Review

CellPress

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).
Keywords: proteostasis; cell-nonautonomous regulation; energy balance; immunity; aging; neurodegeneration; hormesis.

0962-8924/
 http://dx.doi.org/10.1016/j.tcb.2014.08.001

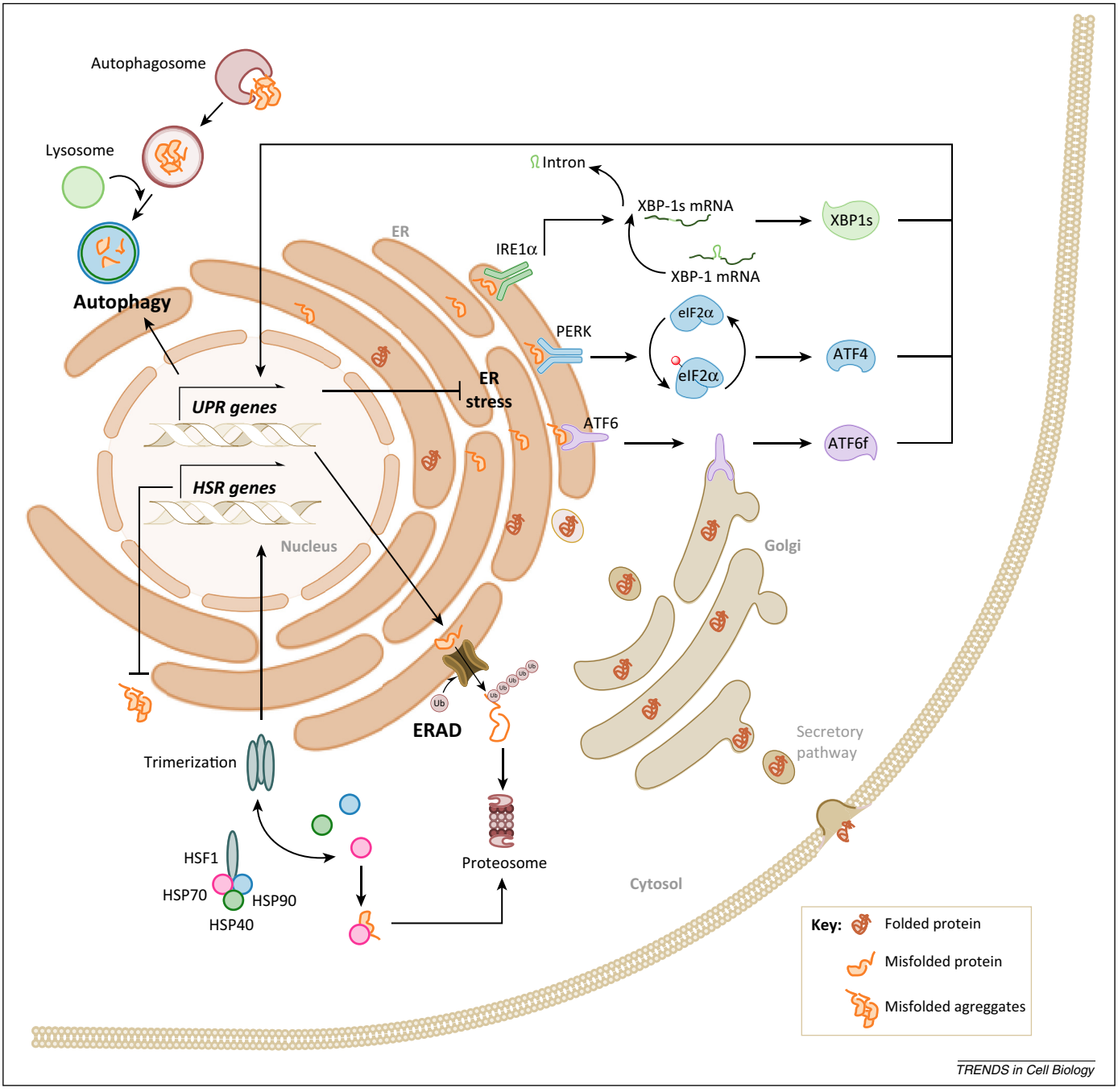

Figure 1. The proteostasis network. Schematic representation of the eukaryotic proteostasis network including the heat shock response (HSR), the unfolded protein response (UPR), the endoplasmic reticulum (ER)-associated degradation pathway (ERAD), autophagy, and the ubiquitin–proteasome system (UPS). 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

mutants [23]. AFD activation is communicated to postsynaptic sensory interneurons (AIY, AIZ), which propagate the signal to motor neurons that ultimately redirect the worms to their preferred temperature [17]. In adult fruit flies, this behavioral modality is more complex and involves distinct sensors of external [24] and internal [25] temperature, mediated by voltage-gated channels of the transient receptor potential (TRP) family that operate as thermosensors in the antenna and within the brain [24,25]. In homeothermic vertebrates, the transient receptor potential vanilloid (TRPV) voltage-gated channel family is activated by both changes in temperature and small molecules that engage heat and cold receptors (e.g., capsaicin, menthol), effectively combining thermo- and chemosensation [26,27].

Until recently, there was no clear evidence connecting the individual response of peripheral cells and the central neuronal responses to thermal stress, but several studies in *C. elegans* unveiled surprising ways of integrating the HSR and protein misfolding at a systemic level through a cell-nonautonomous mechanism. Remarkably, worms subjected to bilateral laser ablation of AFD neurons or with specific mutations affecting AFD-dependent thermosensation (*gcy-8*, *tax-4*) not only are athermotactic [18] but fail to activate the HSR in peripheral tissues, such as the gut, under acute heat stress in an HSF1-dependent manner (Figure 2A) [22]. How do the sensory and behavioral components of neural thermoregulation influence HSF1 activation, protein folding, and thermotolerance at a distance? To date, the molecular mechanism of this phenomenon remains elusive, but it might involve neuropeptide-like molecules released from dense core vesicles in AFD neurons [28]. Given that sensory information processing works at very short timescales and with high dynamic range, stress signals propagating from the central nervous system (CNS) to other tissues might prepare and calibrate slower cellular events at the periphery, such as transcription and translation of HSPs and other protein quality control mechanisms, on an acute change in ambient temperature.

In addition to this feedforward cell-nonautonomous control of peripheral proteostasis, an unexpected feedback mechanism communicating protein misfolding signals from tissues to AFD neurons was recently discovered. *hsf-1* deficiency generates thermotactic defects in worms as a result of changes in the activity of AFD and AWC neurons [29]. These behavioral alterations are rescued by HSF1 expression in the body-wall muscles, suggesting cell-nonautonomous feedback regulation of thermotactic behavior driven by peripheral proteostasis networks [30]. The putative estrogen biosynthetic pathway mediated by *dhs-4* and *cyp-37b1*, together with expression of the putative estradiol nuclear receptor *nhr-69* in AFD neurons, was identified as a necessary component of this transcellular feedback mechanism.

Intriguingly, selective expression of disease-related misfolded proteins in muscle or intestinal cells of *C. elegans* evoked tonic inhibition of peripheral HSR by AFD neurons [28]. This additional cell-nonautonomous mechanism was proposed to maintain responsiveness to acute thermal stress under chronic protein misfolding, allowing peripheral tissues to offset an adequate adaptive response to proteotoxicity. It remains unknown whether this homeostatic connection between peripheral nervous system and CNS pathways of heat stress/protein misfolding operates in homeothermic vertebrates. One of the indications that a similar phenomenon might occur in mammals is an earlier observation linking the release of stress hormones generated along the hypothalamus–pituitary–adrenal axis to the activation of HSF1 and HSP70 in the adrenal gland from rats subjected to restraint stress, which is also observed in rats treated with adrenocorticotropin after surgical removal of the pituitary gland [30]. This result suggests that hormonal stimulation of the adrenal gland may increase the risk of proteotoxicity due to metabolic demands, a phenomenon that may be applicable to other modes of neurotransmission and neuroendocrine stimulation. It remains to be determined whether direct stimulation of TRPVs in mammalian neurons can propagate a signal that upregulates the HSR in innervated tissues.

Thus, a novel concept is emerging where thermosensory neurons may induce a preconditioning effect on peripheral tissues to engage an adaptive reaction to heat shock stress and prepare the cells for otherwise irreversible alterations to the proteome. Fine-tuning of this cell-nonautonomous response could be mediated by a feedback loop from peripheral tissues to the nervous system, implying global and dynamic integration of stress responses throughout the body.

Proteostasis impairment and the neuronal control of lifespan

A hallmark of cellular aging is the progressive loss of proteostasis efficiency involving an attenuated capacity to engage adaptive responses [31]. In addition, some of the downstream targets of the insulin/FOXO pathway (key aging modulators) are proteostasis enhancers [32], which might explain part of its pro-longevity activity.

Several perturbations of the function of the endoplasmic reticulum (ER) can lead to the accumulation of misfolded proteins in the lumen of this organelle, a cellular condition referred to as ER stress. ER stress engages an adaptive reaction, the UPR [6], which is mediated by three main stress sensors known as IRE1α, PERK, and ATF6 (Figure 1). Recent studies have extended the link between the proteostasis network and lifespan modulation to the UPR. Aging *C. elegans* have a drastic reduction in their response to ER stress, reflected in low IRE1α activity, as measured by the expression of its downstream target, the transcription factor XBP1. Hypoactivation of XBP1 in older adults correlated with compromised resistance to systemic ER stress [33]. Previously, it was reported that genetic inactivation of the IRE1α/XBP1 branch of the UPR shortened the lifespan of mutants for *daf-2* (the insulin-like growth factor 1 receptor of *C. elegans*) in a *daf-16/foxo*-dependent manner [34]. Conversely, another study showed that constitutive ectopic expression of *xbp1s* increased ER stress resistance and prolonged lifespan, but only when the transgene was specifically expressed in the nervous system and the intestine [33]. In particular, XBP1s expression in neurons initiated cell-nonautonomous activation of the IRE1α/XBP1 branch of the UPR in the intestine, which was required for lifespan extension [33]. As with the other

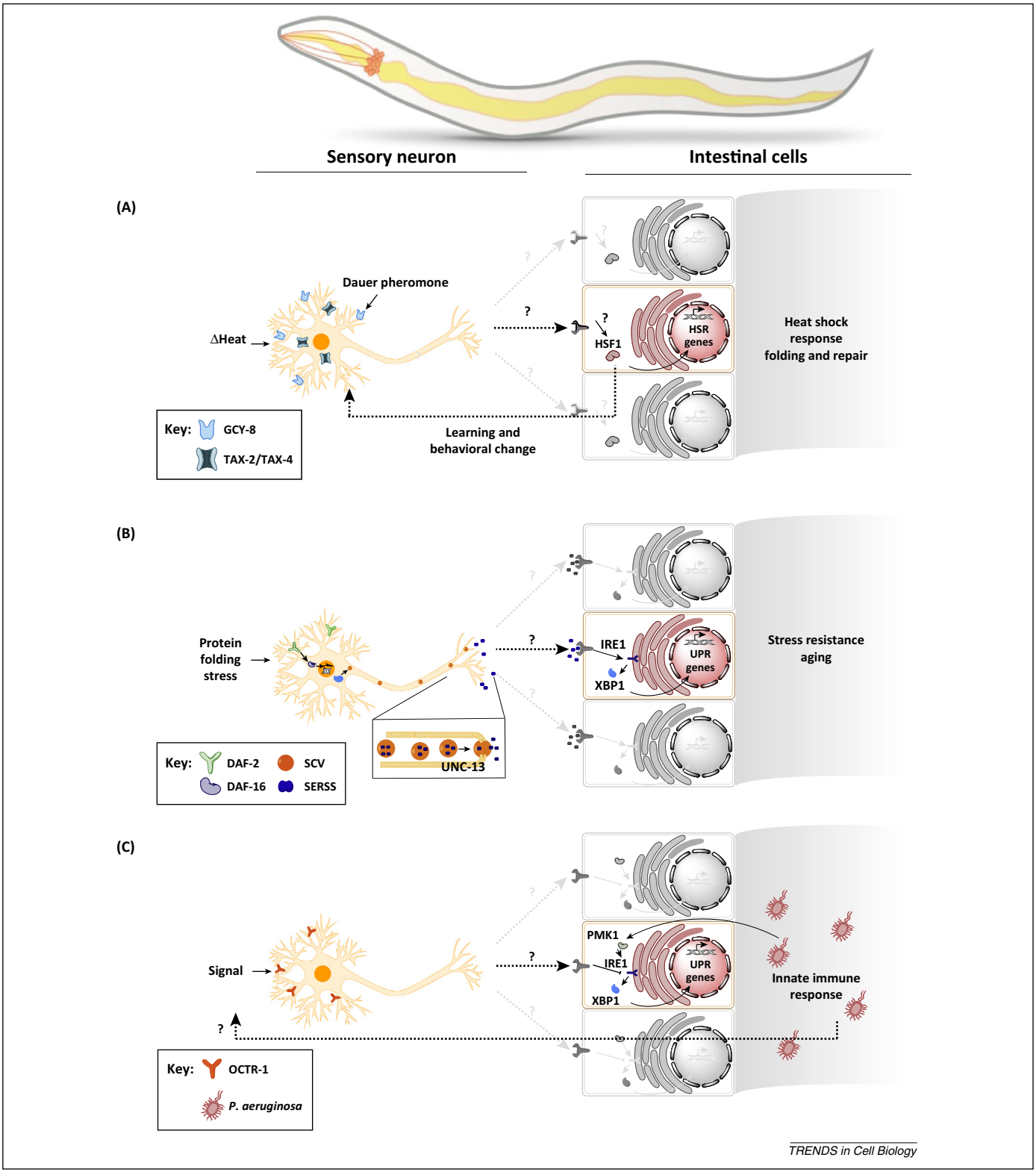

Figure 2. Neuronal control of *Caenorhabditis elegans* proteostasis in thermoregulation, innate immunity, and aging. **(A)** Increases in substrate temperature activate sensory neuronal circuits that regulate thermotactic behavior and modulate the cell-nonautonomous activation of the heat shock response (HSR) in distal tissues. This pathway requires signaling through the guanylyl cyclase GCY-8 and the cGMP-activated channel TAX-2/4. The global HSR in *C. elegans* is negatively modulated by conditions that do not support continuous growth through the dauer pheromone. Peripheral tissues can signal back to the nervous system through steroid hormones to alter behavioral outputs. **(B)** Signaling pathways connected with lifespan control in neurons regulate the unfolded protein response (UPR) in peripheral tissues through a cell-nonautonomous mechanism. The insulin-like growth factor 1 receptor DAF-2 activates the transcription factor DAF-16/FOXO, which modulates lifespan and interacts with XBP1s transcriptional activity. Neuronal XBP1s expression activates the UPR in the intestine, improving stress resistance at a distance and increasing longevity. The molecular signal mediating this effect is unknown but its transmission seems to require the expression of the syntaxin-interacting protein UNC-13, which assists in the secretion of small clear vesicles (SCVs) containing the putative secreted endoplasmic reticulum (ER) stress signal (SERSS). **(C)** Activity of the G protein-coupled receptor OCTR-1, expressed in sensory neurons, represses the IRE1α/XBP1 pathway in intestinal cells of adult worms, modulating innate immunity to pathogens. OCTR-1-expressing neurons also control the p38/PMK-1 mitogen-activated protein kinase (MAPK) pathway in the target organ, which may also modulate this UPR branch.

cell-nonautonomous examples discussed above, the identity of the molecules involved in propagating the signal from neurons to the periphery remains undefined. However, in contrast to the HSR, UPR signaling propagation apparently requires the release of small clear vesicles (SCVs) from synaptic terminals of XBP1s-expressing neurons; possibly involving a small-molecule neurotransmitter rather than a neuropeptide. Overall, this study suggests that the propagation of stress signals through neurotransmission may contribute to keeping peripheral tissues under an adaptive regime [2,3], promoting the expression of UPR target genes to handle environmental challenges to the proteome with a concomitant increase in longevity (Figure 2B). Whether this mechanism of global proteostasis control to handle aging-related disturbances operates in mammals remains an open question.

Apart from the vast range of environmental factors that perturb cellular functions and ultimately lead to lifespan reduction, accumulating discoveries indicate that sensory perception is a potent modulator of organismal longevity [35,36]. In *C. elegans*, for instance, laser ablation of distinct gustatory/chemosensory neurons either extends (ASI, ASG) or shortens (ASK) lifespan [37]. Moreover, in *C. elegans* and *Drosophila* it is possible to revert lifespan extension associated with calorie restriction by exposing experimental animals to food odorants (bacteria and yeast, respectively) [38,39]. The sensory component of lifespan modulation also appears to be connected with insulin/insulin-like peptide signaling and involve the activation of the transcription factor *daf-16/foxo* [40,41]. Remarkably, different sensory modalities affecting lifespan converge into the *daf-16/foxo* signaling pathway [42] and, in *Drosophila*, dFoxo is also associated with lifespan extension through both cell-autonomous and cell-nonautonomous mechanisms requiring insulin-like peptide signaling [43]. To date, the molecular networks connecting sensory perception and lifespan control have not been precisely defined; however, the ability of the nervous system to propagate UPR signals to other tissues, together with the potentially cooperative action of XBP1 and FOXO to extend lifespan [34], opens the intriguing possibility that elements of the UPR may be implicated in the molecular mechanism of the sensory modulation of aging.

Neuronal tuning of innate immunity and proteostasis

One of the first indirect pieces of evidence suggesting that ER stress signals can propagate between cells in mammals comes from studies in cancer models [44]. ER stress has been widely reported as a driver of tumor growth, providing survival signals against microenvironmental changes such as poor nutrient supplies and hypoxia [45–47]. Experimental induction of ER stress in cancer cells has been shown to trigger the secretion of unknown factors that engage a proinflammatory reaction in macrophages, transmitting the ER stress response to these cells [44]. Similarly, ER-stressed tumor cells can release factors that activate the UPR in dendritic cells, having inhibitory effects on immune responses against tumor cells [48]. Many studies have uncovered a crucial role for the IRE1α/XBP1 branch of the UPR in regulating cytokine production and innate immunity through the Toll-like receptors (TLRs) [49]. Remarkably, recent studies in *C. elegans* have demonstrated that neuronal control of the UPR in peripheral tissues also occurs within the context of innate immunity [50]. Targeting specific G protein-coupled receptors in sensory neurons of the worm resulted in the upregulation of non-canonical UPR transcripts (known as *abu* genes) during development, thereby enhancing the resistance to pathogens [51]. In adult animals, this neuronal circuit also negatively modulated the engagement of a classical XBP1-dependent response, directly affecting the survival of animals exposed to pathogenic bacteria [52]. Thus, neuronal control of peripheral proteostasis may also influence the physiology of the immune system (Figure 2C).

Cell-nonautonomous modulation of energy metabolism by the neuronal UPR

The ability to procure food sources, adjust nutrient intake to need, and regulate energy expenditure while maintaining a relatively constant body weight requires a delicate global metabolic balance in the animal. The tissue-specific hormonal regulation of metabolism has been widely studied in mammals and discoveries regarding its relationship to neural circuits controlling hunger and satiety have accelerated, in part due to the expanding obesity epidemic in Western societies. Recent advances have placed the regulation of proteostasis by the UPR in a larger picture of metabolic energy regulation, with implications for obesity, diabetes, and insulin resistance [53,54].

In particular, recent data indicate that IRE1α signaling may have a key role in controlling energy metabolism in a cell-nonautonomous manner [55]. IRE1α is a kinase and endoribonuclease located at the ER membrane that on activation catalyzes the splicing of the mRNA encoding the transcription factor XBP1 to its active form XBP1s [5]. XBP1s translocates to the nucleus and upregulates a cluster of genes involved in protein folding, quality control, lipid metabolism, and many components of the secretory pathway [56,57]. IRE1α also signals through modulation of the RNA stability of a cluster of genes in a cell type-specific manner [known as regulated IRE1-dependent decay (RIDD)] [58], in addition to controlling the activation of stress pathways mediated by c-Jun N-terminal kinase (JNK) and nuclear factor kappa B (NF-κB), among other responses [59].

Consistent with its function in specialized secretory cells [60,61], and its role in coordinating lipid biosynthesis and organelle-membrane remodeling in eukaryotic cells [62,63], the IRE1α/XBP1 branch of the UPR is required for proper insulin production and secretion by pancreatic β cells [64,65], induction of lipogenesis in the liver [66], and the differentiation of adipose tissue in rodents [67]. Pancreas-specific deletion of XBP1 or IRE1α leads to hypoinsulinemia, hyperglycemia, and associated metabolic abnormalities due to a decreased number of β cells in pancreatic islets and a defect in the processing of proinsulin peptides along the secretory pathway [64]. Conversely, a mutation affecting proinsulin folding in mice leads to chronic ER stress and β cell death [68]. In addition, proinsulin mRNA and other transcripts required for insulin secretion are substrates of RIDD, which reduces insulin signaling capacity when IRE1α is overactivated [64]. In the

mouse liver, a high-carbohydrate diet induces XBP1 expression, whereas hepatospecific *Xbp1* ablation leads to pronounced reduction in the expression of lipogenic enzymes and a blunted lipogenic response to carbohydrates [66]. Only recently, the hepatic induction of IRE1α and XBP1s was found to be part of a regulatory response to the fed state and to directly mediate the transcriptional induction of UDP-galactose 4-epimerase (GalE), an enzyme that participates in the generation of substrates for protein glycosylation [69]. Furthermore, inducible XBP1s overexpression in the liver switches this organ to an autonomous postprandial state, dissociated from caloric intake and characterized by a high biosynthetic rate with rerouting of endogenous glucose to protein glycosylation. The net result of this phenomenon is a decrease in glucose release into the circulation, hypoglycemia, and increased insulin sensitivity [69]. Thus, intrinsic cellular stress responses converge into the UPR to modulate glucose and lipid metabolism. However, recent evidence also suggests that activation of the UPR in specific neurons may control cell-nonautonomous responses in the periphery due to global energy requirements (see below).

The pancreas, liver, and adipose tissue, along with the skeletal muscle, are central to glucose/energy homeostasis, owing to their function in the endocrine and metabolic responses to nutritional status/energy expenditure. The brain has a high demand for glucose and manages these responses centrally by sensing circulating glucose, insulin, leptin, and other hormones, peptides, and metabolites carrying information about the nutritional state of the animal (Figure 3A) [70]. The hypothalamus can be considered a central processing unit where many survival signals related to appetite, sleep, and other motivational states converge and the corresponding behavioral outputs are generated [71]. Pro-opiomelanocortin (POMC) and Agouti-related peptide-expressing (AgRP) neurons in the hypothalamic arcuate nucleus respond to insulin, leptin, and free long-chain fatty acids, contributing to orchestrate behavioral responses to hunger and satiety [72].

Diet-induced obesity in rodents stimulates the UPR in the hypothalamus, a finding that has been confirmed in obese human subjects [73,74]. In addition, hypothalamic ER stress induced by a high-fat diet correlates with leptin resistance in mice [74], whereas brain-specific deletion of XBP1 combined with a high-fat diet causes exacerbated leptin resistance, hyperphagia, hypoactivity, and increased adiposity compared with wild type control animals, clearly indicating that hypothalamic ER proteostasis is especially sensitive to dietary changes associated with the metabolic syndrome [74].

A recent study revealed a novel mode of action of hypothalamic ER stress that can modulate global metabolism through a mechanism involving cell-nonautonomous propagation of the UPR to the liver. It was found that POMC-specific transgenesis of active XBP1s protects mice against diet-induced obesity, improves insulin sensitivity, increases energy expenditure, and lowers the endogenous production of glucose by the liver (Figure 3B) [75]. Additionally, treatment of brain tissue with common ER stressors [tunicamycin or dithiothreitol (DTT)] blunts insulin- and leptin-evoked responses in POMC neurons, suggesting that leptin and insulin resistance in obese subjects might be causally connected with early ER stress markers and subsequent inflammation of the hypothalamus. Remarkably, ectopic expression of XBP1s in POMC neurons using transgenic mice triggered the activation of XBP1 mRNA splicing in the liver [75], suggesting, for the first time, the occurrence of cell-nonautonomous UPR signaling propagation across organs in mammals. This circuit enhanced the expression of hepatic GalE and led to a decrease in endogenous glucose release into the circulation [75]. Whether this transcellular UPR activation is directly mediated by a feedforward molecular signal from the brain under nutritional stress or a secondary response to other hypothalamic outputs remains an open question. Interestingly, recent neuroanatomical studies showed the existence of a direct multisynaptic connection between the hypothalamus and the liver that could be explored in future studies to assess this central question [76].

An analogous pathway of cell-nonautonomous regulation of metabolic state through other components of the UPR has been described in *C. elegans*. A dominant mutation in the neuronal insulin-like peptide *daf-28* in two chemosensory neurons (ASI) causes ER stress and UPR activation. This sequence of events proved sufficient to trigger entry into the dauer stage in the absence of environmental stressors [77]. The dauer diapause is a developmental stage characterized by metabolic quiescence, elicited by strongly adverse environmental conditions (starvation, overcrowding, extreme temperatures). In this case, the stress signal propagates from ASI neurons to the rest of the body by unknown mechanisms.

Hormesis and cell-nonautonomous control of proteostasis

Exposure of cells and tissues to low levels (nonlethal) of stress engages adaptive states that render them resistant to a stronger stimulus of the same nature. This mechanism of protection is known as hormesis and has been reported in cells exposed to oxidative stress, heat shock, and ER stress, among other stimuli [78–80]. These cell-autonomous pathways may help protect organisms from an oncoming perturbation of cellular homeostasis. ER-hormesis is emerging as a novel concept in the context of the proteostasis network, with relevance to neurodegenerative diseases involving protein misfolding [81]. Experimental induction of mild ER stress has been shown to protect against Parkinson's disease in mammals and flies through the upregulation of macroautophagy [82]. Similarly, targeting the transcription factor XBP1 in the nervous system provides protection against neurodegeneration, possibly due to upregulation of autophagy [83,84] or adaptive ER stress responses [85]. A recent study in *C. elegans* suggested that expression of heterochromatin factor 1 (HP1) in neurons could affect the sensitivity of intestinal cells to ER stress through a cell-nonautonomous mechanism. This protective response involved the peripheral upregulation of an ER hormesis reaction due to enhanced expression of XBP1 and autophagy [86]. These data suggest that multiple neuronal pathways may influence the adaptive capacity of the whole organism through the modulation of ER hormesis in target tissues.

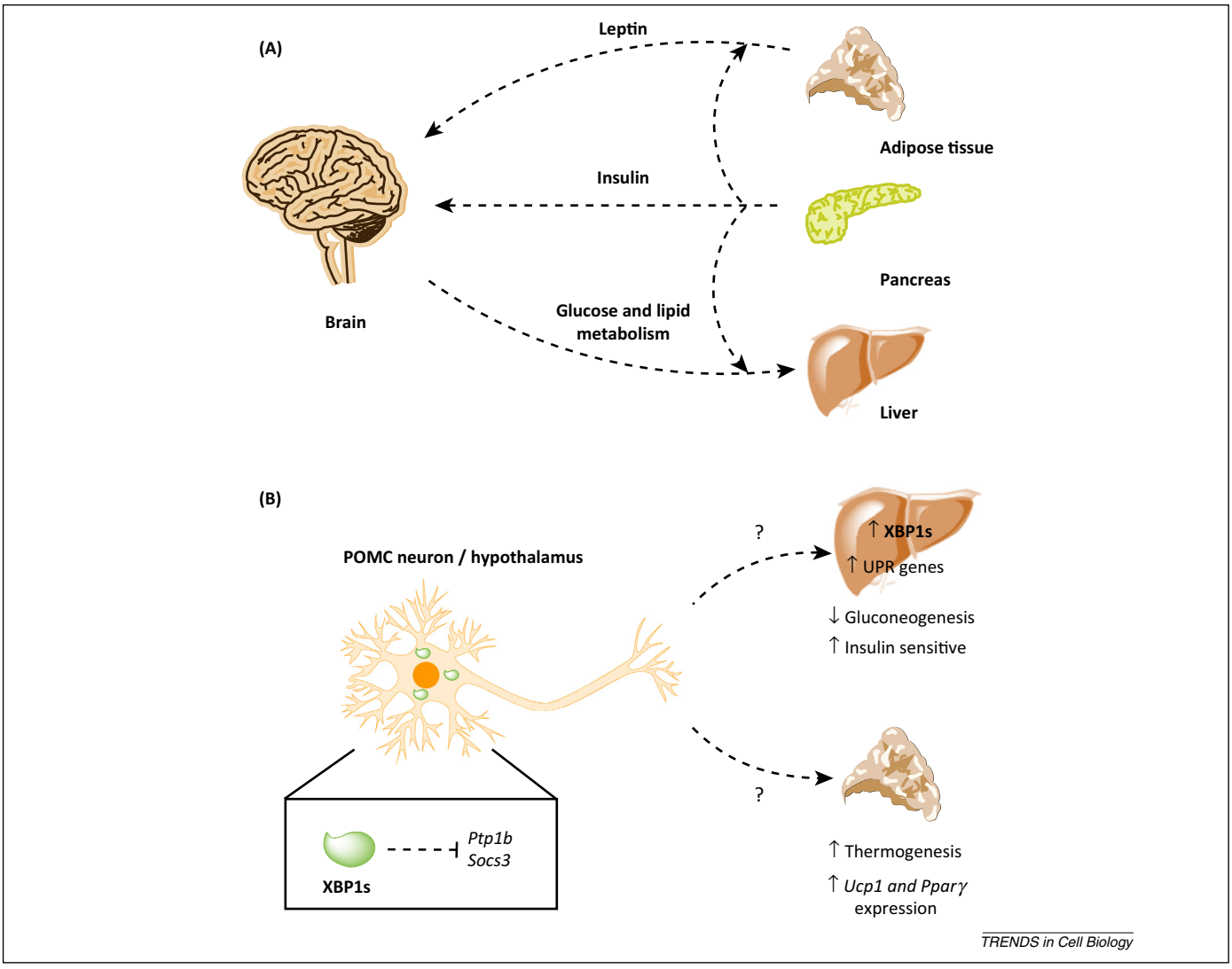

Figure 3. Cell-nonautonomous control of metabolism through hypothalamic unfolded protein response (UPR) signaling in mammals. **(A)** The brain integrates multiple endocrine and nutritional signals that coordinate glucose and energy metabolism. Leptin and insulin signaling converge in hypothalamic neurons, mainly pro-opiomelanocortin (POMC) and Agouti-related peptide-expressing (AgRP) cells, where they activate complex neuronal circuits and signaling pathways that control energy expenditure, feeding behavior, and glucose balance. Insulin receptors are widely expressed throughout the body and have a prominent role in glucose consumption and production in peripheral tissues. The liver can be considered the main regulator of organismal glucose and lipid availability, controlled in part by insulin signaling and neural inputs. **(B)** Expression of transcriptionally active XBP1s in a subset of POMC neurons of the hypothalamic arcuate nucleus inhibits the production of protein tyrosine phosphatase 1B (PTP1B) and suppressor of cytokine signaling 3 (SOCS3), both negative regulators of insulin and leptin signaling in the presence of endoplasmic reticulum (ER) stressors, thus protecting neurons from the deleterious effects of ER stress on these hormonal pathways. Inducible POMC-specific *Xbp1s* expression in mice also generates a hypermetabolic phenotype mediated in part by browning of adipose tissue. Remarkably, expression of XBP1s in these neurons also triggered cell-nonautonomous *Xbp1* splicing and UPR activation in the liver, contributing to improved glucose homeostasis by mimicking a postprandial state of glucose utilization.

Concluding remarks

Here we have reviewed accumulating evidence indicating that diverse physiological processes in the body are orchestrated by the nervous system through fine-tuning of the proteostasis network. These examples illustrate how stress signals spread systemically in the organism of different species and produce either adaptation or non-obvious deleterious effects. From these regulatory pathways, a common theme emerges, where the nervous system exerts previously unrecognized neuroendocrine influence on other tissues to manage and coordinate system-wide stress responses. In turn, peripheral tissues may also signal back to the brain to modulate behavioral outputs. Consequently, the regulation of systemic proteostasis benefits from centralized and distributed control, reflecting how multicellular organisms engage cell-autonomous and -nonautonomous homeostatic mechanisms to respond to environmental changes that affect protein folding and the accumulative damage associated with aging. These events coordinate and possibly predict the need for quantitative adjustments in the buffering capacity of the proteostasis network to manage proteotoxicity. Minor proteotoxic stimuli may be recognized by the nervous system through specialized sensors and propagate rapidly to the rest of the body through electrical or paracrine transmission. Thus, the global robustness of the proteostasis network may be enhanced, generating a state of alert that engages protective mechanisms on an unstressed cell to precondition the tissue to further oncoming perturbations.

Many fascinating questions remain open in this rapidly developing field (Box 1). If stress effectors such as XBP1s or HSF1 are induced on a distal cell in the absence of stress, how are the classical stress sensors activated? This

fundamental issue has not been addressed in the studies reviewed here. Alternatively, cell-nonautonomous mechanisms of proteostasis control may involve the induction of low or even technically undetectable levels of stress in the target cell, triggering a hormetic mechanism of protection. Thus far, in the case of the UPR, the possible recruitment of signaling branches parallel to XBP1 (i.e., PERK and ATF6) has not been explored, and may help in distinguishing between selective signaling activation versus the occurrence of global stress. We can speculate that signals emerging from the nervous system may trigger physiological responses in the target tissue that increase the demand for synthesis and secretion of proteins (basal mild stress), generating a hormetic state at a distance.

Growing evidence indicates that distinct stimuli can engage the UPR in the absence of molecular signatures associated with protein-folding stress, as reported recently for the angiogenic factor vascular endothelial growth factor (VEGF) in endothelial cells [87,88], for glucose-induced insulin production in pancreatic β cells [65], for the activation of TLRs in macrophages [89], and through changes in the lipid composition of ER membranes [90,91]. Similarly, specific extracellular signals such as TLR ligands [92] and fibroblast growth factor 2 (FGF2) [93] can modulate the activity of different branches of the UPR, promoting cell survival under ER stress conditions, opening alternative routes of UPR activation. In addition, recent data show that the electrical activity in motoneurons could engage IRE1α/XBP1 signaling [94] and that the exposure of neurons to brain-derived neurotrophic factor (BDNF) induces XBP1 mRNA splicing [95]. These observations are in agreement with the idea that the UPR has many ER stress-independent functions, where components of the response operate as 'signaling modules' of various interconnected pathways [5]. Thus, we caution that the observed cell-nonautonomous activation of proteostasis responses may be the consequence of regular intercellular communication through signaling pathways that engage UPR components as mediators of alternative physiological outputs unrelated to protein-folding stress, such as energy metabolism and the innate immune response.

Most data available on the cell-nonautonomous control of the proteostasis network have been obtained in *C. elegans*. This is why a major challenge in the field is to uncover analogous mechanisms in mammals and to investigate whether multiple components of the proteostasis network are interconnected in a cell-nonautonomous manner. All of these emerging data in model organisms open previously unpredicted avenues for therapeutic intervention. An elegant study revealed that transcellular transmission of stress signals between peripheral organs occurs through HSP90 expression [96]. In this report, tissue-specific expression of disease-related misfolded proteins triggered local proteostasis perturbations that propagated to other organs. If feedforward/feedback mechanisms of neuronal control of global proteostasis in mammals are discovered in the coming years, transcellular stress signaling may be exploited to target an easily druggable peripheral organ to then affect the adaptive capacity of the brain in the context of neurodegenerative diseases. For example, drugs that efficiently enhance autophagy or stabilize protein conformation but have low access to the CNS due to low blood–brain barrier permeability may prove effective by adjusting neuronal homeostasis through a cell-nonautonomous mechanism.

The identity of the signals emanating from the nervous system to peripheral tissues and organs needs further investigation. Simpler model systems such as *C. elegans* and *Drosophila* might be suitable for pinpointing these molecular targets through a combination of genetic screens for candidate biosynthetic/signaling pathways, pharmacological manipulation of putative neuropeptide/neurotransmitter signaling, and quantitative proteomics. The findings ahead will be crucial not only to complete an important piece of this intriguing biological puzzle, but also to consolidate proteostasis modulation as a promising therapeutic avenue for many devastating diseases involving protein misfolding that affect millions of people worldwide [81,97].

Box 1. Outstanding questions

- What are the signals mediating the propagation of stress responses in a cell-nonautonomous manner?
- Are the HSR and UPR sensors activated through novel stress-independent signaling mechanisms in the target cell?
- Is the cell-nonautonomous control of the proteostasis network conserved in mammals? If so, can peripheral tissues feed back to the nervous system to fine-tune brain function and global proteostasis? What are the implications for animal behavior, innate immunity, and metabolism?
- Can the cell-nonautonomous control of proteostasis be exploited as a therapeutic strategy to treat neurological diseases, metabolic disorders, and other proteotoxic conditions?
- Does the neuronal sensory circuitry in mammals control global proteostasis? Can higher functions of the nervous system (e.g., cognition, perception, motor activity) modulate global proteostasis and its physiological outputs?

Acknowledgments

The authors apologize to all colleagues whose work could not be cited owing to space limitations. This work was funded by FONDECYT No. 1140549, Millennium Institute No. P09-015-F, Ring Initiative ACT1109, FONDEF grant No. D11I1007, CONICYT grant USA2013-0003, the ALS Therapy Alliance, The Michael J. Fox Foundation for Parkinson Research, the Muscular Dystrophy Association, Fundacion COPEC-UC, and the Alzheimer's Disease Association (C.H.) and FONDECYT No. 3140388 (P.M.).

References

1 Powers, E.T. and Balch, W.E. (2013) Diversity in the origins of proteostasis networks – a driver for protein function in evolution. *Nat. Rev. Mol. Cell Biol.* 14, 237–248
2 Wolff, S. *et al.* (2014) Differential scales of protein quality control. *Cell* 157, 52–64
3 Gidalevitz, T. *et al.* (2011) The stress of protein misfolding: from single cells to multicellular organisms. *Cold Spring Harb. Perspect. Biol.* 3, a009704
4 Richter, K. *et al.* (2010) The heat shock response: life on the verge of death. *Mol. Cell* 40, 253–266
5 Hetz, C. (2012) The unfolded protein response: controlling cell fate decisions under ER stress and beyond. *Nat. Rev. Mol. Cell Biol.* 13, 89–102
6 Walter, P. and Ron, D. (2011) The unfolded protein response: from stress pathway to homeostatic regulation. *Science* 334, 1081–1086
7 Morano, K.A. *et al.* (2012) The response to heat shock and oxidative stress in *Saccharomyces cerevisiae*. *Genetics* 190, 1157–1195

8 Niforou, K. *et al.* (2014) Molecular chaperones and proteostasis regulation during redox imbalance. *Redox Biol.* 2, 323–332
9 Varshavsky, A. (2012) The ubiquitin system, an immense realm. *Annu. Rev. Biochem.* 81, 167–176
10 Inobe, T. and Matouschek, A. (2014) Paradigms of protein degradation by the proteasome. *Curr. Opin. Struct. Biol.* 24C, 156–164
11 Haynes, C.M. and Ron, D. (2010) The mitochondrial UPR – protecting organelle protein homeostasis. *J. Cell Sci.* 123, 3849–3855
12 Mizushima, N. and Komatsu, M. (2011) Autophagy: renovation of cells and tissues. *Cell* 147, 728–741
13 Boya, P. *et al.* (2013) Emerging regulation and functions of autophagy. *Nat. Cell Biol.* 15, 713–720
14 Anckar, J. and Sistonen, L. (2011) Regulation of HSF1 function in the heat stress response: implications in aging and disease. *Annu. Rev. Biochem.* 80, 1089–1115
15 Akerfelt, M. *et al.* (2010) Heat shock factors: integrators of cell stress, development and lifespan. *Nat. Rev. Mol. Cell Biol.* 11, 545–555
16 McKemy, D.D. (2007) Temperature sensing across species. *Pflugers Arch.* 454, 777–791
17 Garrity, P.A. *et al.* (2010) Running hot and cold: behavioral strategies, neural circuits, and the molecular machinery for thermotaxis in *C. elegans* and *Drosophila*. *Genes Dev.* 24, 2365–2382
18 Mori, I. and Ohshima, Y. (1995) Neural regulation of thermotaxis in *Caenorhabditis elegans*. *Nature* 376, 344–348
19 Kimura, K.D. *et al.* (2004) The *C. elegans* thermosensory neuron AFD responds to warming. *Curr. Biol.* 14, 1291–1295
20 Komatsu, H. *et al.* (1996) Mutations in a cyclic nucleotide-gated channel lead to abnormal thermosensation and chemosensation in *C. elegans*. *Neuron* 17, 707–718
21 Satterlee, J.S. *et al.* (2004) The CMK-1 CaMKI and the TAX-4 cyclic nucleotide-gated channel regulate thermosensory neuron gene expression and function in *C. elegans*. *Curr. Biol.* 14, 62–68
22 Prahlad, V. *et al.* (2008) Regulation of the cellular heat shock response in *Caenorhabditis elegans* by thermosensory neurons. *Science* 320, 811–814
23 Inada, H. *et al.* (2006) Identification of guanylyl cyclases that function in thermosensory neurons of *Caenorhabditis elegans*. *Genetics* 172, 2239–2252
24 Gallio, M. *et al.* (2011) The coding of temperature in the *Drosophila* brain. *Cell* 144, 614–624
25 Hamada, F.N. *et al.* (2008) An internal thermal sensor controlling temperature preference in *Drosophila*. *Nature* 454, 217–220
26 Caterina, M.J. (2007) Transient receptor potential ion channels as participants in thermosensation and thermoregulation. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 292, R64–R76
27 Pogorzala, L.A. *et al.* (2013) The cellular code for mammalian thermosensation. *J. Neurosci.* 33, 5533–5541
28 Prahlad, V. and Morimoto, R.I. (2011) Neuronal circuitry regulates the response of *Caenorhabditis elegans* to misfolded proteins. *Proc. Natl. Acad. Sci. U.S.A.* 108, 14204–14209
29 Sugi, T. *et al.* (2011) Regulation of behavioral plasticity by systemic temperature signaling in *Caenorhabditis elegans*. *Nat. Neurosci.* 14, 984–992
30 Fawcett, T.W. *et al.* (1994) Effects of neurohormonal stress and aging on the activation of mammalian heat shock factor 1. *J. Biol. Chem.* 269, 32272–32278
31 Ben-Zvi, A. *et al.* (2009) Collapse of proteostasis represents an early molecular event in *Caenorhabditis elegans* aging. *Proc. Natl. Acad. Sci. U.S.A.* 106, 14914–14919
32 Murphy, C.T. *et al.* (2003) Genes that act downstream of DAF-16 to influence the lifespan of *Caenorhabditis elegans*. *Nature* 424, 277–283
33 Taylor, R.C. and Dillin, A. (2013) XBP-1 is a cell-nonautonomous regulator of stress resistance and longevity. *Cell* 153, 1435–1447
34 Henis-Korenblit, S. *et al.* (2010) Insulin/IGF-1 signaling mutants reprogram ER stress response regulators to promote longevity. *Proc. Natl. Acad. Sci. U.S.A.* 107, 9730–9735
35 Linford, N.J. *et al.* (2011) Sensory perception and aging in model systems: from the outside in. *Annu. Rev. Cell Dev. Biol.* 27, 759–785
36 Libert, S. and Pletcher, S.D. (2007) Modulation of longevity by environmental sensing. *Cell* 131, 1231–1234
37 Alcedo, J. and Kenyon, C. (2004) Regulation of *C. elegans* longevity by specific gustatory and olfactory neurons. *Neuron* 41, 45–55
38 Libert, S. *et al.* (2007) Regulation of *Drosophila* life span by olfaction and food-derived odors. *Science* 315, 1133–1137
39 Smith, E.D. *et al.* (2008) Age- and calorie-independent life span extension from dietary restriction by bacterial deprivation in *Caenorhabditis elegans*. *BMC Dev. Biol.* 8, 49
40 Lin, K. *et al.* (1997) daf-16: an HNF-3/forkhead family member that can function to double the life-span of *Caenorhabditis elegans*. *Science* 278, 1319–1322
41 Ogg, S. *et al.* (1997) The fork head transcription factor DAF-16 transduces insulin-like metabolic and longevity signals in *C. elegans*. *Nature* 389, 994–999
42 Apfeld, J. and Kenyon, C. (1999) Regulation of lifespan by sensory perception in *Caenorhabditis elegans*. *Nature* 402, 804–809
43 Alic, N. *et al.* (2014) Cell-nonautonomous effects of dFOXO/DAF-16 in aging. *Cell Rep.* 6, 608–616
44 Mahadevan, N.R. *et al.* (2011) Transmission of endoplasmic reticulum stress and pro-inflammation from tumor cells to myeloid cells. *Proc. Natl. Acad. Sci. U.S.A.* 108, 6561–6566
45 Ma, Y. and Hendershot, L.M. (2004) The role of the unfolded protein response in tumour development: friend or foe? *Nat. Rev. Cancer* 4, 966–977
46 Zanetti, M. (2013) Cell-extrinsic effects of the tumor unfolded protein response on myeloid cells and T cells. *Ann. N. Y. Acad. Sci.* 1284, 6–11
47 Li, X. *et al.* (2011) Unfolded protein response in cancer: the physician's perspective. *J. Hematol. Oncol.* 4, 8
48 Mahadevan, N.R. *et al.* (2012) Cell-extrinsic effects of tumor ER stress imprint myeloid dendritic cells and impair $CD8^+$ T cell priming. *PLoS ONE* 7, e51845
49 Martinon, F. and Glimcher, L.H. (2011) Regulation of innate immunity by signaling pathways emerging from the endoplasmic reticulum. *Curr. Opin. Immunol.* 23, 35–40
50 Aballay, A. (2013) Role of the nervous system in the control of proteostasis during innate immune activation: insights from *C. elegans*. *PLoS Pathog.* 9, e1003433
51 Sun, J. *et al.* (2011) Neuronal GPCR controls innate immunity by regulating noncanonical unfolded protein response genes. *Science* 332, 729–732
52 Sun, J. *et al.* (2012) Organismal regulation of XBP-1-mediated unfolded protein response during development and immune activation. *EMBO Rep.* 13, 855–860
53 Hotamisligil, G.S. (2010) Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* 140, 900–917
54 Lee, J. and Ozcan, U. (2014) Unfolded protein response signaling and metabolic diseases. *J. Biol. Chem.* 289, 1203–1211
55 Mardones, P. *et al.* (2014) Cell-nonautonomous control of the UPR: mastering energy homeostasis. *Cell Metab.* http://dx.doi.org/10.1016/j.cmet.2014.07.009
56 Lee, A-H. *et al.* (2003) XBP-1 regulates a subset of endoplasmic reticulum resident chaperone genes in the unfolded protein response. *Mol. Cell Biol.* 23, 7448–7459
57 Acosta-Alvear, D. *et al.* (2007) XBP1 controls diverse cell type- and condition-specific transcriptional regulatory networks. *Mol. Cell* 27, 53–66
58 Maurel, M. *et al.* (2014) Getting RIDD of RNA: IRE1 in cell fate regulation. *Trends Biochem. Sci.* 39, 245–254
59 Hetz, C. and Glimcher, L.H. (2009) Fine-tuning of the unfolded protein response: assembling the IRE1alpha interactome. *Mol. Cell* 35, 551–561
60 Rutkowski, D.T. and Hegde, R.S. (2010) Regulation of basal cellular physiology by the homeostatic unfolded protein response. *J. Cell Biol.* 189, 783–794
61 Hetz, C. *et al.* (2011) The unfolded protein response: integrating stress signals through the stress sensor IRE1α. *Physiol. Rev.* 91, 1219–1243
62 Ron, D. and Walter, P. (2007) Signal integration in the endoplasmic reticulum unfolded protein response. *Nat. Rev. Mol. Cell Biol.* 8, 519–529
63 Fagone, P. and Jackowski, S. (2009) Membrane phospholipid synthesis and endoplasmic reticulum function. *J. Lipid Res.* 50 (Suppl.), S311–S316
64 Lee, A.H. *et al.* (2011) Dual and opposing roles of the unfolded protein response regulated by IRE1alpha and XBP1 in proinsulin processing and insulin secretion. *Proc. Natl. Acad. Sci. U.S.A.* 108, 8885–8890

65 Lipson, K.L. *et al.* (2006) Regulation of insulin biosynthesis in pancreatic beta cells by an endoplasmic reticulum-resident protein kinase IRE1. *Cell Metab.* 4, 245–254
66 Lee, A.H. *et al.* (2008) Regulation of hepatic lipogenesis by the transcription factor XBP1. *Science* 320, 1492–1496
67 Sha, H. *et al.* (2009) The IRE1alpha–XBP1 pathway of the unfolded protein response is required for adipogenesis. *Cell Metab.* 9, 556–564
68 Wang, J. *et al.* (1999) A mutation in the insulin 2 gene induces diabetes with severe pancreatic beta-cell dysfunction in the Mody mouse. *J. Clin. Invest.* 103, 27–37
69 Deng, Y. *et al.* (2013) The Xbp1s/GalE axis links ER stress to postprandial hepatic metabolism. *J. Clin. Invest.* 123, 455–468
70 Carey, M. *et al.* (2013) Evidence for central regulation of glucose metabolism. *J. Biol. Chem.* 288, 34981–34988
71 Sternson, S.M. (2013) Hypothalamic survival circuits: blueprints for purposive behaviors. *Neuron* 77, 810–824
72 Varela, L. and Horvath, T.L. (2012) Leptin and insulin pathways in POMC and AgRP neurons that modulate energy balance and glucose homeostasis. *EMBO Rep.* 13, 1079–1086
73 Thaler, J.P. *et al.* (2012) Obesity is associated with hypothalamic injury in rodents and humans. *J. Clin. Invest.* 122, 153–162
74 Ozcan, L. *et al.* (2009) Endoplasmic reticulum stress plays a central role in development of leptin resistance. *Cell Metab.* 9, 35–51
75 Williams, K.W. *et al.* (2014) Xbp1s in Pomc neurons connects ER stress with energy balance and glucose homeostasis. *Cell Metab.* http://dx.doi.org/10.1016/j.cmet.2014.06.002
76 Stanley, S. *et al.* (2010) Identification of neuronal subpopulations that project from hypothalamus to both liver and adipose tissue polysynaptically. *Proc. Natl. Acad. Sci. U.S.A.* 107, 7024–7029
77 Kulalert, W. and Kim, D.H. (2013) The unfolded protein response in a pair of sensory neurons promotes entry of *C. elegans* into dauer diapause. *Curr. Biol.* 23, 2540–2545
78 Gems, D. and Partridge, L. (2008) Stress-response hormesis and aging: "that which does not kill us makes us stronger". *Cell Metab.* 7, 200–203
79 Calabrese, E.J. (2013) Hormetic mechanisms. *Crit. Rev. Toxicol.* 43, 580–606
80 Matus, S. *et al.* (2012) Hormesis: protecting neurons against cellular stress in Parkinson disease. *Autophagy* 8, 997–1001
81 Hetz, C. and Mollereau, B. (2014) Disturbance of endoplasmic reticulum proteostasis in neurodegenerative diseases. *Nat. Rev. Neurosci.* 15, 1–19
82 Fouillet, A. *et al.* (2012) ER stress inhibits neuronal death by promoting autophagy. *Autophagy* 8, 915–926
83 Hetz, C. *et al.* (2009) XBP-1 deficiency in the nervous system protects against amyotrophic lateral sclerosis by increasing autophagy. *Genes Dev.* 23, 2294–2306
84 Vidal, R.L. *et al.* (2012) Targeting the UPR transcription factor XBP1 protects against Huntington's disease through the regulation of FoxO1 and autophagy. *Hum. Mol. Genet.* 21, 2245–2262
85 Valdes, P. *et al.* (2014) Control of dopaminergic neuron survival by the unfolded protein response transcription factor XBP1. *Proc. Natl. Acad. Sci. U.S.A.* 111, 6804–6809
86 Kozlowski, L. *et al.* (2014) The *Caenorhabditis elegans* HP1 family protein HPL-2 maintains ER homeostasis through the UPR and hormesis. *Proc. Natl. Acad. Sci. U.S.A.* 111, 5956–5961
87 Karali, E. *et al.* (2014) VEGF signals through ATF6 and PERK to promote endothelial cell survival and angiogenesis in the absence of ER stress. *Mol. Cell* 54, 559–572
88 Urra, H. and Hetz, C. (2014) A novel ER stress-independent function of the UPR in angiogenesis. *Mol. Cell* 54, 542–544
89 Martinon, F. *et al.* (2010) TLR activation of the transcription factor XBP1 regulates innate immune responses in macrophages. *Nat. Immunol.* 11, 411–418
90 Volmer, R. *et al.* (2013) Membrane lipid saturation activates endoplasmic reticulum unfolded protein response transducers through their transmembrane domains. *Proc. Natl. Acad. Sci. U.S.A.* 110, 4628–4633
91 Hou, N.S. *et al.* (2014) Activation of the endoplasmic reticulum unfolded protein response by lipid disequilibrium without disturbed proteostasis *in vivo*. *Proc. Natl. Acad. Sci. U.S.A.* 111, E2271–E2280
92 Woo, C.W. *et al.* (2012) Toll-like receptor activation suppresses ER stress factor CHOP and translation inhibition through activation of eIF2B. *Nat. Cell Biol.* 14, 192–200
93 Li, B. *et al.* (2013) FGF-2 prevents cancer cells from ER stress-mediated apoptosis via enhancing proteasome-mediated Nck degradation. *Biochem. J.* 452, 139–145
94 Kiskinis, E. *et al.* (2014) Pathways disrupted in human ALS motor neurons identified through genetic correction of mutant SOD1. *Cell Stem Cell* 14, 781–795
95 Hayashi, A. *et al.* (2007) The role of brain-derived neurotrophic factor (BDNF)-induced XBP1 splicing during brain development. *J. Biol. Chem.* 282, 34525–34534
96 van Oosten-Hawle, P. *et al.* (2013) Regulation of organismal proteostasis by transcellular chaperone signaling. *Cell* 153, 1366–1378
97 Balch, W.E. *et al.* (2008) Adapting proteostasis for disease intervention. *Science* 319, 916–919