Organismal proteostasis: role of cell-nonautonomous regulation and transcellular chaperone signaling

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Protein quality control is essential in all organisms and regulated by the proteostasis network (PN) and cell stress response pathways that maintain a functional proteome to promote cellular health. In this review, we describe how metazoans employ multiple modes of cell-nonautonomous signaling across tissues to integrate and transmit the heat-shock response (HSR) for balanced expression of molecular chaperones. The HSR and other cell stress responses such as the unfolded protein response (UPR) can function autonomously in single-cell eukaryotes and tissue culture cells; however, within the context of a multicellular animal, the PN is regulated by cell-nonautonomous signaling through specific sensory neurons and by the process of transcellular chaperone signaling. These newly identified forms of stress signaling control the PN between neurons and nonneuronal somatic tissues to achieve balanced tissue expression of chaperones in response to environmental stress and to ensure that metastable aggregation-prone proteins expressed within any single tissue do not generate local proteotoxic risk. Transcellular chaperone signaling leads to the compensatory expression of chaperones in other somatic tissues of the animal, perhaps preventing the spread of proteotoxic damage. Thus, communication between subcellular compartments and across different cells and tissues maintains proteostasis when challenged by acute stress and upon chronic expression of metastable proteins. We propose that transcellular chaperone signaling provides a critical control step for the PN to maintain cellular and organismal health span.

In all biological systems, cells are constantly exposed to diverse physiological and environmental stimuli that range from acute to chronic perturbations, leading to cumulative age-associated damage and dysfunction. Cellular pathways that govern the synthesis, folding, and degradation of proteins are intrinsic and highly conserved in each cellular entity. The proper functionality and robustness of the proteostasis network (PN) is regulated by highly conserved genetic and physiologic stress sensors, which include the heat-shock response (HSR) for the cytoplasm and nucleus, the organellar unfolded protein responses (UPRs) for the endoplasmic reticulum and mitochondria, and other stress signaling pathways that control the expression of molecular chaperones to prevent misfolding and aggregation and allow the clearance of damaged proteins. While the central components of protein quality control in the PN function autonomously within each cell, it has been demonstrated recently that the HSR and the UPR are regulated in different tissues by cell-nonautonomous control via specific neurons and other nonneuronal somatic tissues to orchestrate an integrated organismal response.

Initially observed in *Caenorhabditis elegans*, the organismal HSR requires the activity of the AFD neurons for HSF-1-dependent induction of *hsp70* and other heat-shock genes in multiple tissues, demonstrating that the organismal HSR is regulated by cell-nonautonomous control (Prahlad et al. 2008). Subsequently, it was shown for other cell stress responses, including the UPR of the endoplasmic reticulum (UPR^{ER}) and the mitochondria (UPR^{mito}), that regulation of these pathways is also coordinated through neuronal signaling (Durieux et al. 2011; Sun et al. 2011, 2012; Taylor and Dillin 2013). Complementing the directed neuronal control of the cell stress response is transcellular chaperone signaling that occurs between nonneuronal somatic tissues and neurons to control the PN between tissues in response to the local expression of misfolded proteins or an imbalance in chaperone levels (van Oosten-Hawle et al. 2013). Collectively, these observations reveal that metazoans employ multiple signaling mechanisms across all somatic tissues to coordinate these biological processes, maintain

systemic proteostasis, and promote survival under various stress conditions.

Despite the wealth of knowledge on signaling processes regulating organismal development and life span, the observation that protein folding defects that occur in a single tissue elicit the appropriate stress response not only in that same affected tissue but throughout the organism seemed rather counterintuitive, as the regulation of cell stress responses and maintenance of proteostasis had been considered to be a cell-autonomous process. However, despite this, in the evolution from unicellularity to multicellularity, developmental stages involving spatial organization of specialized cell groups likely increased the requirement for intercellular cooperation to ensure that tissue-level proteostasis was balanced across the organism throughout development and adulthood. Challenges in cellular proteostasis elicited during development or by external stimuli would therefore require particular facets of the PN such as rapid, predictive, and adaptive changes in the expression of specific molecular chaperones, perhaps reflecting its role as an ancient innate defense system that is present in all kingdoms of life. Thus, mechanisms that protect the cellular proteome also need to exchange information on the status of internal cellular proteostasis in order to coordinate these processes across multiple cell types. How are these features of protein quality control linked among cells and tissues of a metazoan? The proposal that tissues exposed to stress secrete "danger signals" (Matzinger 1994) that can be released from inflamed cells to warn and prepare defense responses in surrounding cells could therefore extend to stress conditions that impair proteostasis.

In support of these ideas, molecular chaperones can function as activators of the innate immune response (Melcher et al. 1998), leading to the suggestion that immune responses and cell stress responses may have coevolved with the increasing complexity of metazoan systems. For example, the *hsp70* gene locus in humans is located in the MHC class III region of chromosome 6 (Goate et al. 1987), supporting the idea that the chaperones have a dual role to mediate external stress signals and prevent the accumulation of intracellular protein damage. It is therefore interesting to speculate whether the transcellular signaling molecules that regulate the HSR and other cell stress responses between different tissues to regulate the PN correspond conceptually or functionally to endocrine, paracrine, or immune signals. However, unlike hormonal control, in which signaling emanates from specific cells and tissues to achieve a systemic response, the regulation of the PN can be signaled from any tissue that is at risk. Thus, for the field of cell stress responses, molecular chaperones, and protein folding, the novelty lies in the discovery that these processes, too, require a systemic view to fully understand protein quality control mechanisms in an organism.

In this review, we focus on recent observations demonstrating systemic cell stress signaling in the invertebrate model systems of *C. elegans* and *Drosophila. melanogaster* that have uncovered the cell-nonautonomous control of proteostasis. Unlike plants or mammals, these model systems offer the opportunity to systematically uncover and understand prevalent transcellular communication mechanisms that respond to tissue-specific imbalances of PN components and protein misfolding at a multicellular level and throughout different conditions of stress and aging.

Cell stress responses and systemic integration of cellular proteostasis in a multicellular organism

The PN, by regulation of protein synthesis, folding, trafficking, secretion, and degradation, serves in all cells to maintain proteostasis and prevent protein misfolding in the face of ever-changing conditions of development and aging (Balch et al. 2008). Protein synthesis and folding alone are highly challenging events, as many proteins either do not fold spontaneously or fold inefficiently to the native state, in particular at the high concentrations of proteins within the various compartments of the cell. Folding assistance and suppression of off-pathway aggregation-prone species are provided by molecular chaperones, many of which are heat-shock proteins, a crucial facet in the maintenance of cellular proteostasis (Morimoto 2008). It is a common notion, therefore, that the level and types of chaperones expressed are finely tuned to a cell's individual proteome and specific folding requirements and the physiological niche of each tissue. For example, the proteomes expressed in muscle or neuronal cells are highly distinct according to the specialized function of each tissue (Powers et al. 2009); therefore, the composition of the PN reflects the folding requirements of a given cell type. Even though highly conserved cellular stress responses and survival mechanisms, including the HSR and the UPR, are inherent to each cell type and regulated cell-autonomously in isolated cells (e.g., cells in tissue culture), it is now clear that these processes are communicated between different tissues when embedded in the context of a metazoan.

Neuronal control of the organismal HSR and UPR

The HSR is a highly conserved transcriptional and post-transcriptional response program that is triggered by temperature and other forms of environmental and physiological stress conditions. Transcriptional activation is regulated by a family of heat-shock transcription factors, of which HSF-1 is conserved from yeast to humans (Akerfelt et al. 2010). Induction of HSF-1 activity reduces the load on the PN by elevating the levels of molecular chaperones to prevent misfolding, assist in refolding, and redirect misfolded species toward degradation (Akerfelt et al. 2010). When the capacity of the PN exceeds the demand, the HSR attenuates by negative regulation through an excess of the chaperones Hsp90 and Hsp70 that interact with HSF-1 and by acetylation of the DNA-binding domain accelerating the release of HSF-1 from DNA and attenuation of the HSR (Westerheide et al. 2009).

In *C. elegans*, the control of the HSR is regulated by the thermosensory AFD neurons that sense acute heat stress and transmit stress signals via neuropeptides and neuro-

hormones to the soma to activate HSF-1 and the expression of heat-shock genes (Prahlad et al. 2008). Whether animals respond to the temperature shift by inducing an organismal HSR depends on the function of *gcy-8*, a guanylyl cyclase that is solely expressed in the two AFD neurons (Prahlad et al. 2008), and an as yet unidentified downstream neuronal secreted signal (Table 1). These observations lead to the recognition that not only metabolic and developmental signaling processes but also cell stress responses are coordinated in a systemic manner in metazoans. Subsequent studies have now provided support that neurons have a major role in the orchestration of organismal responses to other cellular stress responses; for example, regulation by the UPR in the endoplasmic reticulum and mitochondria (Durieux et al. 2011; Sun et al. 2011; Taylor and Dillin 2013). Because the UPR regulates the flux of polypeptides in organelles and prevents the accumulation of misfolded proteins in both subcellular compartments, the UPR^{mito} and UPR^{ER} serve as a functional complement to the HSR in the cytoplasm and nucleus. In addition to the responses to acute stress, neurons also seem to have a role in the coordination of chronic misfolding stress, which can occur in somatic tissues (Prahlad and Morimoto 2011), and to restore muscle proteostasis through Ca^{2+}-dependent activation of the HSR via enhanced cholinergic signaling at the neuromuscular junction (Silva et al. 2013).

The mitochondrion also serves as a key subcellular compartment to detect and respond to proteotoxicity. The accumulation of damaged or misfolded proteins in the mitochondrial matrix initiates defense mechanisms in which mitochondria release a stress signal that is transmitted to the nucleus to alter the expression of nuclear encoded mitochondrial genes. The "proteotoxic stress signal" is degraded by ClpXP, resulting in the transport of misfolded proteins to the cytoplasm by the peptide transporter HAF1. This in turn activates the transcription factor ATFS-1 and expression of mitochondrial chaperones (Haynes and Ron 2010; Nargund et al. 2012) to prevent further mitochondrial damage. While mitochondrial dysfunction through expression of mutations in mitochondrial genes is associated with a large number of debilitating and life-threatening diseases (Wallace et al. 1998), mild mitochondrial stress achieved by reducing the expression of mitochondrial proteins has been suggested to be beneficial to health and life span in multiple organisms (Dillin et al. 2002; Hamilton et al. 2005; Copeland et al. 2009). For example, in *C. elegans* or mice expressing lower levels or mutant cytochrome c oxidase assembly factor, there is a perturbation of the electron transport chain (ETC), leading to induction of the UPR^{mito} and extension of life span (Dillin et al. 2002; Dell'agnello et al. 2007). Likewise, perturbation of the ETC by neuron-specific knockdown of *cco-1* induced the UPR^{mito} in a cell-nonautonomous manner throughout *C. elegans* with beneficial effects on life span, which led to the proposal of mitokines that are secreted by neurons (Table 1; Durieux et al. 2011). A comparable observation on mitochondrial dysfunction in mice has been shown to release fibroblast growth factor 21 (FGF21), a secretory factor from muscle tissue, leading to

enhanced metabolic capacity of adipose tissue and protecting the muscle from additional metabolic stress (Kim et al. 2013). Although usually expressed at low levels in muscle, FGF21 concentration is elevated in patients with rare mitochondrial diseases at certain pathological states (Tyynismaa et al. 2011).

Similar to the role of the UPR^{mito}, the UPR^{ER} responds to the accumulation of misfolded proteins in the endoplasmic reticulum, the subcellular compartment for folding of proteins destined for secretion and localization to the membrane. The UPR^{ER} is comprised of three branches, IRE1, PERK, and ATF6, each of which activates distinct downstream transcriptional responses. Activation of the IRE1 pathway by the IRE1 ribonuclease activity leads to splicing of the transcription factor XBP1 (Sidrauski and Walter 1997) to form XBP1 (*xbp1s*), which controls expression of target genes that reduce the endoplasmic reticulum folding load and restore proteostasis in this organelle (Shen et al. 2005; Acosta-Alvear et al. 2007; Ron and Walter 2007).

The cell-nonautonomous control of the UPR^{ER} by the nervous system of *C. elegans* regulates the IRE1/XBP1 branch of the UPR^{ER} in somatic tissue during adulthood but not in development via OCTR-1, a G-protein-coupled receptor expressed in ASH and ASI sensory neurons (Sun et al. 2011, 2012). Expression of a constitutively active *xbp1s* exclusively in neurons was sufficient to induce the UPR^{ER} in the intestine and possibly other tissues, as organismal endoplasmic reticulum stress resistance to tunicamycin was increased in aged animals (Taylor and Dillin 2013). This was proposed to be mediated by neurotransmitters from studies using animals defective in the release of neuronal small core vesicles (SCVs) (Table 1; Taylor and Dillin 2013). Future studies will elucidate whether ASH and ASI neurons regulate the release of SCV-mediated neurotransmitters in response to an activated UPR^{ER} and identification of responsible factors that regulate XBP1 in nonneuronal distal tissues. Of particular interest, the same neurons control the noncanonical branch of the UPR^{ER} by negatively regulating the expression of genes involved in innate immunity controlled by the phagocytic receptor CED-1 (Sun et al. 2011).

Nonneuronal somatic tissues as regulatory units for organismal proteostasis

Neuronal signaling provides rapid systemic communication across tissues to coordinate the cellular and tissue response to proteostatic challenges in metazoans. As indicated above, neurons in *C. elegans* sense and transmit physiological cell stress signals to regulate the HSR and the UPR at a systemic level. These principles of "tissue-to-tissue" communication are not specific to neuronal signaling in metazoans but rather reflect a conserved process of information flow. For example, bacteria employ quorum sensing for communication among individual cells within a population. Likewise, plants use cell-to-cell communication to coordinate environmental and developmental responses across diverse cell types, including transfer of microRNAs between cells (Carlsbecker et al. 2010), mem-

Table 1. *Cell-nonautonomous signaling responses*

Signaling category	Cell-nonautonomous response	Sender tissue	Signal	References
Neuron to nonneuronal soma	HSR	AFD neuron	AFD-dependent neuropeptide?	Prahlad et al. 2008
	UPR	ASH/ASI neurons	Unknown	Sun et al. 2011
	Noncanonical UPR (innate immunity)	ASH/ASI neurons	Unknown	Sun et al. 2012
	UPR^{mito}	Neurons	Neuronal "mitokine"	Durieux et al. 2011
	UPR^{ER}	Neurons	Neurotransmitter?	Taylor and Dillin 2013
Direct signaling between nonneuronal tissues	Gonadal longevity pathway	Steroidogenic tissues	Dafachronic acid	Antebi et al. 1998; Motola et al. 2006; Yamawaki et al. 2010
	HSR and systemic *hsp* epxression	Intestine, muscle, neurons	Transcellular stress factor (TSF)	van Oosten-Hawle et al. 2013
	FOXO-to-FOXO^{-} signaling	Intestine, muscle, hypodermis	*mdt-15*-dependent lipid signals	Zhang et al. 2013
	Innate immune responses	Gonad, intestine	Secreted immune peptides	Ermolaeva et al. 2013
	Longevity	Gonad to soma	*lipl-4*-dependent fatty acids	Lapierre et al. 2011
	Longevity	Gonad to soma	Oleic acid	Goudeau et al. (2011)
	Longevity	Gonad to soma	*let-7* microRNA family	Shen et al. 2012
	FOXO-to-FOXO	Intestine	IGF-like signals	Murphy et al. 2003
Indirect signaling between nonneuronal tissues (neuronal feedback)	Thermotaxis	Muscle, intestine	Estrogen	Sugi et al. 2011
	Longevity and survival	Gonad, neurons, intestine	*mir-71*	Boulias and Horvitz 2012
	FOXO/4EBP signaling (*D. melanogaster*)	Muscle	IGF?	Demontis and Perrimon 2010
	Mitophagy/ILS (*D. melanogaster*)	Muscle	Secreted IGFBP (impL2)	Owusu-Ansah et al. 2013

Categorization for cell-nonautomonous signaling responses in *C. elegans* (unless otherwise noted).

brane proteins (Meng et al. 2010), and mobile transcription factors (Tsukagoshi et al. 2010; Van Norman et al. 2011). Comparably, in *C. elegans*, the secretion of hormonal signaling molecules by specific somatic tissues has been shown to regulate metabolism and developmental processes (Antebi 2013). Recent observations in *C. elegans* now reveal that nonneuronal regulated cell-to-cell communication is essential for organismal proteostasis and stress responses, which ensures that stressed cells do not compromise the health of the organism (van Oosten-Hawle et al. 2013).

Transcellular chaperone signaling between nonneuronal cells

The organismal PN requires the balanced expression of chaperones across tissues for optimal performance, and yet the system must also remain highly sensitive to acute and chronic perturbations of local proteostasis capacity. For example, the expression of a single metastable (temperature-sensitive) protein such as metastable myosin in the body wall muscle cells of *C. elegans* leads to a compensatory up-regulation of muscle-autonomous expression of *hsp90* and a transcriptional feedback that normalizes *hsp90* expression across the organism (van Oosten-Hawle et al. 2013). This coordination of gene expression among multiple tissues reveals that different cell types can function as sentinels to detect and signal local proteotoxic challenges to other tissues throughout the organism. How this integrative transcellular signaling affects the entire organismal response to environmental challenges is shown by imbalanced tissue-specific chaperone expression: While increased *hsp90* expression can be beneficial for metastable proteins (such as the HSP90-dependent client myosin), a higher level of this chaperone could also compromise the response to severe environmental challenge because high levels of HSP90 prevent induction of HSF-1 and expression of heat-shock proteins.

These observations pose a conundrum: Local changes in the intracellular levels of *hsp90* can be compensated in a dose-dependent manner by induction or repression of the HSR within the cell (Bharadwaj et al. 1999; Akerfelt et al. 2010), while at the same time, an imbalance of local *hsp90* expression in a specific tissue affects the regulation of the HSR throughout the entire animal with detrimental consequences for survival during stress (Fig. 1; van Oosten-Hawle et al. 2013).

Therefore, to compensate for HSP90-mediated repression of the HSR and HSF-1 activation (Fig. 1A,B), balanced organismal proteostasis requires an involvement of additional transcription factors, such as the FoxA transcription factor PHA-4, which is cell-nonautonomously regulated in a tissue-selective manner for expression of HSP90 (van Oosten-Hawle et al. 2013). Considering that HSF-1 is vital for the expression of chaperones and maintenance of proteostasis in every cell, repression of HSF-1 activity must therefore be compensated for by increased activity of other transcriptional regulators to maintain the PN. The identification of PHA-4 has introduced a new component into the PN, as PHA-4 had previously been shown

to have a role in tissue (gut and pharynx) development (Gaudet and Mango 2002) and dietary restriction-induced life span extension regulated by TOR pathway signaling (Panowski et al. 2007; Hansen et al. 2008). The role of PHA-4 in chaperone expression is supported by evidence that PHA-4 binds to the *hsp90* promoter, although it remains unclear how higher levels of HSP90 in a sender tissue regulate *hsp90* expression in the receiving tissue (Fig. 1A,B). Interestingly, TOR signaling, which regulates PHA-4 activity, also requires HSP90 for mTORC1 assembly and proper signaling function (Qian et al. 2010). Thus, this may provoke a link between imbalanced chaperone expression and the observed increased PHA-4 activity in animals expressing altered local levels of HSP90 (van Oosten-Hawle et al. 2013). PHA-4 could therefore serve as an effector of the transcellular response in the receiving tissue by regulating *hsp90* expression (Fig. 1B) and, in this sense, compensates for the repression of HSF-1.

Consistent with the negative feedback mechanism that exists between chaperone levels and HSF-1 activation (Ali et al. 1998; Shi et al. 1998; Zou et al. 1998), reduced amounts of HSP90 in an individual tissue would therefore be expected to induce a cell-nonautonomous HSR via HSF-1-dependent signaling to multiple receiving tissues. The stress signal that is propagated to other target tissues within the animal would therefore be predicted to increase stress resistance (Fig. 1C,D). Thus, in response to locally reduced *hsp90* expression, HSF-1 likely acts as an effector in both sending and receiving tissues (Fig. 1C,D).

The identity of the signaling molecules that regulate the transcellular response in the receiving cells has not been determined, and we propose that one or more transcellular stress factors (TSFs) are secreted from the sending tissue to activate HSF-1 or PHA-4 (and possibly other transcription factors) in receiving cells, where they regulate and coordinate the appropriate integrated stress transcriptional response (Fig. 1B,D). These stress signals are likely distinct from the proposed mitokines that transmit mitochondrial proteostasis between cells (Durieux et al. 2011) and may also be distinct from the neuronal-dependent signaling pathways that regulate the HSR (Prahlad et al. 2008; Sun et al. 2011, 2012). We speculate that TSFs also mediate signaling between nonneuronal somatic tissue, such as between muscle and intestine, thus complementing the neuronal signaling cues of metazoans. Although the identity of the TSFs remains to be elucidated, these signals are likely dependent on PHA-4- or HSF-1-dependent downstream events in response to a proteostatic imbalance in the sender cell. Moreover, it is likely that these events are orchestrated by multiple TSFs to regulate the PN of different tissues during development and adulthood.

Chaperone expression and the proper induction of cell stress responses are therefore critical for organismal survival, which suggests that transcellular chaperone signaling may be regulated by an ancient conserved signaling process. Indeed, comparable observations for signaling events between nonneuronal tissues, where the transcriptional program is changed in the receiving cell, have been proposed for neuronal signaling and neurohormonal con-
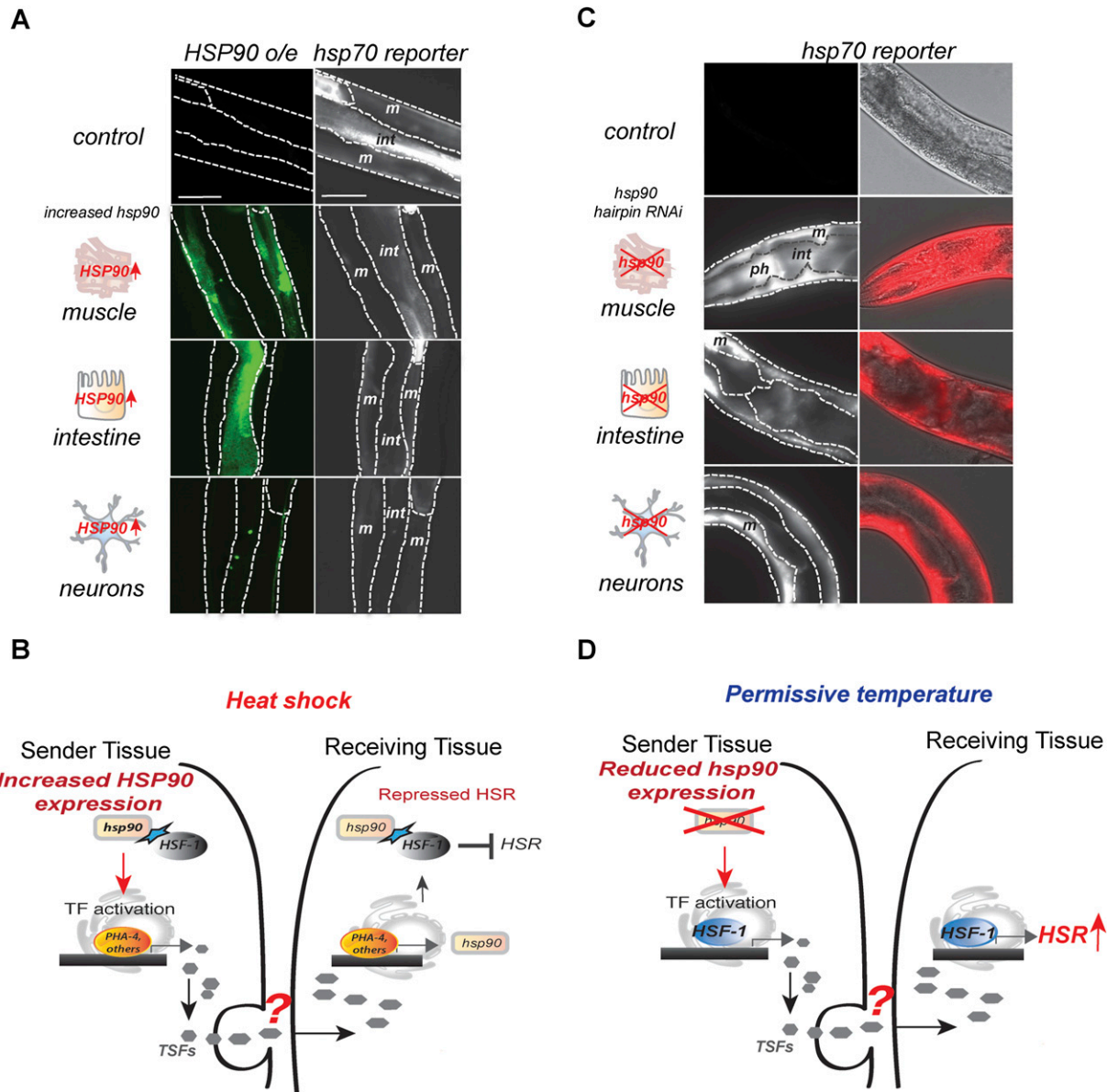
Figure 1. Transcellular chaperone signaling in the regulation of systemic proteostasis. (*A*) Local overexpression of HSP90 represses the HSR cell-nonautonomously during heat stress, as shown by expression of an *hsp70* reporter. (*B*) Model for transcellular chaperone signaling through tissue-specific overexpression of HSP90. Increased expression of HSP90 in the sender tissue potentially activates PHA-4. PHA-4-dependent expression of transcellular stress factors (TSFs) is transmitted from the sender cell to specific receiving cells, where PHA-4-dependent expression of, e.g., *hsp90* is initiated. (*C*) Tissue-specific reduction of *hsp90* expression through *hsp90* hairpin RNAi (hp-*hsp90*) induces the HSR (*hsp70 reporter*) cell-nonautonomously in different tissues at the permissive temperature. (*D*) Model for transcellular chaperone signaling through reduction of *hsp90* expression in the sender tissue. Reduced availability of *hsp90* in the sender cell activates HSF-1 transcriptional activity in the sender cell. A TSF, potentially dependent on HSF-1 transcription, is secreted from the sender tissue and taken up by specific receiving tissues, where it initiates HSF-1 activity and transcription of HSPs. (m) Body wall muscle; (int) intestine. Figures adapted from van Oosten-Hawle et al. (2013), © 2013, with permission from Elsevier.

trol to elicit specific downstream responses but have not been recognized previously in the context of proteostasis. The proposal that immune function not only is based on the ability to detect and address cellular damage and inflammation but, in a multicellular organism, requires the release of stress protein–peptide complexes or "danger signals" to alert the immune system and protect distal cells and tissues shares some conceptual similarities with the observations of cell-nonautonomous control of cell stress responses (Matzinger 1994). Indeed, members of the *hsp60*, *hsp70*, and *hsp90* family have been linked with innate immune response (Osterloh and Breloer 2008), offering the suggestion that heat-shock proteins could also serve as extracellular "danger signals." In further support, *hsp60* can stimulate human monocytes to secrete cytokines, including IL-6 and TNF (Chen et al. 1999; Ohashi

et al. 2000; Vabulas et al. 2001), and *hsp90* has been shown to activate NF-kB signaling and the subsequent secretion of IL-12 and TNF-α (Vabulas et al. 2002).

The hypothesis of "danger signals" affecting a multitissue immune response provides a useful context with the newly emerging field of transcellular chaperone signaling used by metazoans to communicate the presence of misfolded and aggregated proteins. From this perspective, the connection between innate immunity and cell stress responses in *C. elegans* is noteworthy. For example, animals exposed to pathogens are more resistant to subsequent exposures to lethal stress, which has been attributed to secreted immune signals from the intestine or the germline, leading to the systemic activation of the UPS and increased organismal proteostatic capacity independent of HSF-1 (Ermolaeva et al. 2013). Exposure to heat shock can boost innate immune responses in a manner dependent on DAF-2/DAF-16 signaling in *C. elegans* (Singh and Aballay 2006). Likewise, the UPR is also upregulated in response to pathogenic bacterial infection, suggesting increased demand for protein folding to achieve a successful immune response (Richardson et al. 2010; Sun et al. 2011, 2012; Singh and Aballay 2012).

Another link between cell stress responses and immune regulation is the relationship between the UPR and UPR-dependent inflammatory cytokines that promote tumor growth (Mumm and Oft 2008; Wheeler et al. 2008; Zhang and Kaufman 2008). Endoplasmic reticulum stress can be "transmitted" from tumor cells to macrophages that have been treated with conditioned medium of murine cancer cells experiencing endoplasmic reticulum stress in vitro. This results in the up-regulation of UPR signaling as well as increased synthesis of proinflammatory cytokines in the treated macrophages, favoring the tumor microenvironment to facilitate tumor growth (Mahadevan et al. 2011). However, a secreted factor mediating this intercellular communication has not been identified thus far.

Evidence for direct signaling events between nonneuronal tissues

Transcellular signaling between nonneuronal tissues of *Drosophila* and *C. elegans* to affect life span falls into two categories that provide a relevant point of reference. The first category corresponds to direct signaling between nonneuronal tissues, where a signaling molecule secreted from the sender cell directly activates a transcription factor through either immediate interaction with the transcription factor or activation of the correspondent upstream signaling cue in the receiving cell (Fig. 2A; Table 1). The second category corresponds to indirect signaling of a secreted factor between nonneuronal somatic tissues to the nervous system to regulate gene transcription in the periphery through neuroendocrine signaling (Fig. 2B; Table 1).
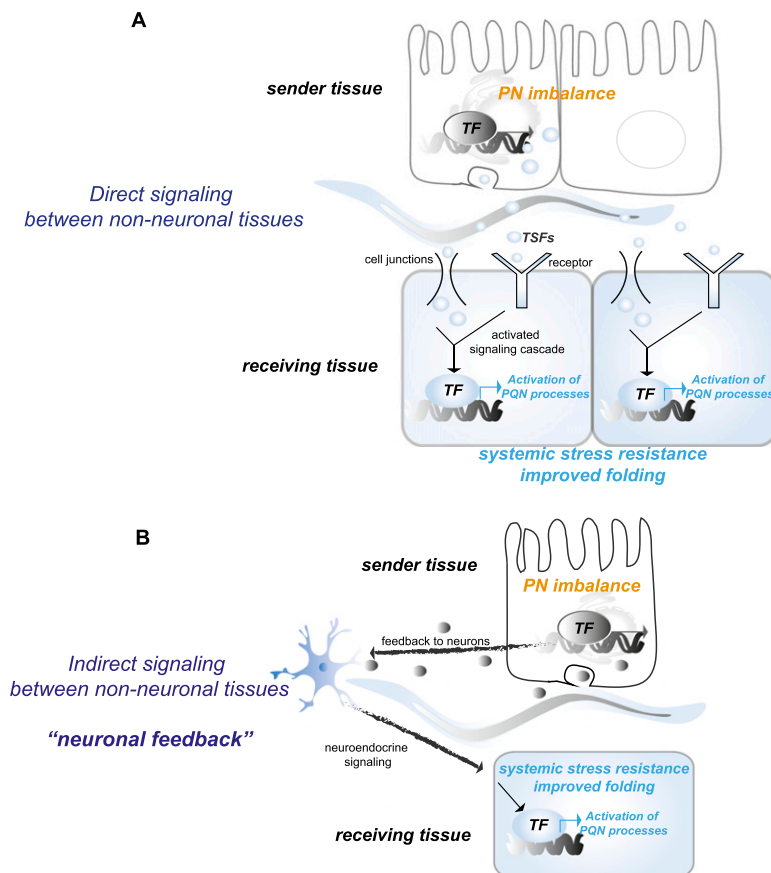

Figure 2. Intertissue signaling mechanisms integrating organismal proteostasis. (*A*) Direct signaling between nonneuronal tissues. An imbalanced PN in the sender tissue triggers activation of transcription factors and corresponding expression of signaling molecules or TSFs. TSFs are potentially secreted and taken up by receiving tissues through cellular junctions and transmembrane channels or by binding to specific receptors, which initiates a responsive signaling cascade in the receiving cell and activates a transcriptional program to increase the expression of PQN components required for stress resistance. (*B*) Indirect signaling between nonneuronal tissues via a neural feedback. An imbalanced PN in a nonneuronal sender tissue is signaled in a feedback response to the nervous system (i.e., estrogen signaling), which activates specific neuroendocrine signaling pathways to rapidly change transcriptional programs in peripheral nonneuronal tissues.

FOXO-to-FOXO signaling

An example of direct intertissue signaling is *FOXO-to-FOXO* signaling in *C. elegans*, in which the up-regulation of DAF-16/FOXO expression in the intestine influences DAF-16/FOXO activity in other receiving tissues (Libina et al. 2003; Murphy et al. 2007). This was shown to occur via feedback regulation through the insulin-like peptide *ins-7* produced in the intestine, therefore denoting the intestine as an important insulin signaling center that coordinates and equalizes DAF-16/FOXO activity among different tissues of the animal (Murphy et al. 2007). A related example for direct signaling between nonneuronal somatic tissue is *FOXO-to-FOXO⁻* signaling, whereby DAF-16/FOXO remotely activates gene expression in distal tissues independently of the presence of DAF-16 in the target cells (Zhang et al. 2013). Consequently, intestine-expressed *daf-16* in *daf-16⁻* animals induces *dod-11* and *hsp-12.6* expression in the intestine and other tissues (muscle and hypodermis) in *daf-16⁻* animals (Zhang et al. 2013). This signal is mediated by the lipid gene regulator *mdt-15* to affect gene expression "at a distance" in target tissues. However, the expression patterns for *mdt-15* are distinct from *dod-11* or *hsp-12.6*. Because MDT-15 functions as a transcriptional regulator of genes involved in lipid metabolism (Taubert et al. 2006, 2008), the activation of lipid signals that act across multiple tissues may be responsible for the observed transcellular effects (Zhang et al. 2013). *mdt-15*-mediated effects of DAF-16 in the intestine result in suppression of Aβ peptide aggregation, paralysis, and muscle dysfunction, revealing a beneficial effect on tissue proteostasis (Zhang et al. 2013).

Dafachronic acid signals

Among the initial observations for transcellular signaling in *C. elegans* is the gonadal longevity pathway regulated by DAF-12 signaling, in which a secreted molecule from somatic tissues regulates the transcriptional output of other somatic tissues with consequences for organismal survival (Antebi et al. 1998; Hsin and Kenyon 1999). Initially discovered as a nuclear hormone receptor that mediates the decision between reproductive development and dauer arrest during development (Antebi et al. 1998), DAF-12 is required to extend adult life span when germline stem cells are removed (Hsin and Kenyon 1999). DAF-12-mediated longevity is achieved through a signaling molecule secreted from the somatic gonad and other steroidogenic tissues, including the hypodermis and the neuroendocrine XXX cells in the head (Gerisch et al. 2001; Yamawaki et al. 2010). The corresponding signaling molecule is a bile acid-like steroid called dafachronic acid that directly binds DAF-12 and triggers its transcriptional activity in the target tissues (Table 1; Motola et al. 2006).

Lipid signals

Another class of signaling molecules that relays information between tissues is lipids and free fatty acids. Germline-less *glp-1* mutant animals exhibit high levels of lipase activity, such as the fatty acid lipase *lipl-4*

(Lapierre et al. 2011) or *lips-17* (McCormick et al. 2012), both of which are required for *glp-1* animals to extend life span. In support, germline ablation induces transcription of the nuclear hormone receptor NHR-80, which triggers induction of *fat-6*, a gene encoding a stearoyl coenzyme A desaturase (Goudeau et al. 2011). FAT-6 converts saturated C16 or C18 fatty acids into their monodesaturated forms, thus leading to increased levels of desaturated fatty acids. Consistent with these observations, germline-less animals contain higher levels of oleic acid, although it is unclear how increased oleic acid exerts its effects on life span extension, while increased expression of fat-processing enzymes, including LIPL-4, and the desaturases FAT-5 and FAT-6, and FAT-7 have an important role in the regulation of longevity (Murphy et al. 2003; Wang et al. 2008; Goudeau et al. 2011; Lapierre et al. 2011). Alternatively, transcellular factors may be modified by fatty acids, as occurs for Hedgehog, to enhance the stability and transport of or interactions with other components for delivery to target tissues (Nusse 2003; Panakova et al. 2005; Linder and Deschenes 2007; Palm et al. 2013). It will therefore be of interest to determine whether components of fat metabolism that contribute to life span do so by enhancing proteostasis capacity.

Evidence for feedback signaling from nonneuronal cells to the nervous system

Many observations support the roles of insulin/IGF secreted molecules and endocrine signaling pathways that coordinate changes in multiple tissues with beneficial effects on longevity (Kenyon 2010). The nervous system is the predominant locus of IGF expression (Pierce et al. 2001) and consequently has a central role as a signaling center through G proteins that integrate responses to extracellular stimuli (Ch'ng et al. 2008) and are expressed throughout the nervous system in *C. elegans*. These signaling responses are not unidirectional—for example, as occurs with G-coupled receptors in AFD neurons in response to thermal stress (from neurons to soma)—but also function in a bidirectional manner with feedback from somatic tissues to neurons. For example, estrogen signaling from peripheral tissue in *C. elegans* is involved in this feedback response, in which HSF-1 expression in muscle or intestinal tissue communicates with NHR-69 on the receiving end in thermosensory AFD neurons to affect thermotactic behavior of the animal (Sugi et al. 2011). Another example of an indirect cell-nonautonomous signaling mechanism likely involving neurons as mediators of complex tissue interplay is the regulation of survival and longevity through microRNA *mir-71* (de Lencastre et al. 2010; Boulias and Horvitz 2012). Loss of *mir-71* abolishes longevity of germline-less *glp-1* mutants and shortens the life span of *daf-2* and *cco-1* oxidase RNAi-treated animals (Boulias and Horvitz 2012). A subsequent analysis of tissue requirement of *mir-71* showed that neuronal expression was sufficient to rescue gonadal longevity, thus indicating a complex interplay between somatic tissues and neuronal feedback that influences *daf-16* activity in the soma.

For *Drosophila*, overexpression of dFOXO in the pericerebrelar fat body decreases expression of the insulin

gene *dilp2* in insulin-producing neurons, revealing indirect feedback from soma to neurons (Hwangbo et al. 2004; Demontis and Perrimon 2010). The activated form of dFOXO in *Drosophila* muscle or fatbody changes the feeding behavior of animals, leading to reduced synthesis of the insulin-like peptide *dilp2* in neurons and increased insulin/IGF-1 signaling in peripheral tissues (Hwangbo et al. 2004; Demontis and Perrimon 2010). While the signaling pathway by which dFOXO activity in peripheral tissues communicates to neurons has not been resolved, signaling could be through secreted insulin-like peptides that act on insulin receptors in neurons. Indeed, mitochondrial injury in *Drosophila* muscle up-regulates the insulin antagonist peptide ImpL2, which systemically down-regulates insulin signaling (Owusu-Ansah et al. 2013). Whether this effect of muscle-secreted ImpL2 is mitigated through a neuronal feedback toward other tissues remains to be addressed.

Conclusion and future aspects

The balance of cellular to organismal requirements of proteostasis through transcellular stress responses represents an important integrative consideration to understand complex biological events of aging and disease. Among the many open questions will be to identify the signaling pathways to achieve this tissue code for transcellular chaperone signaling and the molecules and factors that are transmitted from specific sender tissues upon perturbation of the PN or localized stress to the receiving tissues (Fig. 3). Are these processes regulated by a few identical signals released from different tissues that exert

similar consequences on organismal proteostasis, or does this correspond to a larger collection of factors perhaps specific to tissue lineages with similar organismal benefits? For example, longevity-promoting signals can be released from neurons as well as from the somatic gonad, and although different in nature, they both have similar consequences for organismal survival and aging. In addition to unraveling how the function and activities of signaling factors are integrated into the organism's function, it will be crucial to understand the physiological consequences of the existence of such an intertissue communication network on the local PN and regulation of cell stress responses. Are there costs on organismal morphology and fitness if transmission of transcellular stress signals is disrupted or enhanced? Also, it will be necessary to establish the circuitry and specificity of intertissue stress signaling pathways and molecules for the detection and treatment of protein misfolding diseases that often occur in a tissue-specific manner, such as neurodegenerative diseases, type 2 diabetes, or myopathies.

The recent efforts have benefitted greatly from the use of *C. elegans* as an ideal model system intermediate to isolated cells and even more complex metazoans and have provided a paradigm shift in our understanding of how proteostasis within and between different tissues in an organism relate to each other. Characterization of the biological effects of stress-related signaling molecules and other factors throughout development, adulthood, and aging will provide a rich understanding for years to come.
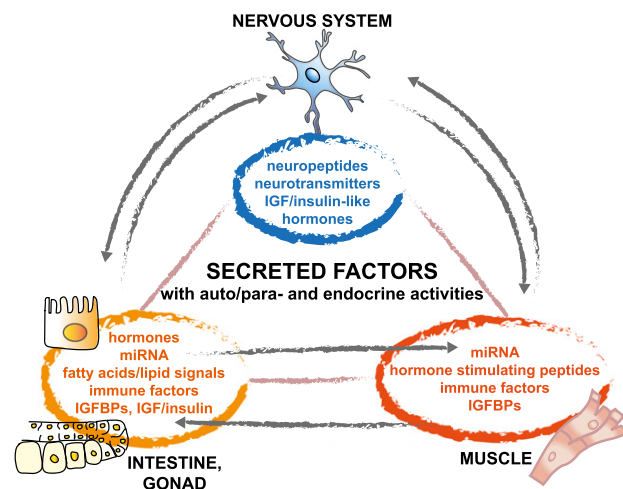
Acknowledgments

Figure 3. Secreted signaling molecules in the regulation of proteostasis via the nervous system and through paracrine communication between nonneuronal somatic tissues. Neurons perceive environmental stimuli and integrate the environmental challenge to fine-tune proteostasis in peripheral tissues through neuronally synthesized neuropeptides, neurotransmitters, and hormones. Nonneuronal tissues such as gonad, intestine, or muscle tissue communicate independently of neural control via autocrine/paracrine and endocrine activities with each other and can also report altered proteostasis conditions back to the nervous system.

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