OPINION

Systemic stress signalling: understanding the cell non-autonomous control of proteostasis

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Abstract | Proteome maintenance is crucial to cellular health and viability, and is typically thought to be controlled in a cell-autonomous manner. However, recent evidence indicates that protein-folding defects can systemically activate proteostasis mechanisms through signalling pathways that coordinate stress responses among tissues. Coordination of ageing rates between tissues may also be mediated by systemic modulation of proteostasis. These findings suggest that proteome maintenance is a systemically regulated process, a discovery that may have important therapeutic implications.

Proteins in correctly folded conformations are essential for the structure and function of cells. The crucial task of assisting protein folding and preserving proteins in their native (correctly folded) conformations, even in the face of challenging and stressful cellular situations, is carried out by the molecules and mechanisms of the protein homeostasis (proteostasis) network[1]. Proteostasis mechanisms include regulated protein translation, protein folding by molecular chaperones, and protein degradation pathways such as autophagy and proteasome-mediated degradation. Adjusting the activity of these mechanisms in response to homeostatic variations or stressful conditions is essential to the maintenance of an appropriately folded proteome. This task is achieved by cellular stress response pathways that include the heat shock response (HSR) and the unfolded protein responses in the mitochondria (UPR^{mt}) and endoplasmic reticulum (UPR^{ER}) (BOX 1).

Defects in the mechanisms that control proteostasis severely disrupt cells and tissues. For example, damaged and misfolded proteins, which have a strong tendency to form aggregates, accumulate during ageing[2,3]. These aggregates seem to have a causative role in tissue decline and in the development of diseases that characterize old age. Mounting evidence suggests that one reason for the accumulation of such toxic protein aggregates with age is a breakdown in proteostatis mechanisms, particularly stress responses, which reduces the ability to respond to misfolded proteins as animals get older[4].

Stress responses alert cells to proteotoxic stress (BOX 1). The presence of misfolded proteins within a cell triggers such responses, as exemplified by the ability of cultured cells to respond autonomously to stresses, such as heat, by activating stress response pathways[5–8]. Stress response activation depends on direct detection of misfolded proteins, intrinsic activation of upstream regulatory molecules and also on molecular chaperones that negatively regulate early steps in the stress response pathway. Binding of these chaperones to proteins that have been damaged by a proteotoxic stress enables the pathway to become active[5,6]. These mechanisms act cell autonomously, as stress responses are specifically activated in the cells experiencing the negative effects of stress on proteins (BOX 1).

However, the diseases and cellular damage associated with misfolded proteins are rarely confined to a single tissue. On the contrary, mechanisms that protect against and mechanisms that promote disease progression rely on coordination and communication between cells and tissues[9]. As organisms age, although tissues decline at different rates, the ageing process still occurs in a coordinated and predictable manner[10]. Pathways that can modulate ageing and prevent the associated decline in proteostasis have been shown to act cell non-autonomously, which influences the ageing rate of all tissues through neuronal communication and/or the release of extracellular signalling molecules[11–16]. For example, the release of insulin or insulin-like growth factor 1 (IGF1) is a powerful modulator of longevity and is regulated by signalling mechanisms that operate throughout the organism[11,12,17–20]. Moreover, the extension of lifespan through dietary restriction requires specific neurons to influence the ageing of the whole animal[14], and removal of the germline in *Caenorhabditis elegans* can alter the rate of ageing through steroid hormone signalling and modulation of transcription in the intestine[15,16,21].

The fact that the accumulation of misfolded proteins is a causative factor in ageing indicates that proteostasis might be controlled in a non-autonomous manner. Recent evidence indicates that this is the case. In this Opinion article we only briefly introduce the autonomous proteostasis network (BOX 1), as it has already been extensively reviewed[1,6,22–25]. Instead, we focus on the evidence suggesting that proteostasis cannot be fully understood without appreciating the mechanisms that enable protection of the proteome to be coordinated throughout an organism. We begin with a discussion of the cell non-autonomous activation of stress responses, including cytosolic, ER and mitochondrial quality control pathways, and then describe the ability of pathways that non-autonomously regulate ageing to modulate proteostasis in a systemic manner. Finally, we consider the potential therapeutic implications of these findings and propose future directions for the study of the cell non-autonomous control of proteostasis.

Systemic stress response activation

Cellular stress response pathways detect and resolve proteotoxic stress. Recent evidence has suggested that stress responses that

guard the proteome of the cytosol, ER and mitochondria can be activated cell non-autonomously. This enables stress which has been sensed in one tissue to activate responses in different tissues.

Non-autonomous activation of the HSR. Neurons are an important means of intercellular communication and are integral to the cell non-autonomous control of longevity[12,20]. We now know that the nervous system is also central to the systemic communication of stress responses. *C. elegans* uses the AFD thermosensory neurons and the AIY interneurons to respond behaviourally to changes in temperature[26].

Box 1 | **Cellular stress responses**

Proteostasis is ensured by the coordinated regulation of mechanisms governing protein translation, folding, trafficking and degradation. Protein misfolding is detected by compartment-specific stress response pathways, which adjust the activity of effector mechanisms of the proteostasis network to ameliorate the misfolded protein load[1,6,22–25]. Autonomous regulation occurs through direct detection of misfolded proteins, intrinsic properties of upstream regulatory molecules and through inhibition of upstream activating molecules by chaperones, which are sequestered by misfolded proteins during times of stress.

The HSR

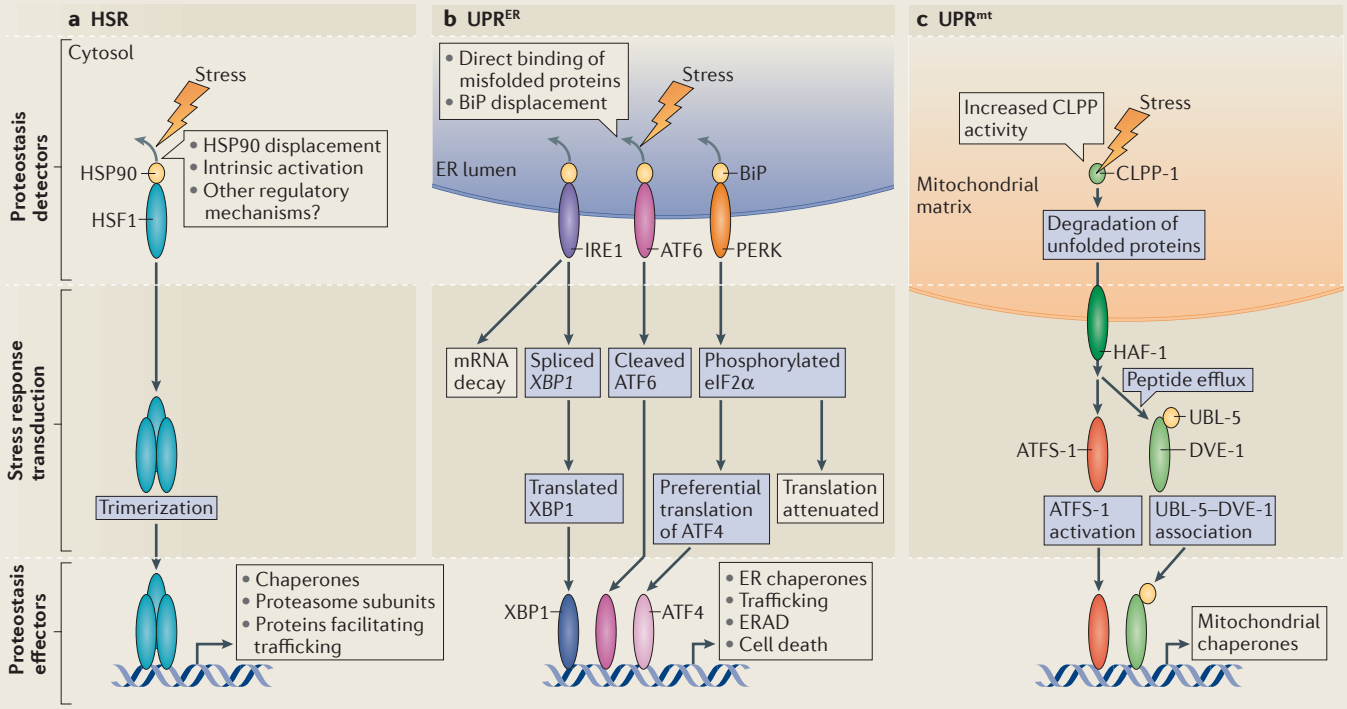
The cytoplasmic heat shock response (HSR) (see the figure, part **a**) is regulated by the heat shock factor (HSF) transcription factor family, primarily HSF1, which responds to numerous proteotoxic insults[24]. When released from its basal inhibited state (bound to heat shock protein 90 (HSP90), HSF1 trimerizes and binds to heat response elements in the genome to upregulate networks of genes, including multiple cytosolic chaperone families and proteasome subunits, which culminates in the improvement of protein folding, increased efficiency of protein trafficking pathways and increased protein degradation.

The UPR^{ER}

Proteostasis surveillance in the endoplasmic reticulum (ER) is mediated by the unfolded protein response (UPR^{ER}), which is activated by an imbalance between unfolded proteins inside the ER and the capacity of the ER proteostasis machinery[6] (see the figure, part **b**). Such imbalances activate three signalling pathways, resulting either in attempts to ameliorate the imbalance or in cell death. These three branches each have an upstream 'detector' component — inositol-requiring protein 1 (IRE1), activating transcription factor 6 (ATF6) and protein kinase RNA-like ER kinase (PERK), which are activated by direct binding to misfolded proteins and are released from inhibition by the molecular chaperone binding immunoglobulin protein (BiP) — each linked to a downstream transcriptional response that induces chaperone expression, membrane expansion, increased efficiency of membrane trafficking pathways, degradation mechanisms (such as ER-associated protein degradation (ERAD)) or cell death. Translation can also be reduced to decrease the load of proteins entering the ER. Translational reduction is primarily mediated through phosphorylation of eukaryotic translation initiation factor 2α (eIF2α) by PERK, which leads to decreased overall rates of translational initiation. However, preferential translation of specific mRNAs also occurs, including the UPR^{ER} transcription factor ATF4. In addition, ER-localized transcripts are degraded through regulated mRNA decay (RIDD) by IRE1.

The UPR^{mt}

Mitochondria possess an adaptive quality control response that detects disturbances in the stoichiometry of mitochondrial proteins, which increases expression of the mitochondrial protease caseinolytic peptidase P (CLPP) and matrix-localized chaperones that aid in folding and import[25] (see the figure, part **c**). Screening in *Caenorhabditis elegans* has identified mitochondrially- and nuclearly-localized proteins that probably form a mitochondrial UPR (UPR^{mt}) pathway, in which the half transporter 1 (HAF-1) ATP-binding cassette (ABC) transporter at the mitochondrial membrane enables an efflux of peptides, generated by the CLPP-1 protease, into the cytosol. This leads to activation of the transcription factors ATFS-1 (activating transcription factor associated with stress 1) and DVE-1 (defective proventriculus 1), association of the cofactor UBL-5 (ubiquitin-like 5) with DVE-1 and transcriptional upregulation of targets that include mitochondrial chaperones.



XBP-1, X box-binding protein 1.

Surprisingly, activity of the AFD or AIY neurons is also essential for full activation of the HSR, which is the cytosolic response to misfolded proteins dependent on the heat shock transcription factor 1 (HSF-1)[24,27] (BOX 1). Worms that lack functional AFD neurons fail to accumulate heat shock proteins (HSPs) in response to heat stress, which results in reduced thermotolerance and a shorter lifespan at high temperatures[27,28]. However, counter-intuitively, animals that lack AFD neurons and an intact HSR are more resistant to the effects of chronic expression of misfolded proteins in muscle cells[29]. The role of the nervous system in controlling HSR activation may extend to other neurons of the broader thermosensory circuit. This is suggested by the requirement for *GPCR thermal receptor 1* (*gtr-1*), which is expressed in chemosensory neurons that are implicated in thermoregulation, in systemic HSR activation and in suppressing resistance to the chronic stress associated with misfolded proteins[30–32]. In addition, release of acetylcholine (ACh) or GABA (γ-aminobutyric acid) from stimulatory or inhibitory motor neurons can increase or decrease, respectively, aggregation of poly-Gln repeats in postsynaptic muscle cells[33].

Neurons are not alone in mediating systemic activation of cytosolic chaperones. Muscle-specific expression of metastable proteins that require chaperone activity to remain folded can induce multi-tissue activation of the chaperone heat shock protein 90 (HSP90). Moreover, expression of HSP90 in tissues other than muscle can protect against the misfolding of proteins in muscle cells[34]. Despite this protection from the chronic stress of misfolded proteins, however, tissue-specific HSP90 expression fails to activate the HSR and animals become hypersensitive to acute stress induced by heat shock. Conversely, tissue-specific knockdown of HSP90 activates a systemic HSR and increases resistance to heat stress.

Finally, the HSR in peripheral tissues of mammals is also subject to neuroendocrine regulation, as the hypothalamic–pituitary–adrenal axis regulates adrenal HSF1 levels. Restrained, and thus stressed, animals with higher levels of cortisol, which is secreted by the pituitary gland, show increased trimerized HSF1 with higher DNA binding activity and increased levels of the HSP70 chaperone in the adrenal glands[35].

These studies indicate that control of HSR activation is integrally regulated by inter-tissue communication (FIG. 1). They also suggest an interesting inverse relationship between responses to acute and chronic cellular stresses. Although no specific signalling molecules or distal cell receptors that mediate these effects have yet been identified, there are intriguing clues. Importantly, the effect of the AFD neurons on misfolded protein expression depends on the ability to release dense core vesicles, which implies the role of a secreted neuropeptide-like signalling molecule in this process[29,36]. Lifespan regulation by the same neurons seems to rely on a steroid hormone signalling pathway[28]. The *trans*-tissue effects on protein folding mediated by HSP90 also seem to involve the cell fate- and dietary restriction-regulating FOXA (forkhead box A) transcription factor PHA-4 (defective pharynx development 4)[34]. Determining the roles of and the connections between these pathways, as well as the identification of specific signalling mediators, is essential to understand the systemic nature of the HSR.

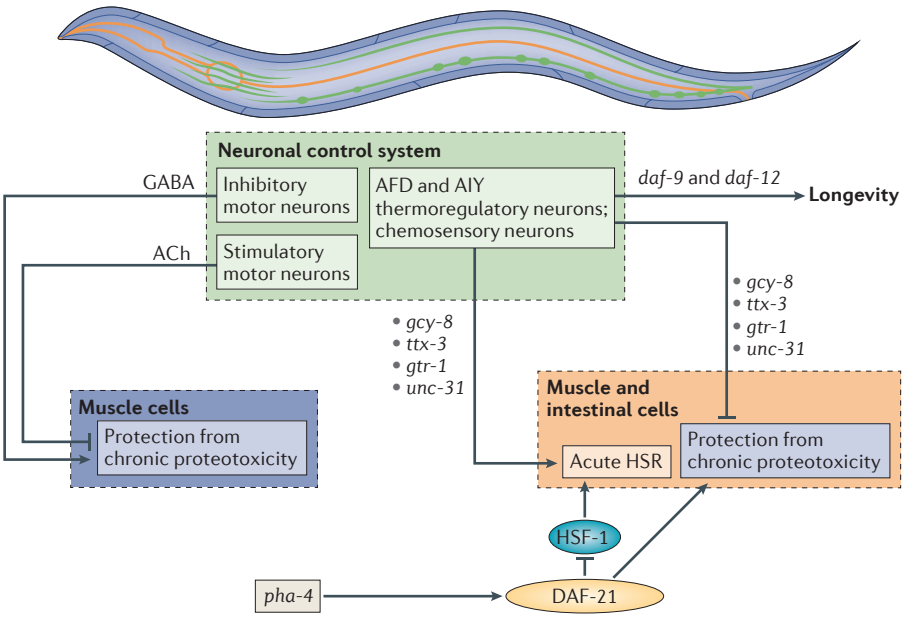


Figure 1 | **A model for the cell non-autonomous regulation of the cytosolic HSR in *Caenorhabditis elegans*.** Release of the neurotransmitters GABA (γ-aminobutyric acid) or acetylcholine (ACh) from inhibitory and stimulatory motor neurons can activate or suppress, respectively, heat shock factor 1 (HSF-1)-mediated protection against proteotoxicity in muscle cells. Activation of neurons of the thermoregulatory circuit by increased temperature triggers the activation of the heat shock response (HSR) in intestinal cells, which is protective under conditions of acute stress. Neuronal genes involved in the activation of this pathway include *guanylyl cyclase 8* (*gcy-8*), the LIM homeodomain-containing *abnormal thermotaxis 3* (*ttx-3*), the G protein-coupled receptor (GPCR) *GPCR thermal receptor 1* (*gtr-1*), and the CAPS homologue *uncoordinated 31* (*unc-31*). However, the specific roles of these molecules are so far unclear. These neurons also inhibit the protective effects of HSF-1 against chronic proteotoxic stress. Activation of thermoregulatory neurons leads to increased longevity through the abnormal dauer formation 9 (DAF-9) and DAF-12 steroidal signalling pathway. Finally, expression levels of DAF-21 (the homologue of heat shock protein 90 (HSP90) in *C. elegans*), which mediates the folding of client proteins but also inhibits HSF-1 and its downstream protective effects, can be communicated between tissues dependent on the defective pharynx development 4 (PHA-4) transcription factor.

Non-autonomous activation of the UPR^{mt}. The existence of an UPR that specifically aims to detect and to respond to misfolded proteins in the mitochondria has only recently been appreciated[25,37–40] (BOX 1). The non-autonomous nature of this response was discovered through efforts to determine the tissues in *C. elegans* in which the reduction of the mitochondrial electron transport chain (ETC) subunit levels leads to increased longevity[13,41]. Surprisingly, neuron-specific knockdown of ETC components leads to upregulation of mitochondrial stress responses in non-neuronal tissues[13]. The specific knockdown of a subunit of the respiratory chain complex IV within neurons extended lifespan to the same degree as knockdown in the entire organism, and it also upregulated transcription of mitochondrial chaperones in the intestine (FIG. 2).

Non-autonomous signalling of mitochondrial stress is not confined to invertebrates. Signalling from the muscle to peripheral

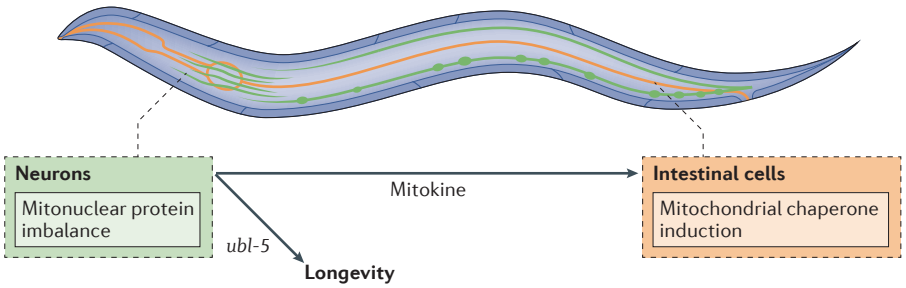


Figure 2 | **Cell non-autonomous regulation of the UPR^{mt} in *Caenorhabditis elegans*.** Imbalance between mitochondrial- and nuclear-encoded proteins in neurons gives rise to mitochondrial unfolded protein response (UPR^{mt}) activation in intestinal cells, and increased longevity through the UPR^{mt} regulator ubiquitin-like 5 (UBL-5). The proposed secreted mediator of this communication between neurons and intestine has been termed a 'mitokine'.

tissues in response to mitochondrial dysfunction in mice is mediated by fibroblast growth factor 21 (FGF21) signalling[42]. This signalling results in resistance to obesity and improved insulin sensitivity, but it has not yet been shown to be dependent on the mitochondrial quality control machinery in non-muscle tissues. Interestingly, FGF21 has been suggested as a novel biomarker for the severity of mitochondrial dysfunction in patients with primarily muscle-related mitochondrial disease[43]. In addition, recent evidence has demonstrated that stoichiometric imbalance in mitochondrial proteins, which is induced by lower levels of mitochondrial ribosomal proteins, or by increased NAD^+ levels and enhanced sirtuin activity, is associated with UPR^{mt} activation and delayed ageing in mice, as well as in *C. elegans*. This suggests mitonuclear protein imbalance as a conserved regulator of longevity and implies that non-autonomous regulation of the mammalian UPR^{mt} might also have a fundamental role in this process[44,45].

Again, molecular mediators of UPR^{mt} transmission have so far not been identified. One group of candidate signalling molecules is the recently described mitochondrially-derived peptides (MDPs) — novel peptides that are encoded within the mitochondrial genome. An example is humanin, a secreted MDP that is stress-responsive and has cytoprotective functions[46,47]. Further research is required to shed light on the potential role of these enigmatic peptides in non-autonomous UPR^{mt} function.

Non-autonomous activation of the UPR^{ER}. Another major stress response, the UPR^{ER}, consists of three primary signalling pathways that monitor the folding of proteins within the ER[6] (BOX 1) and it is also regulated cell non-autonomously. Evidence for the neuronal control of this pathway in *C. elegans* initially emerged from studies of the innate immune response, which requires UPR^{ER} activation[48,49]. Disabling specific neurons through mutation of the G protein-coupled receptor *octopamine receptor 1* (*octr-1*) increases expression of non-canonical UPR^{ER} genes, which induces resistance to bacterial pathogens[50,51]. Animals with a mutation in *octr-1* also have increased organism-wide expression of targets of the canonical IRE-1 (inositol-requiring protein 1)–XBP-1 (X box-binding protein 1) UPR^{ER} pathway[52] (BOX 1). These studies imply that loss of *octr-1* function disables a pathway that suppresses UPR^{ER} activity in non-neuronal tissue under basal conditions in adult animals. Additional evidence that the UPR^{ER} can be activated cell non-autonomously has come from the expression of the spliced and active form of the UPR^{ER} transcription factor XBP-1, *xbp-1s*, in the neurons of *C. elegans*, which induces distal UPR^{ER} activation in the intestine that leads to increased stress resistance and longevity[53]. Again, the conclusion is that neurons exert tight control over the coordination of UPR^{ER} activation across animal tissues (FIG. 3A).

Intriguingly, this coordination is also not specific to invertebrates. Activation of the UPR^{ER} in tumour cell lines leads to UPR^{ER} activation and the production of pro-inflammatory cytokines in macrophages, which suggests coordination of this response between human tissues[54]. In addition, medium in which ER-stressed tumour cells

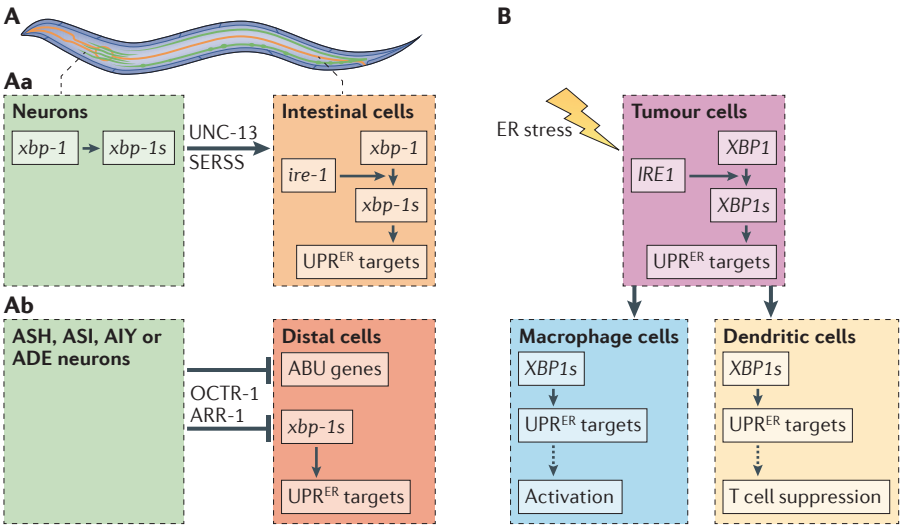


Figure 3 | **Cell non-autonomous regulation of the UPR^{ER} in *Caenorhabditis elegans* and mammalian cells. A** | In *Caenorhabditis elegans*, two models for neuronal control of the endoplasmic reticulum (ER)-mediated unfolded protein response (UPR^{ER}) have been proposed. **Aa** | Expression of the spliced and activated form of the UPR^{ER} transcription factor X box-binding protein 1 (XBP-1), *xbp-1s*, in neurons leads to activation of inositol-requiring protein 1 (IRE-1) and XBP-1 and to transcription of UPR^{ER} targets in distal intestinal cells, which is dependent on the release of a secreted signal (the secreted ER stress signal (SERSS)) that is mediated by uncoordinated 13 (UNC-13), a regulator of syntaxin. **Ab** | The second model suggests that expression of octopamine receptor 1 (OCTR-1), a G protein-coupled receptor, and arrestin 1 (ARR-1; a homologue of β-arrestin) in the chemosensory ASH, ASI, AIY or ADE neurons functions to suppress XBP-1 activation and expression of the non-canonical activated in blocked unfolded protein response (ABU) UPR^{ER} genes in distal cells under basal unstressed conditions. **B** | In human cell culture and mouse models, induction of ER stress and splicing of *XBP1* in tumour cells has been shown to induce UPR^{ER} activation and *XBP1* splicing in macrophages and dendritic cells, which results in activation and a suppressive phenotype that favours tumour growth.

have been cultured can induce the UPR^{ER} in dendritic cells, which activates them and leads to a suppressive phenotype that impairs T cell proliferation and facilitates tumour growth[55] (FIG. 3B). However, neither the invertebrate studies nor the cell culture studies have identified an inter-tissue signalling molecule that directly activates the UPR^{ER}. The ability of neurons to induce distal UPR^{ER} activation in *C. elegans* requires *uncoordinated 13* (*unc-13*), a mediator of neuronal vesicle release[56], which suggests that a secreted factor is involved in signal transmission; however, the identity of this secreted molecule is unknown[53].

The UPR^{ER} can be activated in multiple tissues by systemic changes in physiology: for example, when levels of glucose or oxygen decrease[57,58]. It is also induced as a response to increased protein production, as seen in the intestinal cells of *C. elegans* when an immune response is initiated[48]. The HSR and UPR^{mt} may be similarly systemically activated as a response to global changes in physiology. This raises the important question of whether the disturbance of protein folding in one tissue may indirectly activate stress responses in other tissues, through either downstream global changes in physiology or functional interconnections between tissues. Nonetheless, the evidence supporting the role of specific neurons and mediators of neuroendocrine signalling suggests that specific signals do exist to mediate distal stress response activation[27,29,30,50,52,53]. Furthermore, the specific activation of the UPR^{mt} or UPR^{ER}, rather than other stress responses, downstream of the activation of each pathway in neuronal cells implies the existence of specialized cell non-autonomous stress signalling pathways[13,53]. The possibility of indirect activation of stress response pathways should, however, be kept in mind when assessing observations of inter-tissue coordination between stress responses.

Ageing and long-range proteostasis

Although we have only recently begun to understand the ways in which proteostasis status can be directly communicated between tissues, the non-autonomous nature of ageing and its modulation has been long appreciated. Nonetheless, through studies in model organisms, it is becoming increasingly apparent that one way in which non-autonomous pathways influence ageing is by the long-range control of specific cellular proteostasis mechanisms. Two such pathways that systemically regulate proteostasis are the insulin signalling and germline longevity pathways.

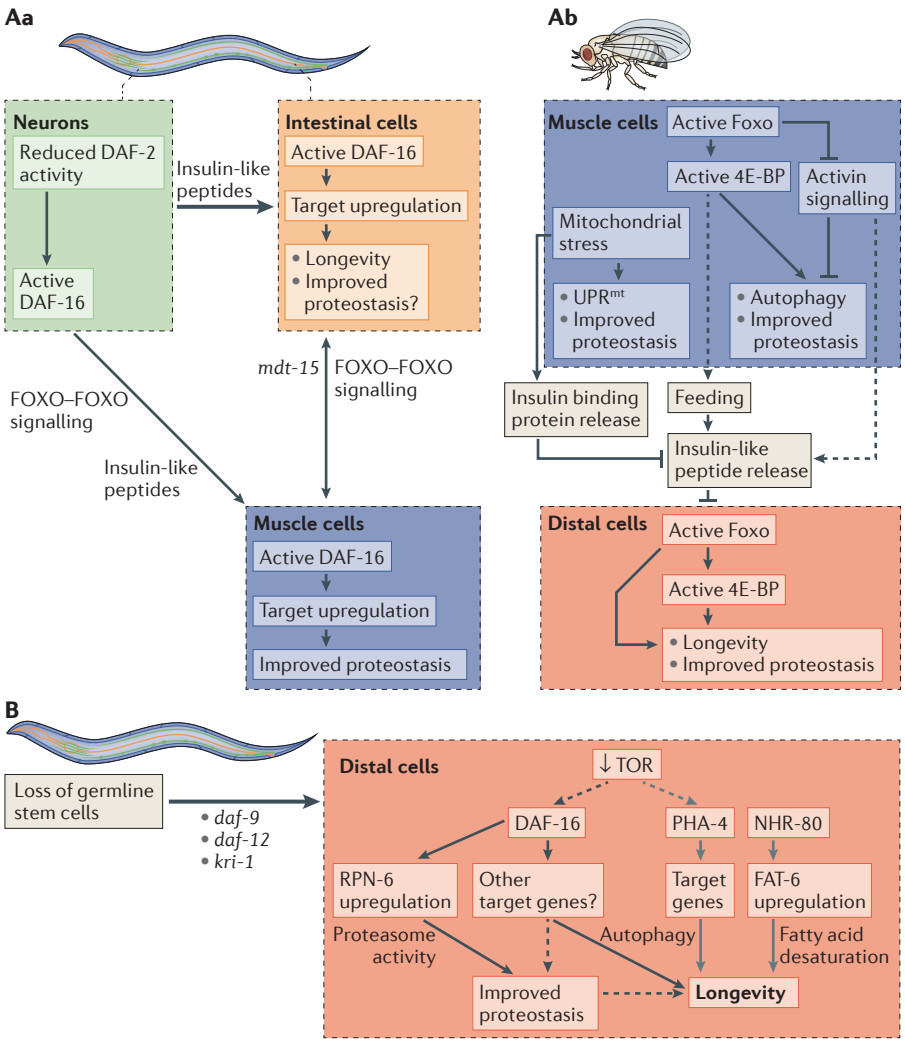


Figure 4 | **Cell non-autonomous regulation of proteostasis by insulin-like signalling and gonadal signalling.** **A** | Insulin-like signalling. **Aa** | In *Caenorhabditis elegans*, reduced activity of the abnormal dauer formation 2 (DAF-2) insulin-receptor homologue in neurons results in activation of the DAF-16 insulin-like signalling transcription factor in intestinal and muscle cells. Activation of DAF-16 may occur through two mechanisms: changes in insulin-like peptide release and/or a novel forkhead box O (FOXO)–FOXO signalling pathway, which both lead to upregulation of different sets of DAF-16 target genes. DAF-16 activation in intestinal cells results in extended longevity, whereas DAF-16 activation in muscle cells leads to improvements in proteostasis. Bidirectional communication of DAF-16 activity between these tissues depends on the transcriptional co-regulator mediator 15 (MDT-15). **Ab** | In *Drosophila melanogaster*, activity of Foxo causes an increase in activity of the Foxo target 4E-BP, a regulator of translation. 4E-BP activity improves muscle cell proteostasis and delays muscle decline, which is mediated in part by autophagy. Moreover, 4E-BP activity results in changes in feeding behaviour, which alters insulin-like peptide release and therefore the regulation of Foxo activity and proteostasis in distal tissues, and ultimately influences longevity. Activation of Foxo in muscle cells also reduces activin signalling, which leads to an increase in autophagy, improved proteostasis and a reduction in insulin-like peptide release from the brain. Finally, mitochondrial stress activates the mitochondrial unfolded protein response (UPR^{mt}) in muscles, increasing proteostasis and the release of an insulin-binding protein, Ecdysone-inducible gene L2 (ImpL2), which reduces systemic insulin circulation and increases longevity. **B** | Gonadal signalling in *C. elegans*. Loss of germline stem cells activates signalling pathways involving DAF-12, DAF-9 and krev interaction trapped/cerebral cavernous malformation 1 (KRI-1) that upregulate or downregulate multiple pathways in distal cells to increase longevity (for example, target of rapamycin (TOR)). Proteostasis and stress resistance are also increased, and this is at least in part mediated by an increase in proteasome activity through DAF-16-mediated upregulation of the proteasome subunit regulatory particle non-ATPase 6 (RPN6). Solid arrows indicate direct regulatory interactions, dashed arrows represent regulation that may be indirect. Black arrows indicate pathways that regulate longevity and proteostasis; grey arrows indicate pathways known to influence lifespan, but that are not currently known to modify proteostasis. FAT, fatty acid desaturase; NHR, nuclear hormone receptor; PHA, defective pharynx development.

Insulin signalling

The insulin and IGF1-like signalling (IIS) system is a powerful modulator of lifespan in a range of organisms from invertebrates to mammals[17–20]. It operates in an inherently non-autonomous manner through the release of insulin and/or IGF1-like peptides. For example, activity of abnormal dauer formation 2 (DAF-2), the only human insulin receptor homologue in *C. elegans*, is required in neurons to extend lifespan, whereas the FOXO transcription factor DAF-16 is required to extend lifespan in the intestine of the animal[11,12,59]. Similarly, expression of Foxo in *Drosophila melanogaster*, specifically in the fat body, is sufficient to increase longevity and stress resistance[18,19], and adipose tissue-specific knockout of the IGF receptor is sufficient to extend longevity in mice[60]. Reduced IIS influences multiple cellular processes to extend longevity, including improvements in cellular proteostasis in multiple tissues[61–67].

Evidence now suggests that IIS-regulated FOXO transcription factors are themselves able to affect proteostasis non-autonomously (FIG. 4A). Specific intestinal expression of *daf-16* in *C. elegans* induces target gene expression in muscle cells, prevents muscle deterioration with age and protects against the toxicity of muscle-specific misfolded proteins; *daf-16* expression in muscle cells can influence target gene expression in the intestine[59,68]. This implies a signalling mechanism that enables the communication of *daf-16* activation between tissues, with a non-autonomous increase in proteostasis capacity (FIG. 4Aa). In *D. melanogaster*, expression of Foxo in muscle cells is sufficient to extend longevity and to rescue proteostasis in multiple tissues. This is mediated by the Foxo target 4E-BP (also known as Thor), which improves muscle cell proteostasis and changes feeding behaviour, leading to changes in systemic insulin signalling, longevity and improvements in proteostasis in distal tissues[65] (FIG. 4Ab). In addition, reduced expression of the activin-like ligand *dawdle*, which is repressed by Foxo, in muscle cells leads to improved proteostasis through transcriptional induction of the autophagy gene *Atg8a* and subsequent increased levels of autophagy; this results in systemic effects on insulin secretion and longevity[66]. Finally, recent evidence indicates that induction of mitochondrial stress in *D. melanogaster* muscle cells improves the function of ageing muscles and increases longevity through two mechanisms: an autonomous induction of the UPR^{mt} and a non-autonomous activation of systemic insulin signalling through transcriptional induction of an insulin-binding protein, Ecdysone-inducible gene L2 (ImpL2), which leads to improved proteostasis by increasing autophagy[67]. It is crucial to determine whether these non-autonomous effects of FOXO activation are conserved in mammalian systems, in which they may reflect important disease mechanisms.

Gonad signalling

Another cell non-autonomous mechanism that modulates ageing operates through signals from the gonad[15,16]. In *C. elegans*, gonad ablation increases lifespan through endocrine signalling, intestinal *daf-16* expression and multiple transcriptional pathways[21]. Evidence suggests that this non-autonomous signalling improves proteostasis in distal tissues[59,69]. Animals lacking germline stem cells preserve their capacity to respond to heat stress in multiple tissues, and are more protected against the expression of toxic or metastable proteins in muscle cells[69]. One key mechanism is the upregulation of proteasome activity in somatic cells through *daf-16*-mediated upregulation of the regulatory particle non-ATPase 6 (RPN6) proteasome subunit[70]. Increased proteasome activity in distal cells during germline stem cell loss protects from proteotoxic stress that has been induced by heat or misfolded protein expression. Again, therefore, non-autonomous regulation of ageing relies on the non-autonomous control of proteostasis, with considerable effects on the ability to withstand proteotoxicity (FIG. 4B).

Systemic proteostasis: implications

The mechanisms of ageing and proteostasis maintenance are intimately connected[22]. It now seems that the pathways underlying their non-autonomous regulation are also linked, which enables ageing and proteostasis decline to be coordinated between tissues. Many cellular processes are regulated non-autonomously — metabolism, for example, is tightly regulated by neuroendocrine and secreted factors to coordinate metabolic function with nutrient supply and nutritional state. The relative importance of non-autonomous versus autonomous stress response activation is not yet clear. However, the fundamental importance of cellular stress responses and their role in mediating cellular protection against outside stressors suggests that a similar endocrine coordination of stress response pathways might have an important role in organismal stress resistance.

This shift in our understanding of proteostasis control, which is primarily based on studies in invertebrate species, has important implications for the understanding of numerous diseases of protein misfolding. Cell non-autonomous effects have been observed in multiple neurodegenerative diseases such as amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease. The phenotypes associated with these conditions are not confined to the brain — they frequently involve the peripheral tissues and metabolism in ways that we are only beginning to understand[9,71–73]. Defining the mechanisms behind cell non-autonomous proteostasis through further study in invertebrate species, as well as studies of the conservation of these pathways in vertebrates, promises to shed light on both pathogenic mechanisms and future avenues for disease treatments.

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Competing interests statement

The authors declare no competing interests.