety of exogenous factors and toxins directly impact on either protein folding or UPR mechanisms. The AB₅ subtilase cytotoxin expressed by Shiga toxigenic *Escherichia coli*, which cleaves grp78 and thereby leads to massive ER stress, may serve as an extreme example of such a mechanism [19].

It is thus increasingly recognized that the UPR as a genetically regulated integrator of host responses to environmental cues plays an essential role as an important contributor to and protector from a variety of complex diseases. In light of this, in this issue of *Seminars in Immunopathology*, the

profound contribution played by ER stress and UPR-related mechanisms in disease pathophysiology is extensively reviewed. A variety of organ systems are covered in this issue which highlights new information in this increasingly important and therapeutically relevant topic. Given the role of the UPR in enabling cells to adapt to environmental exposures and the needs required for responding to these, this issue opens with a discussion by Masanori Kitamura on the myriad range of environmental factors that impinge upon and trigger the UPR. In subsequent contributions, we hear from Victor Hugo Cornejo and Claudio Hetz on the role of the UPR in the pathogenesis of Alzheimer's disease as a prototype for diseases of the central nervous system. The lung is a major site of environmental contact, and Fabiolo Osorio, Bart Lambrecht and Sophie Janssens discuss the burgeoning knowledge about the role of the UPR in dealing with these challenges. Another large environmental surface of the body that requires a robust UPR is the gastrointestinal tract, and in this context, Arthur Kaser and Richard Blumberg discuss the role played and the consequences of an abnormal UPR in the pathogenesis of inflammatory bowel disease. A variety of metabolic diseases that are environmentally induced in the appropriate genetic context are rapidly increasing in westernized societies, and a key to understanding their pathophysiology and potential approaches to treatment is through an understanding of the role played by the UPR. Consistent with this, Alex Zhou and Ira Tabas provide insights into the role played by the UPR in the pathogenesis of atherosclerosis, and Takaso Iwawaki and Daisuke Oikawa discuss the pervasive role of the UPR in allowing the host to respond to its metabolic needs associated with glucose handling and, when abnormal, to development of diabetes mellitus as a consequence. To conclude this issue of *Seminars in Immunopathology*, Umut Ozcan and Sang Won Park discuss the potential for therapeutic manipulation of the UPR in treating disease.

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References

1. Schroder M, Kaufman RJ (2005) The mammalian unfolded protein response. *Annu Rev Biochem* 74:739–789
2. Hetz C, Martinon F, Rodriguez D, Glimcher LH (2011) The unfolded protein response: integrating stress signals through the stress sensor IRE1 α . *Physiol Rev* 91:1219–1243

3. Ron D, Walter P (2007) Signal integration in the endoplasmic reticulum unfolded protein response. *Nat Rev Mol Cell Biol* 8:519–529
4. Wang S, Kaufman RJ (2012) The impact of the unfolded protein response on human disease. *J Cell Biol* 197:857–867
5. Calton M, Zeng H, Urano F, Till JH, Hubbard SR, Harding HP et al (2002) IRE1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA. *Nature* 415:92–96
6. Ye J, Rawson RB, Komuro R, Chen X, Dave UP, Prywes R et al (2000) ER stress induces cleavage of membrane-bound ATF6 by the same proteases that process SREBPs. *Mol Cell* 6:1355–1364
7. Iwakoshi NN, Lee AH, Vallabhajosyula P, Otipoby KL, Rajewsky K, Glimcher LH (2003) Plasma cell differentiation and the unfolded protein response intersect at the transcription factor XBP-1. *Nat Immunol* 4:321–329
8. Walter P, Ron D (2011) The unfolded protein response: from stress pathway to homeostatic regulation. *Science* 334:1081–1086
9. Reimold AM, Iwakoshi NN, Manis J, Vallabhajosyula P, Szomolanyi-Tsuda E, Gravalles EM et al (2001) Plasma cell differentiation requires the transcription factor XBP-1. *Nature* 412:300–307
10. Turner MJ, Sowders DP, DeLay ML, Mohapatra R, Bai S, Smith JA et al (2005) HLA-B27 misfolding in transgenic rats is associated with activation of the unfolded protein response. *J Immunol* 175:2438–2448
11. Ordonez A, Snapp EL, Tan L, Miranda E, Marciniak SJ, Lomas DA (2013) Endoplasmic reticulum polymers impair luminal protein mobility and sensitize to cellular stress in alpha -antitrypsin deficiency. *Hepatology* (in press)
12. Gooptu B, Lomas DA (2008) Polymers and inflammation: disease mechanisms of the serpinopathies. *J Exp Med* 205:1529–1534
13. Rottner M, Freyssinet JM, Martinez MC (2009) Mechanisms of the noxious inflammatory cycle in cystic fibrosis. *Respir Res* 10:23
14. Zhao F, Edwards R, Dizon D, Afrasiabi K, Mastroianni JR, Geyfman M et al (2010) Disruption of Paneth and goblet cell homeostasis and increased endoplasmic reticulum stress in *Agr2*^{-/-} mice. *Dev Biol* 338:270–279
15. Kaser A, Lee AH, Franke A, Glickman JN, Zeissig S, Tilg H et al (2008) XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. *Cell* 134:743–756
16. Ozcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Ozdelen E et al (2004) Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* 306:457–461
17. Richardson CE, Kooistra T, Kim DH (2010) An essential role for XBP-1 in host protection against immune activation in *C. elegans*. *Nature* 463:1092–1095
18. Todd DJ, Lee AH, Glimcher LH (2008) The endoplasmic reticulum stress response in immunity and autoimmunity. *Nat Rev Immunol* 8:663–674
19. Paton AW, Beddoe T, Thorpe CM, Whisstock JC, Wilce MC, Rossjohn J et al (2006) AB5 subtilase cytotoxin inactivates the endoplasmic reticulum chaperone BiP. *Nature* 443:548–552