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Protein homeostasis networks in physiology and disease

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Although most text books of biochemistry describe the process of protein folding to a three dimensional native state as an intrinsic property of the primary sequence, it is becoming increasingly clear that this process can go wrong in an almost infinite number of ways. In fact, many different diseases are caused by the misfolding and aggregation of certain proteins without genetic mutations in the primary sequence. An integrative view of the mechanisms that maintain protein folding homeostasis is emerging, which could be thought as a balanced and dynamic network of interconnected processes tightly regulated by a series of quality control mechanisms. This protein homeostasis network involves families of folding catalysts, co-factors under specific environmental and metabolic conditions. Maintaining protein homeostasis is particularly challenging in specialized secretory cells where the high demand for protein synthesis generates a constant source of stress that could lead to proteotoxicity.

Protein folding is assisted and monitored by diverse interconnected processes that follow a sequential pattern over time. The calnexin/calreticulin cycle ensures the proper folding of glycosylated proteins through the secretory pathway, which establishes the final pattern of disulfide bond formation through interactions with the disulfide isomerase ERp57. Coupled to this cycle is the ER-associated degradation (ERAD) pathway, which translocates terminally misfolded proteins to the cytosol for degradation by proteasomes. In addition, macroautophagy is becoming a relevant mechanism for the clearance of damaged proteins and abnormal protein aggregates through lysosomal hydrolysis, a process also referred to as ERAD-II. The folding status at the ER is constantly monitored by the Unfolded Protein Response (UPR), a specialized signaling pathway initiated by the activation of three types of stress sensors. The process underlying the surveillance of protein folding stress by the UPR is not fully understood, but it may require coupling to key folding mediators such as BiP or the direct recognition of the misfolded peptides by stress sensors. The UPR regulates genes and processs related to almost every folding step in the secretory pathway to reduce the load of misfolded proteins, including protein translation into the ER, translocation, folding,

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quality control, ERAD, the redox status, and many other related functions. Protein folding stress is observed in many disease conditions such as cancer, diabetes, and neurodegeneration. For example, abnormal protein aggregation and the accumulation of protein inclusions is associated with Parkinson's and Alzheimer's Disease, and amyotrophic lateral sclerosis. In those diseases and many others, neuronal dysfunction and disease progression correlates with the presence of a strong ER stress response; however, the direct *in vivo* role of the UPR in the disease process has been experimentally defined in only a few cases. Therapeutic strategies are currently being developed to increase protein folding and clearance of misfolded proteins, with the goal of alleviating ER stress.

In this issue of *Current Opinion in Cell Biology* we present a series of focused reviews from recognized experts in the field, that provide an overview of mechanisms underlying protein folding and quality control, and how balance of protein homeostasis is maintained in physiology and deregulated in diseases. Daniela Roth and William Balch integrate the concept of protein homeostasis networks into an interesting model termed FoldFx, showing how the interconnection between different pathways in the context of the cellular proteome determines the energetic barrier required to generate a functional folded peptide. The authors have previously proposed the term *Proteostasis* to refer to the set of interacting activities that maintain the health of the proteome and the organism (protein homeostasis). The ER is a central subcellular compartment for protein synthesis and quality control in the secretory pathway. Yukio Kimata and Kenji Kohno give an overview of the signaling pathways that control adaptation to ER stress and maintenance of protein folding homeostasis. The authors summarize the models proposed so far for the activation of UPR stress sensors, and discuss how this directly or indirectly relates to the accumulation of unfolded proteins in the ER lumen. Chronic or irreversible ER stress triggers cell death by apoptosis. Gordon Shore, Feroz Papa, and Scott Oakes summarize the complex signaling pathways initiating apoptosis by ER stress, where cross talk between the ER and the mitochondria play a central role. The authors focus on addressing the role of the BCL-2 protein family on the activation of intrinsic mitochondrial apoptosis pathways, highlighting different cytosolic and transcriptional events that determine the transition between adaptive responses to apoptosis programmed by the UPR to eliminate irreversibly injured cells.

Although diverse families of chaperones, foldases and co-factors are expressed at the ER, only a few protein folding networks have been well defined. However, molecular explanations for specific substrate recognition and quality control mechanisms are poorly defined. Here we present a series of reviews covering different aspects of protein maturation. Amy Lee summarizes what is known about the biology of the key ER folding chaperone BiP/Grp78, and its emerging role in diverse pathological conditions including cancer. In two reviews, David B. Williams and Linda M. Hendershot describe the best characterized mechanism of protein quality control at the ER, the calnexin cycle. In addition, they give an overview of the function of a family of ER foldases, the protein disulfide isomerases (PDIs), in folding, quality control and degradation of abnormally folded proteins. PDIs are also becoming key factors in establishing the redox tone of the ER. Riccardo Bernasconi and Maurizio Molinari overview the ERAD process and how this pathway affects the efficiency of the protein folding process at the ER and its relation to pathological conditions.

Lysosomal-mediated degradation is becoming a fundamental process for the control of the haft-life of proteins and the degradation of misfolded, aggregate prone proteins. Ana Maria Cuervo reviews the relevance of Chaperone-mediated autophagy in the selective degradation of soluble cytosolic proteins in lysosomes, and also points out a key role for Chaperone-mediated autophagy in the cellular defense against proteotoxicity. David Rubinsztein and Guido Kroemer present two reviews highlighting the emerging relevance of

macroautophagy in maintaining the homeostasis of the nervous system. They also discuss the actual impact of macroautophagy in the clearance of protein aggregates related to neurodegenerative diseases, including Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease among others. In addition, recent evidence suggesting an actual impairment of macroautophagy as a causative factor in aging-related disorders is also discussed.

Alterations in protein homeostasis underlie the etiology of many diseases affecting the nervous system, in addition to cancer and diabetes. Fumiko Urano summarizes the impact of ER stress in β cell dysfunction and death during the progression of type 1 and type 2 diabetes, as well as in genetic forms of diabetes such as Wolfram syndrome. The occurrence of basal ER stress is observed in specialized secretory cells and organs, including plasma B cells. Roberto Sitia covers several aspects of how proteotoxic stresses physiologically contribute to regulate the biogenesis, function and lifespan of B cells, and speculates about the possible impact of ER stress in the treatment of multiple myeloma. Claudio Soto describes the specific role of calcineurin, a key phosphatase in the brain, in the occurrence of synaptic dysfunction and neuronal death in prion-related disorders. We also present provide a review summarizing the emerging role of ER stress and the UPR in most neurodegenerative diseases related to protein misfolding. We also discuss the particular mechanisms currently proposed to be involved in the generation of protein folding stress at the ER in these pathologies, and speculate about possible therapeutic interventions to treat neurodegenerative diseases.

Strategies to increase the efficiency of quality control mechanisms, to reduce protein aggregation and to enhance folding are suggested to be beneficial in the setting of diseases associated with the disruption of protein homeostasis. Finally, Jeffery Kelly overviews recent chemical and biological therapeutic strategies to restore protein homeostasis, which could be achieved by enhancing the biological capacity of the proteostasis network or through small molecule to stabilize misfolding-prone proteins. In summary, this volume of *Current Opinion in Cell Biology* compiles the most recent advances in understanding the impact of protein folding stress in physiology and disease, and integrates a variety of complex mechanisms that evolved to maintain protein homeostasis in a dynamic way in the context of a changing environment. The biomedical applications of developing strategies to cope with protein folding stress have profound implications for the treatment of the most prevalent diseases in the human population.

Biographies

Claudio Hetz PhD is Full Professor at the Institute of Biomedical Sciences of the University of Chile, adjunct professor at Harvard, and co-Director of The Biomedical Neuroscience Institute in Chile. His research focuses on understanding the molecular basis of adaptation to protein folding stress and its relationship to pathological conditions affecting the nervous system.

Laurie H. Glimcher MD is the Irene Heinz Given Professor of Immunology at the Harvard School of Public Health, and Professor of Medicine at Harvard. Her laboratory uses cellular, biochemical and genetic approaches to elucidate the pathways that regulate immune cell development and activation. She identified several novel transcriptional regulatory proteins critical for the function of the immune system and human diseases.