Review

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Control of systemic proteostasis by the nervous system

Pablo Mardones[1,2], Gabriela Martínez[1,2], and Claudio Hetz[1,2,3,4]

[1] Biomedical Neuroscience Institute, Faculty of Medicine, University of Chile, Santiago, Chile
[2] Program of Cellular and Molecular Biology, Center for Molecular Studies of the Cell, Institute of Biomedical Sciences, University of Chile, Santiago, Chile
[3] Neurounion Biomedical Foundation, CENPAR, Santiago, Chile
[4] Department of Immunology and Infectious diseases, Harvard School of Public Health, Boston, MA, USA

Maintenance of organismal homeostasis depends on the integration of intracellular and external signals, involving the ability to detect molecular perturbations. An explosion of studies in model organisms indicates the occurrence of dynamic communication between alarm pathways engaged by protein-folding stress in neurons that activate adaptive programs in peripheral organs to control cellular proteostasis. Here we review emerging concepts that highlight the contribution of the proteostasis network to the regulation of several aspects of animal physiology through central integration of signals spanning multiple tissues and organs. These recent findings uncover a new layer of functional interrelation between cells that handle and orchestrate the global maintenance of the proteome at the organismal level in a cell-nonautonomous manner.

The eukaryotic proteostasis network

Protein folding into native conformations is indispensable to cell survival, manifesting in numerous general and specialized mechanisms of assisted folding and quality control. These pathways provide cells with effective molecular responses to meet environmental challenges that affect the stability of the proteome, including temperature, pH, ionic strength, and oxidative stress [1]. Misfolded proteins usually expose internal domains that are not normally in contact with the milieu (hydrophobic patches, random coils), impacting their structural stability, molecular partnerships, and tendency to aggregate [2]. In turn, cells trigger a series of molecular events that monitor and assist the efficiency of protein folding while removing potentially cytotoxic misfolded proteins and abnormal aggregates [2,3]. These molecular networks maintain protein homeostasis (referred to as proteostasis) under constant surveillance, preventing irreparable cellular damage within a range of suboptimal conditions, beyond which cell death is ultimately triggered.

The proteostasis network can be clustered into a few functional pathways that synergize in proteome housekeeping: the heat shock response (HSR) [4]; the unfolded protein response (UPR) [5,6]; antioxidant responses [7,8]; the ubiquitin–proteasome system [9,10]; the mitochondrial UPR [11]; and macroautophagy (Figure 1) [12,13]. Although the control of intrinsic responses to altered proteostasis (cell-autonomous mechanisms) have been extensively studied, recent advances have revealed the regulation of stress responses at distances, largely mediated by the nervous system, in a cell-nonautonomous manner. In this review we discuss different examples depicting the occurrence of cell-nonautonomous control of the adaptive capacity of a tissue to stress, with an emphasis on neuronal control of systemic proteostasis. We also highlight possible implications for the understanding of how global physiology is integrated in the whole organism.

Neuronal control of systemic HSR and thermoregulation

One of the most-conserved and best-understood regulatory pathways of cellular homeostasis is the HSR [1,4]. The HSR comprises several protein chaperones and chaperonin complexes that assist in the folding of mature and nascent polypeptides in the cytosol, controlled by the prokaryotic transcription factor σ^{32} or its eukaryotic counterpart heat shock factor-1 (HSF1). HSF1 is activated under thermal stress via a combination of mechanisms that include release of inhibitory interactions with chaperone complexes, such as heat shock protein 90 (HSP90), post-translational modifications (phosphorylation, sumoylation, acetylation), and trimerization into its active form triggered by an increase of misfolded proteins [14]. HSF1 not only regulates the expression of HSPs but also controls target genes related to cell differentiation and development [14,15]. The detailed signaling pathways involved in adaptation to protein-folding stress under heat shock are reviewed elsewhere [4,14,15].

Multicellular organisms of diverse taxa such as nematodes, insects, and mammals display this cell-autonomous line of defense against thermal stress, regardless of their particular mechanism of body-temperature regulation. However, the emergence of the nervous system through evolution added an additional layer of control and autonomy to thermoregulation [16].

Thermosensation has been studied in considerable detail, from neuronal circuits to molecular mediators, in

Corresponding author: Hetz, C. (chetz@med.uchile.cl, chetz@hsph.harvard.edu).
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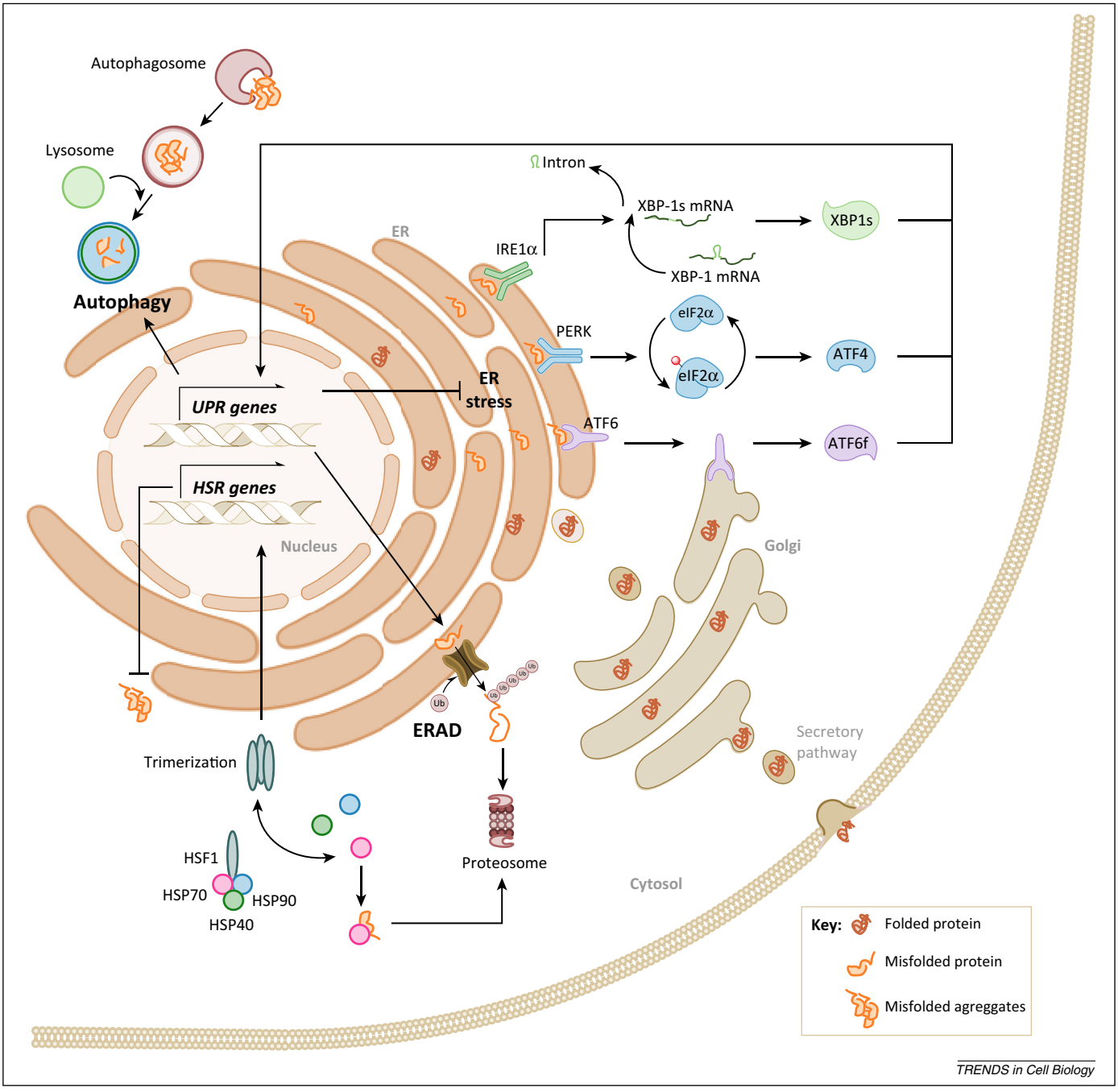

Figure 1. The proteostasis network. Schematic representation of the eukaryotic proteostasis network including the heat shock response (HSR), the unfolded protein response (UPR), the endoplasmic reticulum (ER)-associated degradation pathway (ERAD), autophagy, and the ubiquitin–proteasome system (UPS). These protein quality control systems are mechanistically interconnected to promote dynamic adaptation to protein-folding stress. The HSR is activated on the accumulation of misfolded proteins by multiple mechanisms, including the release of the inhibitory interactions of heat shock factor-1 (HSF1) with heat shock protein 90 (HSP90), which induces its trimerization and transport to the nucleus where it regulates heat shock target genes that enhance protein quality control pathways. The UPR is a complex and integrated signal transduction pathway evolved to overcome the accumulation of unfolded or misfolded proteins at the ER lumen or to trigger cell death on irreversible stress. The autophagy pathway comprises a catabolic process involved in the degradation of protein aggregates and damaged organelles by lysosomes and can be directly activated by the UPR. The ERAD is also modulated by the UPR and targets misfolded proteins from the ER to the cytosol, followed by their ubiquitination and subsequent proteasomal degradation. Finally, the UPS is the major pathway for non-lysosomal degradation of intracellular proteins whose central event is the covalent linkage of ubiquitin to target proteins that are then recognized by the 26S proteasome for proteolysis in the cytosol.

different model systems including *Caenorhabditis elegans*, *Drosophila melanogaster*, and rodents. Invertebrate thermosensory circuits are relatively simple and control thermotactic behavior, guiding the organism toward environments that quickly equilibrate to an optimal body temperature [17]. The simplicity of the *C. elegans* nervous system made it possible to dissect the sensory components that control thermotaxis and circumscribe them to a single pair of amphid finger (AFD) neurons [18,19]. These neurons express a cGMP-dependent cyclic nucleotide-gated channel (CNGC), encoded by *tax-2* and *tax-4*, responsible for detecting minor fluctuations in ambient temperature and producing stimulus-evoked Ca^{2+} transients [20–22]. The AFD-specific guanylyl cyclases GCY-8, GCY-18, and GCY-23 are essential for the activation of this CNGC, as demonstrated by the athermotactic phenotype of triple