Trends in Biochemical Sciences

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Review

Expanding the Organismal Proteostasis Network: Linking Systemic Stress Signaling with the Innate Immune Response

Jay Miles,[1] Ruth Scherz-Shouval,[2] and Patricija van Oosten-Hawle[1,*]

Stress response pathways regulate proteostasis and mitigate macromolecular damage to promote long-term cellular health. Intercellular signaling is an essential layer of systemic proteostasis in an organism and is facilitated via transcellular signaling molecules that orchestrate the activation of stress responses across tissues and organs. Accumulating evidence indicates that components of the immune response act as signaling factors that regulate the cell-non-autonomous proteostasis network. Here, we review emergent advances in our understanding of cell-non-autonomous regulators of proteostasis networks in multicellular settings, from the model organism, *Caenorhabditis elegans*, to humans. We further discuss how innate immune responses can be players of the organismal proteostasis network and discuss how both are linked in cancer.

Highlights

Cellular stress response pathways, such as the heat shock response and unfolded protein responses in the endoplasmic reticulum and mitochondria, are regulated cell-non-autonomously via intercellular signaling processes.

Immune signals can be components of the expanded cell-non-autonomous proteostasis network that activate protein quality control mechanisms from one cell to another.

Transcellular chaperone signaling is a systemic proteostasis mechanism that requires transcellular signaling molecules such as neurotransmitters, neuropeptides, and immune effectors for the intercellular activation of protective chaperone expression.

The cell-non-autonomous co-ordination of proteostasis and immune responses is implicated in human pathological conditions including cancer.

The Cellular and Organismal Proteostasis Network

The ability to maintain homeostasis in a dynamic environment is one of the most fundamental aspects of survival for all organisms. Each individual cell is a site of constant activity possessing rapid turnover of RNA, proteins, and other cellular components. As most cellular activities are performed by proteins, the maintenance of **proteostasis** (see Glossary) is a high priority. Because the function of each protein is determined by its structure, a functional **proteome** relies heavily on **molecular chaperones**, important components of the **proteostasis network (PN)** [1,2]. Chaperones are vital for cellular and organismal physiology as they form core constituents of the translational machinery by assisting in co-translational folding at the ribosome [3]. Because of their importance for the PN, the 'human chaperome' comprises a vast network of 330 chaperone components, consisting of distinct gene families with different functions toward substrate proteins [4,5]. Many chaperones are upregulated by robust stress response mechanisms to counteract protein misfolding and cellular damage imposed by **proteotoxic stresses**; such stresses include heat, oxidative stress, and pathogenic infections [6–8]. Another important aspect of the PN is the removal of misfolded or aggregated proteins by proteolytic degradation. This is accomplished by two major pathways: the ubiquitin proteasome system (UPS) and autophagy [9]. While the UPS is mainly responsible for targeting individual proteins to the proteasome, autophagy contributes to the clearance of large aggregates [9]. The UPS also interfaces with protein synthesis to remove defective nascent chains as part of the ribosomal quality-control pathways [10].

With the increasing complexity of multicellular organisms, regulation of stress responses and other protein quality control mechanisms relies on intercellular signaling pathways to systemically coordinate protein quality control processes across tissues and organs. This requires differential activation of appropriate tissue-specific PN components, as different cell types and tissues are characterized by their specific proteomes and different PN requirements [4,11,12]. **Transcellular activation** of stress responses is achieved by endo- and paracrine signaling pathways including hormones, cytokines, and other secreted peptides, as well as long-range neuroendocrine signaling mechanisms that are mediated via neurotransmitters and neuropeptides to induce protective transcriptional responses from one tissue to another [13–17].

The idea that cells and tissues experiencing proteotoxic stress communicate and transmit stress to other tissues is highly reminiscent of danger signals that activate immune defense responses across different cells [18] (Box 1). It also raises the question of whether intercellular immune signals used in the immune response could function as signaling components to mediate systemic proteostasis

[1]School of Molecular and Cell Biology and Astbury Centre for Structural Molecular Biology, University of Leeds, Leeds, UK

[2]Department of Biomolecular Sciences, Weizmann Institute of Science, Rehovot, Israel

*Correspondence:
p.vanoosten-hawle@leeds.ac.uk

Box 1. Linking Stress Response and Immune Response Mechanisms: Of DAMPS, Extracellular Chaperones, and Cytokines

Stress responses and immune responses are different, yet share striking similarities. While immune responses are specifically designed to target foreign molecules and pathogens in an organism, cellular stress response mechanisms generally act to promote and maintain proteostasis in response to environmental stress or chronic intracellular stress conditions that challenge the integrity of the cellular proteome. The fact that both are connected and more closely related than they first appeared was recognized in the 1990s by several observations. For example, cells exposed to heat shock prior to pathogenic infection are protected against the consequences of pathogenic infection, due to increased levels of the heat-inducible Hsp72 chaperone [133]. Later on, the discovery that HSPs such as Hsp70 and Hsp60 also exist extracellularly [134,135] led to the realization that HSPs are also modulators of the immune system by regulating the production and secretion of immunoregulatory cytokines [86,87,131]. Cytokines are a large group of small proteins facilitating paracrine and autocrine intercellular signalling processes that have been associated with immunity and inflammation [136]. They are induced by PAMPs as a first line of response to pathogenic microbial infections. In 2002, Polly Matzinger described the concept of danger signals in the immune response as a mechanism to respond to danger molecules such as free radicals, nucleotides, pathogens, and HSPs among many others [18]. This concept was then merged with the concept of PAMPs to result in the acronym DAMPs: damage-associated molecular patterns [137]. eHSPs can act as DAMPs and so function as signalling molecules that regulate the production and secretion of cytokines in response to pathogenic infection and inflammation. It is now well established that eHSPs function as inducers of proinflammatory cytokine production [138], and, conversely, molecular chaperone expression can be upregulated by cytokines in response to an infection [116]. For example, eHsp70 stimulates macrophage proinflammatory cytokine synthesis [93], whereas exposure of cardiomyocytes to cytokines promotes expression of Hsp70 [139]. Thus, cytokines and eHSPs appear to be the interface where intercellular responses relevant for proteostasis and innate immunity converge.

across tissues. Indeed, both immune responses and stress response pathways are tightly linked and can be activated by either proteotoxic stress or pathogen infection to provide cellular protection – a concept that was recognized early on in the field (Box 1) [19–21]. These intercellular protection mechanisms come at a cost, however. In cancer, both immune and stress responses are hijacked to promote survival of cells in the stressful tumor microenvironment [22–26].

In this review, we first highlight how canonical stress responses are regulated via **cell-non-autonomous** signaling pathways. Because the majority of these findings were discovered using *Caenorhabditis elegans*, we provide a particular emphasis on this model organism when describing the distinct systemic stress response pathways and their related endocrine signaling molecules. We then characterize **innate immune response** pathways in both vertebrates and invertebrates and connect them to proteostasis, by exploring systemic stress signaling pathways and how molecular chaperones are involved in the innate immune response. Vice versa, we also discuss how immune effectors, such as cytokines in mammals and potential secreted **immune peptides** in *C. elegans* could act as regulators of systemic proteostasis. Finally, we describe how cancer cells connect systemic stress signaling with immune responses to promote their survival at the expense of the host.

Regulation of Stress Response Pathways in a Systemic Manner: The Search for the Cell-Non-autonomous Stress Signal

Heat Shock Response in Systemic Stress Signaling

The **heat shock response (HSR)** is arguably one of the most well-characterized stress responses and is activated by misfolded proteins in the cytosol or nucleus [27,28]. The eukaryotic HSR is coordinated by the highly conserved transcription factor heat shock factor (Hsf)1, which, under basal conditions, is maintained in an inactive form in the cytosol through post-translational modifications and interaction with heat shock proteins (HSPs) including Hsp90 and Hsp70 [29]. Upon proteotoxic stress, these chaperones preferentially bind to misfolded proteins and dissociate from Hsf1, enabling it to trimerize and translocate into the nucleus [30,31]. Nuclear Hsf1 trimers then bind **heat shock regulatory elements** in DNA [28], promoting rapid upregulation of HSR genes including Hsp70, increased protein folding,

Glossary

Cell-autonomous: cellular process initiated within and affecting a single cell.
Cell-non-autonomous: cellular process initiated within one cell that affects other cells via intercellular signalling processes.
Exosomes: lipid vesicles produced inside intracellular endosomes. Upon fusion of the endosome with the cell membrane, exosomes within the endosomal lumen are released from the cell as a method of cell–cell signalling.
Heat shock regulatory element: DNA consensus sequence (nGAAnnTTCn) in the promoter of heat shock factor 1 (Hsf1) – responsive genes, leading to transcription of heat shock response genes.
Heat shock response (HSR): cytosolic stress response to conditions that adversely affect protein structure or function, such as extreme temperature. The HSR is mediated by Hsf1 and promotes increased levels of molecular chaperones in order to maintain normal protein function under these conditions.
Immune peptides: proteins such as antimicrobial peptides that mediate immune responses.
Innate immune response: immune mechanisms that are nonspecific rather than targeted to a particular invading organism, enabling a fast but generalized response to infection.
Intracellular pathogen response: a *C. elegans* transcriptional immune response occurring upon infection with intracellular pathogens such as *Nematocida parisii*.
Mitogen Activated Protein Kinase (MAPK) pathways: kinase signalling cascades that are activated downstream of cell surface receptors and communicated to intracellular components, leading to changes in gene expression or protein function related to cell survival or proliferation.
Molecular chaperones: proteins that mediate the folding or refolding of other proteins into functional structural conformations.
Proteome: entity of all proteins at the cellular or organismal level. For example, the proteome of a cell would be all proteins within that cell.

and a return to proteostasis [30]. Once the stress is resolved, excess Hsp70 exerts negative feedback on Hsf1, which in combination with various post-translational modifications returns the system to its original state [32].

Evidence for the existence of a cell-non-autonomous HSR began to emerge as early as the 1990s with the demonstration of neuroendocrine activation of the adrenal HSR in rats upon behavioral stress [33]. This was followed by numerous studies of thermolocomotion in the nematode *C. elegans*, which have provided further insight into neuronal regulation of the organismal HSR [13,34–39]. *C. elegans* thermosensation is primarily mediated by a pair of amphid finger (AFD) neurons and their postsynaptic amphid Y (AIY) interneurons in response to temperature changes [34]. Briefly, in AFD neurons, the transmembrane guanylyl cyclases GCY-8, GCY-18, and GCY-23 are activated by increasing temperatures, enabling activation of the cGMP-gated ion channels TAX-2 and TAX-4 and subsequent generation of Ca^{2+} gradients [37,39]. The postsynaptic AIY interneurons signal via the LIM homeobox protein TTX-3 to motor neurons innervating the body wall muscle and promotes movement of the organism towards areas of previous cultivation temperatures [38]. However, this thermosensory neural circuit has an additional function: activation of the organismal HSR. Mutation of either GCY-8 or TTX-3 prevents the upregulation of heat-inducible *C. elegans* HSP-70 (Hsp72) across various tissues following acute heat stress [13], demonstrating that activation of the somatic HSR is dependent on the activity of the AFD and AIY neurons (Figure 1). Recently, the identity of the endocrine signaling molecule that activates HSF-1 in nonneuronal somatic tissues has been identified as the neurotransmitter serotonin [36]. For example, direct optogenetic activation of the AFD neuron activates HSF-1 in noninnervated germline cells, even in the absence of stress in a serotonin-dependent manner [36]. This induces the increased expression of *hsp-70* at an organism-level and was shown to suppress aggregation of disease proteins expressed in *C. elegans* muscle tissue [36,40].

The Unfolded Protein Response of the Endoplasmic Reticulum (UPR^{ER}) in Systemic Stress Signaling

The **unfolded protein response (UPR)** of the endoplasmic reticulum (ER) consists of three pathways coordinated by the luminal ER chaperone BiP/Grp78 [41]. Under basal conditions, BiP represses the three transmembrane UPR^{ER} effector proteins IRE1, ATF6, and PERK by binding their domains that project into the ER lumen [41]. If misfolded proteins accumulate in the ER lumen, BiP will preferentially bind to these over the effectors, enabling them to activate their respective pathways [42]. When released from BiP, the stress sensor IRE1 that is located at the ER membrane, homodimerizes and trans-autophosphorylates, thereby gaining endoribonuclease activity. Once activated, IRE1 catalyzes the processing of the mRNA encoding the transcription factor XBP1. This shifts the coding frame and leads to expression of an active transcription factor known as XPB1s that promotes UPR^{ER} target gene expression [42].

In *C. elegans*, the IRE1 arm of the UPR^{ER} is regulated cell-non-autonomously by the nervous system [16,43]. While overexpression of XBP-1s in the intestine or body wall muscle results only in **cell-autonomous** upregulation of BiP/HSP-4, XBP-1s overexpression in neurons triggers BiP/HSP-4 induction in both the neurons and the intestine (Figure 1) [16]. This cell-non-autonomous signaling coincides with increased longevity and negates the decline in UPR^{ER} function normally seen during aging. The endocrine signal regulating this cell-non-autonomous response is not clear at the moment, although several indications in *C. elegans* suggest that it is neurotransmitter dependent [16], and possibly regulated via octopaminergic signaling as the UPR^{ER}-mediated innate immune response depends on the octopamine [G-protein-coupled receptor (GPCR)] receptor OCTR-1 (Figure 1 and Figure 2, Key Figure, pathways 1 and 3) [43].

In a mammalian example of transcellular UPR^{ER} activation, overexpression of Xbp1s in the pro-opiomelanocortin (POMC) neurons of mice results in upregulation of both Xbp1s and its target genes in the liver, which is accompanied by increased energy expenditure and improved liver glucose homeostasis (Figure 1) [44]. Although the endocrine signaling molecule regulating this response in mammals

Proteostasis: protein homeostasis, or the maintenance of a functional proteome. This includes protein synthesis, folding, refolding, and degradation, in order to promote normal protein function, prevent misfolding and as well clear the cell from irreversibly misfolded or aggregated proteins.
Proteostasis network (PN): network of cellular components that maintains proteostasis. This includes molecular chaperones, cochaperones, and elements of the proteasome system.
Proteotoxic stresses: conditions that challenge proteostasis by promoting increased occurrence of damaged or misfolded proteins, such as extreme temperature, oxidative stress, or chronic expression of aggregation-prone disease proteins.
Transcellular activation: cell-non-autonomous activation of a cellular process.
Transcellular chaperone signalling (TCS): cell-non-autonomous regulation of chaperone protein expression in response to tissue-specific alterations of Hsp90 expression levels in *C. elegans*.
Unfolded protein response (UPR): stress response mechanism that senses the presence of misfolded proteins in the lumen of the endoplasmic reticulum (called UPR of the ER) or the mitochondrial matrix (called UPR of the mitochondria). Activation of the UPR in either case promotes increased chaperone expression and other factors required to refold or degrade misfolded proteins.

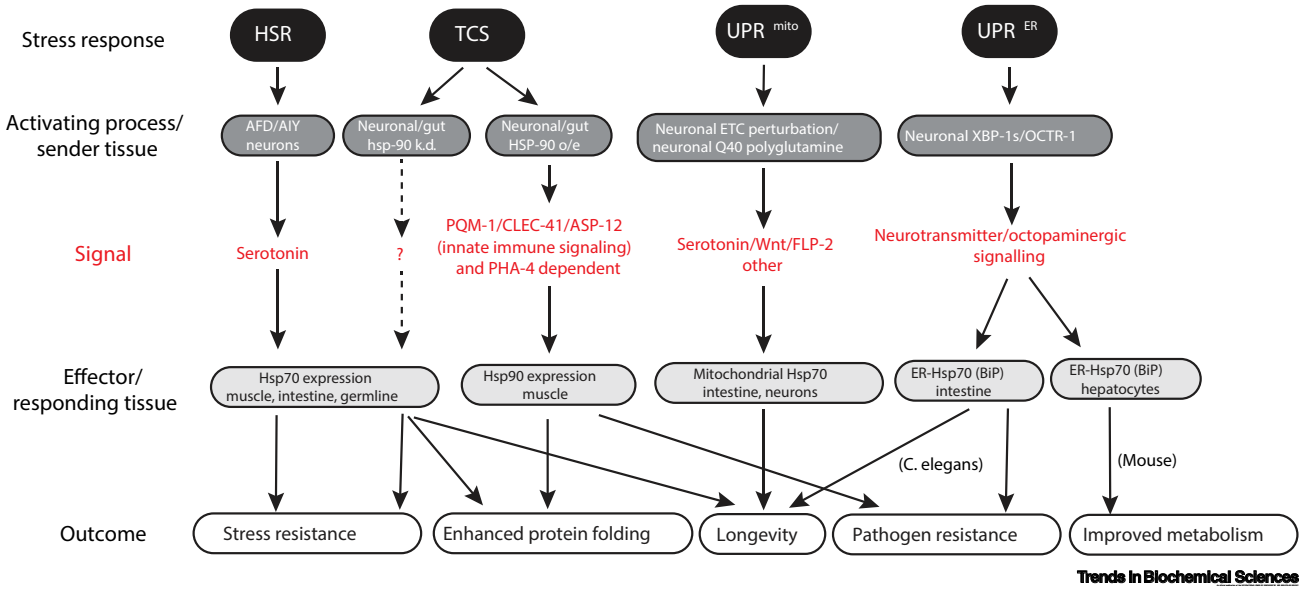

Figure 1. Schematic Summary of Known Transcellular Signalling Processes Regulating Organismal Proteostasis.
Stress response pathways that function in a cell-non-autonomous signalling manner are indicated (black) and include the heat shock response (HSR), transcellular chaperone signalling (TCS), the unfolded protein response in mitochondria (UPR^{mito}), and the unfolded protein response in the endoplasmic reticulum (UPR^{ER}). The tissues that activate the pathways are indicated (grey). So far identified neuroendocrine (e.g., neurotransmitters) or paracrine signals that mediate the transcellular signalling process are also indicated (red). Further down the pathway are the activated chaperones in tissues responding to transcellular signalling (light grey), as well as the corresponding phenotypic outcome (white). All shown pathways have been observed in *Caenorhabditis elegans* so far, with the exception of cell-non-autonomous UPR^{ER} signalling, that has also been observed in mice, as indicated. Abbreviations: ETC, electron transport chain; HSP, heat shock protein; k.d., knockdown; o/e, overexpression.

has not been identified thus far, it is known that Xbp1s in POMC neurons represses induction of suppressor of cytokine signaling (SOCS)3 and tyrosine phosphatase 1B (PTB1B), thereby negating leptin and insulin resistance and improving metabolic homeostasis (Figure 2, pathway 2) [44]. This shows that neuronal control of proteostasis via the cell-non-autonomous UPR^{ER} not only has far reaching benefits and implications for systemic metabolic control and energy balance, but that this cell-non-autonomous signaling process is also evolutionary conserved, at least from *C. elegans* to mammals.

The UPR of the Mitochondria (UPR^{mito}) in Systemic Stress Signaling

As the primary sites of aerobic respiration and oxidative phosphorylation, mitochondria are major producers of reactive oxygen species (ROS) in a membrane potential-dependent manner [45]. Due to the proteotoxic nature of ROS, the UPR^{mito} is vital for maintaining a healthy mitochondrial proteome and is facilitated by chaperones Hsp10 and Hsp60, mitochondrial specific chaperones mtHsp70 and mtDnaJ, as well as proteases such as ClpP [46]. When the unfolded protein load in the matrix exceeds chaperone capability, excess misfolded proteins undergo proteolytic degradation by ClpP and their cleavage products are exported to the cytosol by the peptide transporter HAF-1 [47]. This inhibits mitochondrial protein import not only by reducing nascent peptide chain influx to the organelle but also by promoting nuclear translocation of the transcription factor ATFS-1, which in turn promotes expression of UPR^{mito} chaperones [48].

The UPR^{mito} is also regulated cell-non-autonomously in invertebrate model systems [14,49,50]; whether the same occurs in vertebrates is however still unknown. In *C. elegans*, knockdown of the electron transport chain (ETC) component *cco-1* in neurons results in a cell-non-autonomous activation of the intestinal UPR^{mito} and increased lifespan (Figure 1) [50]. However, there is a tissue-

Key Figure

Innate Immune Signals Regulating Proteostasis and Components of the Proteostasis Network Regulating Immune-Related Responses in *C. elegans* and Mammalian Cell Lines

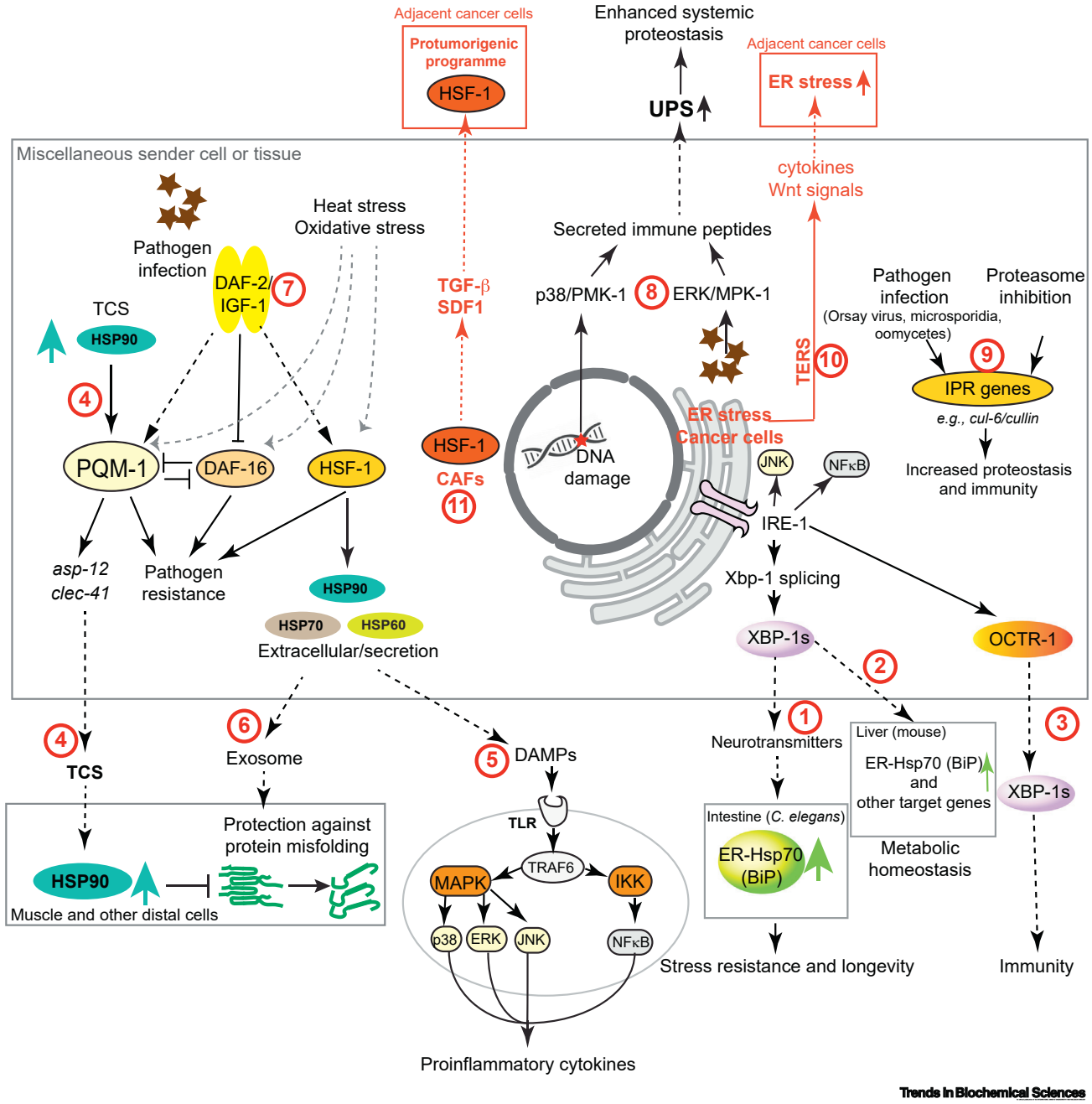

Figure 2. (1) The IRE1 branch of the unfolded protein response in the ER (UPR^{ER}) regulates endoplasmic reticulum (ER) proteostasis intracellularly, and transcellularly via XBP-1s dependent neurotransmitter signalling. (2) Activated XBP1s in pro-opiomelanocortin (POMC) neurons (mouse) leads to

(Key figure legend continued at the bottom of the next page.)

dependent element to this form of cell-non-autonomous UPR^{mito} signaling – while *cco-1* knockdown in the intestine or neurons increases lifespan in a nonsynergistic manner, knockdown in the body wall muscle has the opposite effect [50]. Interestingly, the neuron-specific expression of polyglutamine (polyQ) 40-repeat protein (Q40), an aggregation-prone, Huntington-disease- associated protein, activates both the cell-autonomous and cell-non-autonomous upregulation of mtHsp70/HSP-6 [49]. The neuroendocrine signal responsible for mtHsp70 induction in the intestine is the neurotransmitter serotonin [49], albeit it is not clear whether this is directly mediated via ATFS-1 in the intestine. Recently, Zhang *et al.* used this as the basis for a genetic screen in *C. elegans*. This led to the discovery of a second endocrine signal that regulates the cell-non-autonomous induction of the UPR^{mito} which involves both canonical (β-catenin-dependent) and noncanonical (retromer-dependent) Wnt signaling [14]. A third secreted factor and neuroendocrine signal was identified as the neuropeptide FLP-2 [51]. FLP-2 mediates neuroendocrine-regulated activation of the UPR^{mito} in response to disruption of neurospecific expression of a mutant SPG-7 protease, which also disrupts neuronal proteostasis [51]. Other paracrine signals, such as the human ortholog of ImpL2 (IGFBP7), have been identified in *Drosophila*, where mild ETC perturbation in larval flight muscles upregulates expression of UPR^{mito} markers and promotes longevity by cell-non-autonomous upregulation of insulin suppression markers *4e-bp* and *inr* in the abdomen and head [52].

Transcellular Chaperone Signaling: A Systemic Stress Response Relying on Innate Immune Signaling

Another noncanonical systemic stress response is **transcellular chaperone signaling (TCS)**, which responds to altered tissue-specific expression of the molecular chaperone HSP-90 in *C. elegans* [15]. TCS leads to activation of chaperones in other, nonstressed tissues and functions independently of HSF-1 to communicate a protective chaperone response across different tissues [15]. For example, tissue-specific HSP-90 over-expression in the intestine or neurons of *C. elegans* can protect against metastable myosin misfolding or amyloid β (Aβ) aggregation in the body wall muscle due to transcellular upregulation of HSP-90 (Figure 1) [15,17]. TCS is mediated by the zinc finger transcription factor PQM-1, which is normally associated with the innate immune response [53], along with its downstream effectors the innate-immunity-associated c-type lectin *clec-41* and aspartic protease *asp-12*. All three function as signaling nodes required to activate increased *hsp-90* expression in *C. elegans* muscle cells (Figure 1 and Figure 2, pathway 4) [17]. Thus, TCS demonstrates how components usually associated with the immune response can activate chaperone expression from one tissue to another. While CLEC-41 is required to activate *hsp-90* expression in the muscle via glutamatergic neuronal signaling, it is currently not clear whether it also is the 'sought after' signaling molecule itself, as it may associate with membrane-spanning proteins such as neuronal receptors or ion channels through its CUB domain [17]. ASP-12, which is induced by TCS in the gut, has the potential to be secreted and thus could act as a true intercellular signaling molecule between the intestine and the muscle to activate *hsp-90* expression [17]. Thus, this form of systemic stress signaling

upregulation of BiP and improved glucose metabolism in hepatocytes. (3) ER stress activates the neuronal G-protein-coupled receptor (GPCR) OCTR-1 in an IRE1-dependent manner that regulates innate immune responses. (4) Increased tissue-specific expression of Hsp90 activates transcellular chaperone signalling (TCS), a response mediated through PQM-1 and innate immune effectors *asp-12* and *clec-41*. Potential secretion of these effectors promotes Hsp90 expression in distal muscle cells to protect against protein misfolding. (5) Extracellular heat shock proteins (HSPs) can function as damage-associated molecular patterns (DAMPs) to regulate the expression of proinflammatory cytokines in other cells. (6) Heat shock factor (HSF-1) upregulates expression of molecular chaperones, including Hsp70, Hsp90, and Hsp60 that can be secreted via exosomes to replenish proteostasis in mammalian cells affected by protein misfolding or via noncanonical secretory pathways. (7) Stress-responsive transcription factors HSF-1, DAF-16/FOXO, and PQM-1 respond to proteotoxic stresses such as heat or oxidative stress, as well as pathogen infections. (8) DNA damage and pathogen infection stimulate p38 and ERK MAPK (mitogen-activated protein kinase) signalling cues to upregulate secreted innate immune peptides that trigger activity of ubiquitin proteasome system. (UPS) transcellularly in other somatic tissues. (9) Pathogen infection or proteasome inhibition stimulates an HSF-1 independent pathway regulating IPR genes such as *cul-6*, that contribute to increased organismal proteostasis and immunity in *C. elegans*. (10) Cancer cells transmit ER stress intercellularly via transmissible ER stress (TERS) which depends on upregulated cytokines, Wnt signalling, and reduced activation of the PERK arm of the UPR^{ER}. (11) Cytokines transforming growth factor beta (TGF-β) and SDF1 activate a cancer specific HSF1 transcriptional program transmitted from cancer-associated fibroblast (CAF)s to adjacent cancer cells. Abbreviations: TLR, Toll-like receptor.

relies on potentially secreted innate immune peptides to mediate chaperone expression across tissues and to enhance organismal proteostasis.

In summary, it is interesting to note that the same signaling molecule can regulate neuroendocrine activation of different stress responses (Figure 1). For example, serotonin mediates cell-non-autonomous activation of both the HSR and the UPR^{mito} [36,49]. Vice versa, the UPR^{mito} can also be mediated via Wnt dependent signals or a neuropeptide [14,51]. The reason for this diversity could be the different stress conditions in the sender tissue, that is, neuron-specific expression of PolyQ 40 versus a neuronally expressed mutant protease.

While the search for the cell-non-autonomous signaling molecule regulating systemic stress responses is still ongoing, the overall picture is becoming more refined in *C. elegans*, and so far implies that systemic stress responses likely require a network of different endocrine and paracrine signaling molecules responding to different activating conditions in a variety of target tissues.

Although many of these systemic stress responses are regulated via neuroendocrine signalling (i.e., neurotransmitters and neuropeptides), some depend on potentially secreted peptides that are normally involved in the innate immune response as observed in TCS. We further explore the connection between systemic stress responses and immune responses in the following sections and give specific examples of how proteostasis mechanisms are linked with immunomodulatory roles.

Innate Immune Response Signaling Pathways during Infection and Inflammation

Regulation of the Innate Immune Response in Invertebrates by Mitogen-Activated Protein Kinase Pathways

In addition to the canonical cell stress pathways described above, **Mitogen Activated Protein Kinase (MAPK) pathways** comprise another conserved group of response pathways that are stimulated by proteotoxic stress, as well as pathogenic threats in evolutionary diverse organisms [54,55]. For example, in *C. elegans*, the PMK-1/p38 and MPK-1/ERK MAPK pathways are core signal transduction cues regulating protective responses to fungal or pathogenic bacterial infections, while the orthologues corresponding MAPK pathways in yeast, Hog1/p38 and Slt2/ERK respectively, respond to osmotic or thermal stress [56,57].

More specifically, in *C. elegans*, the PMK-1/p38 pathway is activated via stimulation of the Toll–interleukin-1 receptor (TIR) domain adaptor protein TIR-1, followed by signaling through NSY-1/SEK-1/PMK-1 (Figure 3A) [58–60]. This signaling pathway functions in the intestine to promote resistance to pathogenic bacteria and in the epidermis in response to fungal infection or wounds [61]. Downstream targets of PMK-1/p38 in response to bacterial infection of the intestine include ATF-7, a transcriptional repressor that is activated upon phosphorylation by PMK-1 [62]. This results in the expression of predicted secreted innate immune peptides, including C-type lectins, CUB domain proteins and antimicrobial peptides [62,63].

Additionally, the MPK-1/ERK pathway (Figure 3A) is activated upon infection of rectal epidermal cells by *Microbacterium nematophilum*, a Gram-positive bacterium that adheres to rectal cuticle and induces a tail-swelling response after passage through the *C. elegans* intestine [64]. Although the transcriptional response mediated by MPK-1 is similar to the one promoted by PMK-1 as mentioned above, the exact nuclear factor triggering gene expression in this case is still unknown [63].

The Innate Immune Response in Mammals: Toll-like Receptor (TLR) Signaling Pathways

In contrast to *C. elegans*, vertebrates use a specialized set of cells that regulate innate immune responses by inducing specific signaling pathways to clear pathogenic infections. These include mast cells, neutrophils, monocytes, macrophages, dendritic cells (DCs), and natural killer cells (NKs) [65]. They are able to recognize a broad range of pathogen-associated molecular patterns (PAMPs), such as bacteria and viruses, and so-called damage-associated molecular patterns (DAMPs) or danger signals, which includes molecular chaperones (Box 1). Both PAMPs and DAMPs are

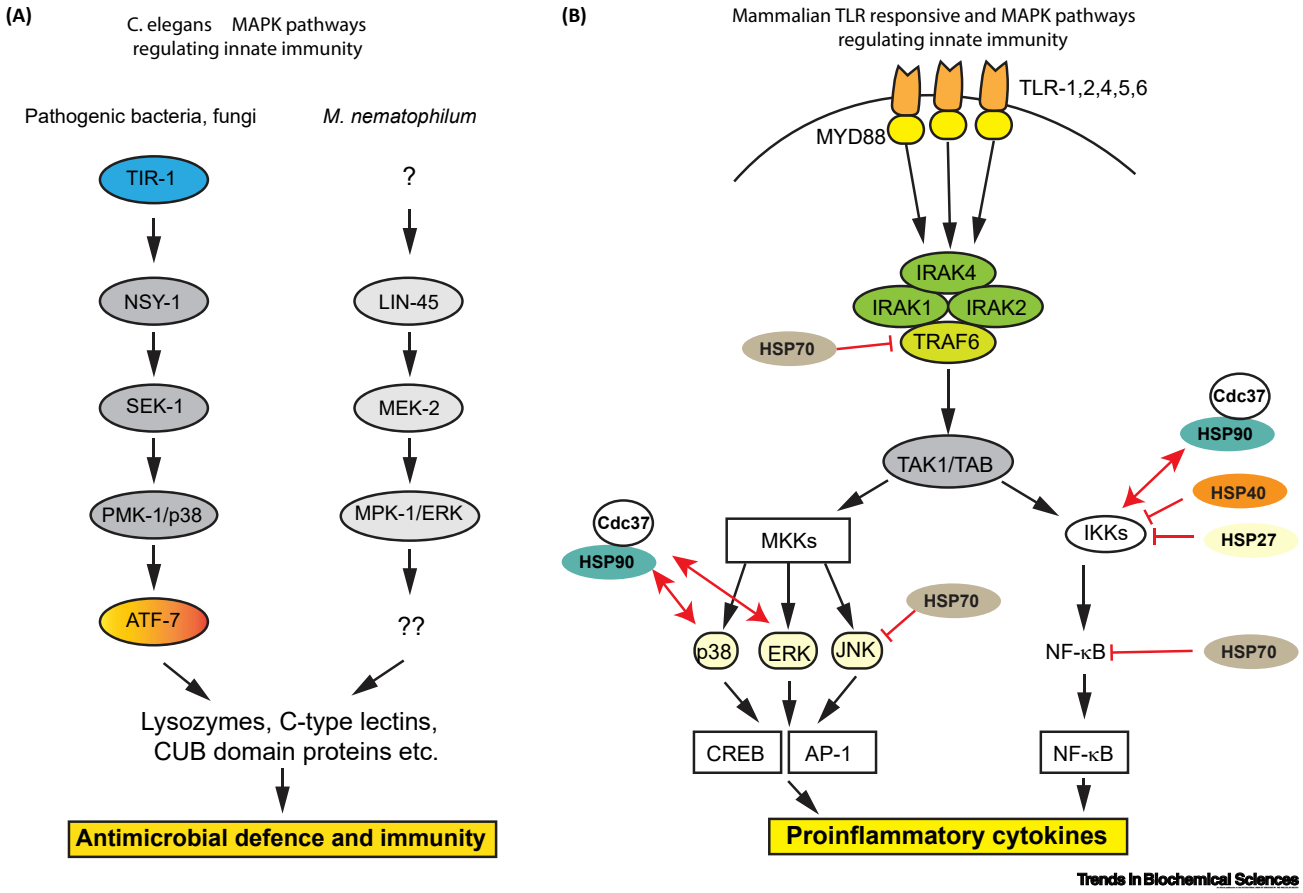

Figure 3. Innate Immune Signalling Pathways in *Caenorhabditis elegans* and Mammals.

(A) *C. elegans* antimicrobial response mediated by conserved mitogen-activated protein kinase (MAPK) signalling pathways. Exposure to fungi or extracellular bacterial intestinal infection induces the p38/PMK-1 signalling cascade via kinases NSY-1 and SEK-1 and the scaffold protein TIR-1. p38/PMK-1 activates the transcription factor ATF-7, which leads to expression of innate immune peptides. The MAPK homologue MPK-1/ERK is activated upon infection with *Microbacterium nematophilum* leading to signalling through LIN-45 and MEK-2 kinases. MPK-1 activates a, as yet unknown, transcription factor, leading to a similar transcriptional response as the p38/PMK-1 pathway. (B) Mammalian Toll-like receptor (TLR) signalling pathways involved in the innate immune response. TLRs at the cell surface initiate the MyD88-dependent signalling pathway, resulting in activation of the downstream IKK/NF-κB and MAPK signalling routes. Each of these signalling routes induces expression of proinflammatory cytokines including tumor necrosis factor alpha (TNF-α), and interleukin (IL)-6 by the transcription factors NF-κB, CREB, and AP-1. Regulatory interactions of heat shock proteins with the individual signalling components are indicated by red arrows. Abbreviations: HSP, heat shock protein; TIR, Toll–interleukin-1 receptor.

recognized by pattern recognition receptors (PRRs) such as TLRs (Figure 3B). TLRs are membrane-spanning receptors that activate either the transcription factor NF-κB via TAK1/IKK signaling or the MAPKs p38, JNK, and ERK pathway which subsequently activates the transcription factors CREB and AP-1 [66]. Both NF-κB and AP-1 promote expression of proinflammatory cytokines, including tumor necrosis factor (TNF)α, interleukin (IL)-6, IL-1β, and chemokines. Although invertebrates such as *C. elegans* lack the NF-κB-like transcription factor, the p38 MAPK pathway is considered as its analogue ancestral immune pathway, conserved in yeast, invertebrates and vertebrates alike [67].

Systemic Stress Signaling Pathways Regulating Innate Immunity

HSR and the Innate Immune Response

In *C. elegans*, the master regulator of the HSR, HSF-1, is also involved in the innate immune response. HSF-1 activity is regulated by the insulin growth factor (IGF)-like insulin signaling pathway (ILS/DAF-2

signalling pathway) to control cell-non-autonomous signaling processes relevant for organismal immunity, health-span, and longevity (Figure 2, pathway 7) [68,69]. For example, heat stress and the induction of the HSR can increase *C. elegans* immunity to *Pseudomonas aeruginosa* in an HSF-1 dependent manner and the increased resistance to the pathogen particularly depends on HSF1-mediated expression of molecular chaperones *hsp-90* and *hsp-16* [69].

Furthermore, in mammals, HSF1 also plays an important role in cell-non-autonomous stress signaling and immune responses. Specifically, fever-induced HSR leads to direct binding of HSF1 to heat shock elements (HSEs) of several chemokines in human cell lines [70]. Conversely, also in human cell lines, cytokines such as IL-1β and transforming growth factor (TGF)-β may activate HSF1 during inflammation [71]. Such activation has been shown to induce expression of the collagen-specific molecular chaperone Hsp47 *in vitro* and could thus affect collagen secretion and fibrosis [72]. This shows that components of the mammalian innate immune and inflammatory response, such as cytokines and interleukins, can function to promote activation of stress response pathways. This is an important aspect in cancer cells and the tumor microenvironment, as discussed in a later section of this review.

The UPR^{ER} and Innate Immune Response

The UPR^{ER} plays a particularly important role in the regulation of **innate immune responses** due to the increased demands on protein folding in the ER that occur during pathogenic infections (Figure 1) [73–75]. This branch of the UPR^{ER} can be activated by exposure to *P. aeruginosa* and, in that respect, is essential for survival of *C. elegans* larvae infected with the pathogenic bacteria [43,62,76]. UPR^{ER} responses to pathogenic infection are controlled cell-non-autonomously via OCTR-1, a neuronal catecholamine receptor expressed in ASH and ASI neurons that mediates expression of BiP/HSP-4 and other genes in distinct tissues of the animal to confer immunity (Figure 1 and Figure 2, pathway 2) [43,77].

An interesting link between ER stress and the innate immune response can be drawn in mammals, where, similar to *C. elegans*, pathogenic bacteria in the intestine activates ER stress in intestinal epithelial (Paneth) cells [78]. This triggers secretory autophagy in Paneth cells and mediates antimicrobial protein secretion required for intestinal defense [78]. This apparent link between the UPR^{ER} and a pathogen response effectively demonstrates how a proteostasis-related stress signaling pathway can be involved in the innate immune response.

The UPR^{mito} and Innate Immune Response

Activation of the UPR^{mito} can also induce innate immunity via ROS production to counteract pathogenic microbial infection [79,80]. For example, hyperactivation of the transcription factor ATFS-1 improves clearance of *P. aeruginosa* from the *C. elegans* intestine and increases survival to pathogen infection [80], that depends on ATFS-1-mediated expression of innate immunity target genes [81]. Although the UPR^{mito} is involved in the promotion of metastasis in human cancer [82], it yet needs to be determined whether it is required for the mammalian innate immune response.

Molecular Chaperones Link Proteostasis and Immunity

Molecular chaperones are a group of key effectors of the proteostasis network [1,83]. As such, they are also involved in the regulation of innate immune signaling processes by facilitating the function of their client proteins p38, ERK, JNK, and IKK (Figure 3B). For example, Hsp90 and its cochaperone Cdc37 are required for the activation of the IKK complex [84], whereas Hsp70 inhibits TRAF6 ubiquitination and so prevents activation of inflammatory signaling responses [85]. Hsp90 and Cdc37 are also crucial for the function of the p38 and ERK MAPK orthologues Hog1 and Slt2 in *Saccharomyces cerevisiae* [145], corroborating the functional interdependence and evolutionary involvement of chaperones with immune response signaling cues. In addition, Hsp70 can bind to and inhibit JNK and NF-κB activation [86,87].

The link between molecular chaperones and the innate immune response pathways is, however, more intertwined than just chaperoning the activity of its signaling kinase clients. In addition to being an

integral component of the intracellular chaperone machinery, HSPs act as important immunomodulators controlling inflammation [88]. For example, Hsp60, Hsp70, Hsp90, and Hsp110 can be secreted and function as DAMPs [89] that directly bind to TLRs and activate innate immune signaling cues to increase the release of inflammatory cytokines (Figure 2, pathway 5) [20,90]. Although controversial, Hsp70 and Hsp60 in particular are indicated to have both pro- and anti-inflammatory roles. The proinflammatory role is evidenced through their interactions with monocytes, macrophages, and DCs, by activating the innate immune response and cytokine production [91–94]. Their anti-inflammatory effects are shown through their ability to downregulate inflammation by promoting T cells to produce regulatory cytokines IL-4 and IL-10 [95–98]. The particular immunomodulatory function of Hsp90 in both *C. elegans* and mammalian cells is described in Box 2. It is now widely established that HSPs such as Hsp40, Hsp60, Hsp70, and Hsp90 can be secreted from many cell types via nonclassical pathways [99–102]. Once released, these extracellular HSPs (eHSPs) can elicit immune responses through binding to cell surface receptors on antigen presenting cells (APCs) and presentation of peptides from chaperoned clients [93,103–105]. In cancer, such antigen presenting activities are tumor suppressive. Yet, eHSPs play important tumor-supportive roles through binding to oncogenic cell surface receptors such as HER2 [106,107] and chaperoning of metalloproteases [108–110].

More recent advances indicate that eHSPs could also be utilized to integrate proteostasis systemically across tissues. For instance, in mammalian cell lines, Hsp70/Hsp40 and Hsp90 can be shuttled between different cell types via **exosomes** to replenish and improve proteostasis in a damaged cell in need (Figure 2, pathway 6) [102]. This can suppress the formation of polyQ aggregates in polyQ-expressing cells, indicating that chaperones can cell-non-autonomously improve the protein-folding environment via exosome-mediated transmission [102]. In cancer, increased secretion of Hsp90, Hsp70, and Hsp60 via exosomes contributes to the antitumor immune response by stimulating the migratory and cytolytic activity of NK cells [111,112].

Innate Immune Pathways Regulating Organismal Proteostasis

While stress response pathways and chaperones can be involved in the regulation and activation of immune signaling pathways, the converse is also true as innate immune effectors (such as cytokines in mammals; Box 1) can activate chaperone expression and other protein quality control mechanisms; this has been observed in both invertebrate and vertebrate model organisms alike [17,113–116]. Specific examples of how secreted immune peptides can regulate protein quality control mechanisms cell-non-autonomously in an organism such as *C. elegans* are given below.

DNA-Damage Response Regulates the UPS via Induced Immune Signals

DNA damage occurring in the *C. elegans* germline not only induces the immune responsive ERK/MAPK signaling pathway within that tissue, but also the p38 MAPK pathway in the intestine, which then triggers proteostasis mechanisms in other somatic tissues (Figure 2, pathway 8) [115,117]. The transcriptional response mediated by these MAPK pathways is associated with an increased

Box 2. Hsp90 – Proteostasis Effector or Immunomodulator?

In addition to the role of secreted Hsp90 as a DAMP that activates immune response pathways, altered intracellular levels of this chaperone can be a signal that triggers proteostasis or innate immune response pathways. In *C. elegans*, depletion of the molecular chaperone HSP-90 (*hsp-90*) by RNAi not only mounts the HSF-1-mediated HSR to induce *hsp-16* and *hsp-70* expression, but also activates genes associated with the innate immune response, possibly via a DAF-16-dependent signalling cue [140]. Expression of these genes occurs primarily in the *C. elegans* intestine and is shared with the immune response to *Vibrio cholerae* and *P. aeruginosa* [141,142], although it remains to be tested whether *hsp-90* RNAi can be protective against the same pathogens. That HSP-90 itself has a protective effect to *P. aeruginosa* infection is shown by TCS, where neuron-specific overexpression of HSP-90 activates systemic expression of the same chaperone and increases immunity against the pathogen, in addition to enhancing systemic proteostasis [15,17]. Interestingly, such a role is reported for Hsp90 in mammalian cells, where extracellular Hsp90 induces inflammatory effectors and the secretion of cytokines in response to pathogenic stress [143,144].

expression of putatively secreted immune peptides, such as C-type lectins and lysozymes, which have been proposed to activate the UPS and hence increase *C. elegans* stress resistance. In addition to MAPK signaling, many genes induced by DNA damage in *C. elegans* are also targets of DAF-16/FOXO [118]. Indeed, DNA damage causes the translocation of DAF-16 to intestinal nuclei, where it acts with a GATA transcription factor to govern target gene expression and maintain cellular homeostasis [118]. Similarly, defense genes are induced in *Drosophila* as a response to fragmented DNA in germ cells [119]. DNA damage therefore appears to represent a stressor that can activate both immune responses and proteostasis mechanisms such as the UPS, leading to whole-organism effects on systemic stress resistance.

Intracellular Pathogen Response Pathway

Another example that links innate immunity with proteostasis is the recently discovered **intracellular pathogen response** pathway in *C. elegans* [114,120]. The transcriptional response activated by this pathway provides resistance against pathogens such as microsporidia and Orsay virus, but also enhances thermotolerance and protects animals cell-non-autonomously from proteotoxic stress via increased expression and activity of CUL-6, a cullin-containing ubiquitin ligase (Figure 2, pathway 9) [114]. This pathway is not dependent on canonical response pathways through p38 MAPK, ILS/DAF-16, or HSF-1 signaling, suggesting that immune responses are novel enhancers of proteostasis which promote resistance against diverse stressors [114]. Thus, immune-responsive pathways can function as activators of chaperone expression and other protein quality control mechanisms, thereby increasing both immunity and also general stress resistance.

While the majority of these findings using the invertebrate model *C. elegans* show how immune effectors can regulate proteostasis in an organismal setting, they may also compensate for the lack of an adaptive immune system in invertebrate species lacking such a system. However, comparable observations are found in mammals, particularly with relation to cancer as described in the next section, where cytokines are hijacked to activate PN components such as HSF1 and chaperone expression [24,26,121–126]. The cell-non-autonomous co-ordination of immune responses and proteostasis is therefore potentially a novel avenue for cancer research in humans.

Proteostasis and Immune Signals in Cancer

Tumors are stressful environments, and chaperones such as Hsp70 and Hsp90 are often overexpressed in tumors where they carry out both their canonical chaperone activities, as well as noncanonical activities [124,127–129]. Prominent among these noncanonical activities is the modulation of immune responses in cancer cells and, importantly, in the tumor microenvironment [24,26,127–130]. The ER chaperone BiP, for example, is activated in macrophages and T cells in the tumor microenvironment, where it regulates the activity of several cancer-associated cytokines, such as MIF, IL-6, TGF-β, and IL-10 [131]. The cytosolic Hsp70 is also activated in macrophages, and this activation promotes macrophage migration into tumors [130].

A form of TCS has also been reported in cancer. In this form of TCS, termed transmissible ER-stress, conditioning of macrophages with medium from ER-stressed cancer cells leads to induction of ER stress in the macrophages themselves, with upregulation of *Grp78* and the Xbp1 arm of the UPR^{ER} [26], as well as proinflammatory cytokines and activation of Wnt signaling (Figure 2, pathway 10) [123].

The coevolution of cancer cells with cells of the tumor microenvironment is mediated by another form of cell-non-autonomous stress-response activation regulated by HSF1. HSF1 is activated in cancer cells where it promotes proliferation, invasion, and migration through activation of a set of genes that is distinct from the classic HSR [25]. In addition to this cell-autonomous tumor-promoting pathway, HSF1 is also activated in cancer-associated fibroblasts (CAFs) in the tumor microenvironment. In these nonmalignant cells, HSF1 drives a protumorigenic transcriptional program, promoting growth and malignancy of the adjacent cancer cells in a cell-non-autonomous manner (Figure 2, pathway 11) [24,132]. The transcriptional program activated by HSF1 in CAFs is distinct from the

classical HSR and from the cancer program, and is mediated by TGF-β, SDF1 (CXCL12), and DKK3 from one cell to another.

It is now well accepted that tumors are complex entities in which malignant and nonmalignant cells coevolve to the detriment of the host. Similar to pathogens invading a host, tumors exploit the PN and adapt the cell-non-autonomous stress signaling pathways described above to communicate and thrive in their host.

Concluding Remarks and Future Directions

Our understanding of systemic regulation of the proteostasis network has made remarkable progress in recent years. Since its recognition in 2008 [13], different layers of signaling mechanisms regulating proteostasis at the organismal level have been identified, encompassing neuroendocrine and paracrine signaling molecules. The apparent diversity of systemic proteostasis regulators not only highlights the complexity of the process, but also reflects different flavors of the proteostasis network tailored to fit tissue-specific requirements. This suggests a highly regulated signaling circuitry between tissues, with various modalities of cell-non-autonomous signals released and received depending on the cell type or tissue in which the signal originates. A striking facet uncovered in recent years is the fact that immune signals appear to play a crucial role in the regulation of systemic proteostasis and intercellular communication of stress responses. This important knowledge is now converging with the new role for paracrine and autocrine immune signals as components of the expanded systemic proteostasis network. Future research should focus on identifying and categorizing the network of paracrine signals capable of activating proteostasis responses, as well as mapping out the tissue circuitry and specificity of the response, both in physiological and disease settings (see Outstanding Questions). Identified cell-non-autonomous signals could have potential therapeutic benefits to either enhance the capacity of the proteostasis network when needed during, for example, conditions of age-associated protein misfolding disease, or by blocking it in tumors, which thrive on transmitting the activation of stress responses for oncogenic transformation from one cell to another.

Outstanding Questions

What is the identity of transcellular (paracrine, endocrine) signals that activate cell-non-autonomous stress responses, and could these signals form a specific transcellular proteostasis network?

How is the specificity of a cell-non-autonomous stress response determined? For example, which receptors and downstream signaling cascades are activated by a specific transcellular signal in the responsive tissues?

Is there a map of tissue circuitry that responds to different extracellular or intracellular proteotoxic stress conditions in an organism?

Can the co-ordination of immune responses and proteostasis mechanisms be targeted for novel therapeutic interventions, for example, in cancer?

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