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The Biology of Proteostasis in Aging and Disease

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Abstract

Loss of protein homeostasis (proteostasis) is a common feature of aging and disease that is characterized by the appearance of nonnative protein aggregates in various tissues. Protein aggregation is routinely suppressed by the proteostasis network (PN), a collection of macromolecular machines that operate in diverse ways to maintain proteome integrity across subcellular compartments and between tissues to ensure a healthy life span. Here, we review the composition, function, and organizational properties of the PN in the context of individual cells and entire organisms and discuss the mechanisms by which disruption of the PN, and related stress response pathways, contributes to the initiation and progression of disease. We explore emerging evidence that disease susceptibility arises from early changes in the composition and activity of the PN and propose that a more complete understanding of the temporal and spatial properties of the PN will enhance our ability to develop effective treatments for protein conformational diseases.

Keywords

chaperones; protein folding; stress response; neurodegenerative disease; protein misfolding; aggregation

Introduction

Proteome fidelity is maintained by the protein homeostasis (proteostasis) network (PN), a multi-compartmental system that coordinatesprotein synthesis, folding, disaggregation, and degradation (1). Despite the common factors required for protein synthesis and maintenance, the expression of many PN components is tailored to the specific proteomic demands of different cells and tissues (1). Furthermore, the activity of the PN can be altered permanently or transiently by development and aging, alterations in physiology, or exposure to environmental stress (1). As PN activity changes, so too does the capacity of cells to buffer against the accumulation of misfolded and damaged proteins. Therefore, temporal and spatial fluctuations in the PN could have profound consequences for disease presentation and progression.

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Whereas the classical view of the PN in relation to aging and disease has been described as "young versus old" or "before and after," there has been considerably less attention devoted to the malleability and dynamism of PN properties and composition with respect to different tissue types and life stages; however, it is likely that the relationship between the PN and disease encompasses these complexities. Here, we review the intra- and intercellular organization of the PN and discuss how temporal and spatial changes in PN composition and activity can influence proteostasis, aging, and disease. We focus on the relationship between the PN and neurodegenerative disorders such as Huntington's disease (HD), Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) (for reviews of these diseases, see References 2–5). Note, however, that the importance of proteostasis extends to many diseases (Table 1) (1, 6).

Defining the Proteostasis Network

Proteostasis is achieved by the coordinated action of many proteins known collectively as the PN (1). Here, we define the PN as a protein network with an immediate role in protein synthesis, folding, disaggregation, or degradation. This definition encompasses the translational machinery, molecular chaperones and cochaperones, the ubiquitin–proteasome system (UPS), and the autophagy machinery (Figure 1). Although essential for PN function and proteostasis, transcription factors (TFs), chromatin remodelers, structural components, signaling pathways, metabolic factors, general import/export machinery, and regulators of posttranslational modifications (PTMs) are considered auxiliary to the PN. Likewise, we consider stress response pathways such as the heat shock response (HSR) (7) and unfolded protein response (UPR) (8) to be critical and essential modifiers of PN composition rather than direct components of the PN.

The PN spans all subcellular compartments and is integral for cell viability and organismal health (1). Within the cell, compartmental subnetworks of the PN exist that are uniquely tailored both to the specific biochemical and functional properties of the proteome that they encounter and to the cellular environments they must inhabit (9). Importantly, these subnetworks cooperate substantially to monitor and maintain proteostasis across the cell (9).

Molecular Chaperones

Molecular chaperones are central to the function of the PN and can be broadly grouped into the HSP70, HSP90, DNAJ/HSP40, chaperonin/HSP60, and small HSP (sHSP) families (10, 11). Chaperones can act alone or in various combinations with different cochaperones to regulate client–substrate interactions, folding, disaggregation, degradation, and trafficking within the cell (11). Many molecular chaperones are highly conserved and pivotal, but the best studied are members of the HSP70 and HSP90 families. Although more than 15 mammalian HSP70 homologs and 4 HSP90 homologs exist, most of our understanding of HSP70 and HSP90 function comes from studies of the cytosolic/nuclear HSC70, HSP90, and inducible HSP70 (*HSPA1A*/*B*). However, homologs of HSP70 and HSP90 are also integral to endoplasmic reticulum (ER) (BiP and GRP94) and mitochondrial (Mortalin and TRAP1) function (12).

HSP70 and HSP90 are highly abundant proteins with levels estimated to make up 1–2% of the total protein in some cells (12). ATP hydrolysisis essential for the chaperone activity of HSP70 and HSP90, causing conformational changes that result in substrate binding (11). Nucleotide exchange releases bound substrates; several rounds of binding and release by HSP70 are sometimes required for complete client refolding (11, 13). When protein refolding is inefficient, the cochaperones C terminus of HSC70-interacting protein (CHIP) and Bcl2-associated athanogene 1 (BAG1) can interact with HSP70 and HSP90 complexes to promote substrate ubiquitylation, thereby redirecting HSP70 and HSP90 clients to the proteasome for degradation (14, 15). As such, HSP70 and HSP90 are central to the process of triaging proteins for refolding or elimination. The client specificity and functional properties of HSP70 and HSP90 are strongly influenced by interactions with a range of cochaperones (16). HSP90 associates with more than 20 cochaperones, the combinations of which dictate HSP90 function, whereas HSP70 is regulated principally by HSP40/DNAJ chaperones (12, 13). Although distinct, the HSP90 and HSP70 machines also cooperate, most notably in steroid hormone and signal transduction kinase maturation through the cochaperone HSC70/HSP90 organizing protein (HOP/STI1). HOP/STI1 simultaneously binds HSC70 and HSP90 through multiple tetratricopeptide repeat (TPR) domains, thereby facilitating maturation of clients through the sequential action of both HSP70 and HSP90 (12). HSP70 is also recruited to newly synthesized polypeptides by the ribosome-associated complex (RAC), which in mammals is formed from the HSP40/DNAJ protein MPP11 and HSP70L1 (17). RAC binds near the ribosome exit tunnel and stimulates HSP70 binding to nascent polypeptides, thus complementing the role of the nascent polypeptide chain–associated complex (NAC), the initial factor that binds and protects newly synthesized proteins, maintaining them in a folding-competent state for HSP70 (17).

HSP70 and HSP90 homologs are exceeded by the number of HSP40/DNAJ chaperones. HSP40/DNAJ chaperones contain a conserved J domain that mediates interactions with HSP70 but otherwise exhibit heterogeneity in structure, localization, and function. Due to this diversity, HSP40/DNAJ chaperones can be thought of as adaptors that provide versatility to HSP70 function (13). HSP40/DNAJ chaperones assist protein refolding by presenting misfolded proteins to HSP70 and by stimulating HSP70 ATPase activity (13). Efficient protein folding by HSP70 is also influenced by nucleotide exchange factors (NEFs), such as BAG1, that promote ADP/ATP exchange at the N terminus of HSP70 and form distinct functional complexes with the HSP70/HSP40 machinery (13). Perhaps the most significant example of this process is that the HSP110 molecular chaperone, long considered simply a NEF, can catalyze protein disaggregation as part of a complex containing HSP70 and DNAJ/HSP40 (18). This capability provides an extra mechanism by which mammalian cells can eliminate protein aggregates and suppress proteotoxicity, a function carried out by the dedicated chaperones HSP104 and ClpB in yeast and bacteria, respectively (19).

In addition to the HSP40/DNAJ family and cochaperones, the sHSP family facilitates client refolding by HSP70. There are 10 mammalian sHSPs, all of which are cytosolic and most of which contain an α-crystalline domain (10). sHSPs influence protein folding by forming large homo-oligomeric cages that trap misfolded clients and prevent them from forming undesirable intra-or intermolecular interactions in the cytosol. This process is ATP

independent and presumed to create a reservoir of refolding competent clients for the HSP70 machinery. Although the full repertoire of sHSP clients is still unclear, it is assumed that sHSPs act broadly, although some degree of selectivity is expected between family members (10).

In addition to the more general chaperone functions carried out by the HSP70/HSP40 and HSP90 machines, some proteins require the specialized functions afforded by the HSP60/chaperonin family. Chaperonins consist of two large hexameric ring complexes that form a cylindrical structure whose core provides a protected environment for protein refolding (11). Two classes of chaperonins exist, the class I mitochondrial HSP60, which is similar to bacterial GroEL, and the class II TCP-1 ring complex (TRiC), which is found in the eukaryotic cytosol (11). HSP60 is essential for maturation and maintenance of the mitochondrial proteome and is therefore intimately linked to energy production. TRiC is essential for proper posttranslational folding of the cytoskeletal components actin and tubulin and is therefore essential for cell structure, division, and cargo delivery (11).

Protein Degradation Pathways

When protein functionality cannot be restored from misfolded and aggregated states, chaperones help redirect nonnative clients toward degradation pathways. Proteins can be degraded either individually or en masse by proteasomes (20) or lysosomes (21), respectively. Proteasomes are large multisubunit complexes that consist of a 19S regulatory cap and a 20S proteolytic core (22). The 19S regulatory particle recognizes ubiquitylated substrates, removes ubiquitin chains, and unfolds the client to allow entry into the 20S core, where it is rapidly degraded into peptides (20, 23). This process is initiated by the addition of polyubiquitin chains through the stepwise activity of E1 ubiquitin–activating enzymes, E2 ubiquitin–conjugating enzymes, and E3 ubiquitin ligases (20).

Ubiquitin chains are formed through conjugation of ubiquitin monomers to clients via distinct lysine residues. This process can take the form of a variety of linkages; however, K48-linked ubiquitin chains are directed primarily to the proteasome (24). Once ubiquitylated, chaperone– cochaperone complexes direct clients to the proteasome, where deubiquitylating enzymes (DUBs) remove ubiquitin chains to allow substrate entry into the 20S core (20). DUBs can be associated with a commitment to degradation and bulk removal of ubiquitin, as is the case for PSMD14, or they can operate independently of client degradation through sequential “trimming” of ubiquitin chains, as is observed with UCHL37 and USP14 (25–28). These opposing activities are proposed to allow “tuning” of proteasomal degradation to be either general or selective as required (20). Despite their cytosolic and nuclear localization, proteasomes are an important site of ER protein quality control through the ER-associated degradation (ERAD) pathway (29). Misfolded proteins in the ER lumen are recognized by the ER membrane–associated HRD1–SEL1–HERP complex and retrotranslocated to the cytoplasm by the AAA ATPase VCP/p97–NPL4–UFD-1 complex (several client-specific forms of this process requiring specialized adapters of the VCP/p97 and HRD1 complexes have been described). The retrotranslocated protein is then ubiquitylated and delivered to the proteasome for degradation, thereby eliminating terminally misfolded proteins from the ER. Distinct ERAD mechanisms are utilized

depending on whether protein misfolding is exposed to the ER lumen (ERAD-L), exposed within the ER membrane (ERAD-M), or exposed to the cytosolic face of the ER membrane (ERAD-C), demonstrating the degree to which quality-control pathways can be tailored to substrate type and location (29). A recent study showed that some mutant forms of gonadotropin-releasing hormone receptor (GnRHR) are resistant to ERAD and are instead degraded by ER quality-control (ERQC) autophagy, a complementary pathway modulated by DNAJB12 when ERAD fails (30).

Although the proteasome is the primary source of protein degradation in the cell, biophysical limitations of the central pore of the 20S core do not permit the degradation of unfolded or large protein complexes (20). How, then, do cells remove large protein aggregates? As discussed above, one approach is to employ specialized molecular chaperone machines to release misfolded proteins from aggregates and direct them to the proteasome for degradation (19). Alternatively, bulkier substrates, such as large inclusions, can be directed to the lysosome, a membrane-bound organelle containing a host of nonspecific proteases that can degrade a wide range of substrates (21). Proteins and organelles are directed to lysosomes as the terminal step of autophagy. Autophagy complements the UPS in three mechanistically distinct forms: macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy (21). Macroautophagy is the best-studied form and entails the sequestration of organelles or regions of the cytosol into a double-membrane vesicle structure known as an autophagosome. The resulting autophagosome is then transported to, and fuses with, the lysosome, thereby delivering its cargo for degradation (21). In contrast, microautophagy occurs by direct engulfment of the cytosol at the lysosome membrane, and CMA occurs through HSC70-mediated delivery of proteins across the lysosomal membrane via the LAMP2A receptor (21, 31). Autophagy is regulated by the mammalian target of rapamycin complex 1 (mTORC1) and mTORC2, thereby integrating the PN with the nutritional status of the organism, the metabolic state of the cell, and rates of protein synthesis (21).

Stress Response Pathways Alter Proteostasis Network Composition

The composition of the PN is highly dynamic; the levels of molecular chaperones, cochaperones, and proteasomal subunits can be increased globally or in a compartment-specific manner to provide additional protection against acute and chronic protein misfolding in the cell (1). Malleability of the PN is provided by dedicated stress responsive TFs with distinct and complementary transcriptional targets. Although a number of stress response pathways can greatly influence proteostasis, aging, and disease (see the sidebar), here we focus our attention on the HSR, which is regulated by heat shock transcription factors (HSFs) and augments the cytosolic/nuclear arm of the PN (7) and the UPRs of the ER (UPR^{ER}) and mitochondria (UPR^{mito}), which respond to protein misfolding through the TFs XBP1, ATF6, and ATF4 (8) and through ATFS1, respectively (32).

Stress response TFs are maintained in a repressed or inactive state that is distinct for each stress response pathway. In mammalian cells, despite the existence of multiple HSFs, HSF1 is considered the master regulator of the HSR (7). HSF1 is maintained as an inactive monomer in the cytosol through transient interactions with HSP70 and HSP90 (33, 34).

Upon increased levels of nonnative proteins, HSF1 is released from its repressive complex, acquires DNA-binding activity through homotrimerization, and rapidly translocates to the nucleus to induce expression of genes encoding molecular chaperones (7, 35). Once stress has been relieved, HSF1 activity is repressed through acetylation and binding to molecular chaperones (34, 36, 37).

In contrast, the UPR^{ER} is a more elaborate process that involves three stress responsive arms. IRE1 is a transmembrane protein with kinase and endoribonuclease (RNase) activity that senses misfolding in the ER directly, leading to autophosphorylation, oligomerization, and acquisition of RNase activity (8). This process allows active IRE1 to cleave *XBP1* messenger RNA (mRNA), thereby generating a spliced transcript (*XBP1s*) that encodes a stable form of XBP1 that binds DNA and induces transcription of UPR target genes (8). In parallel, ER stress promotes the relocation of ATF6 from the ER membrane to the Golgi apparatus, where it is cleaved by SP1 and SP2 proteases. The cytosolic N-terminal fragment of ATF6 that is generated translocates to the nucleus, binds DNA, and drives expression of a complementary set of UPR genes (8). Finally, a third ER transmembrane protein, PERK, promotes translation of the TF ATF4 by phosphorylating the translation initiation factor eIF2α in response to ER stress. Under these conditions, ATF4 mRNA is preferentially translated, leading to selective expression of the proapoptotic TF CHOP, which elicits apoptosis if ER stress is not resolved, presumably to ensure that irreversibly damaged cells are removed from the population.

Although the UPR^{mito} has been less extensively studied than the HSR and UPR^{ER}, a mechanistic basis for this process is emerging. In the absence of stress, the TF ATFS1 is transported into the mitochondria and degraded by LON protease (32). However, upon mitochondrial stress, import is impaired, allowing ATFS1 to accumulate in the cytosol and translocate to the nucleus, where it regulates transcription of genes encoding mitochondrial chaperones, mitochondrial import machinery, and glycolysis components (32).

As a complement to stress-inducible transcription, global reductions in RNA splicing and translation are also observed upon stress. These changes suppress the de novo synthesis of the majority of the proteome and prioritize the expression of chaperones and other stress response proteins until more favorable conditions are achieved (38, 39). In yeast, the expression of chaperones involved in nascent chain folding is reduced upon stress, consistent with a global repression of protein synthesis (40). Similarly, in mammalian cells, heat shock results in a global pausing of translation elongation due to reduced association of HSP70 with translating ribosomes (39). Interestingly, a recent screen for regulators of HSF1 activity in yeast suggests that stalled ribosomes can also signal back to the PN through the ribosome-associated quality-control complex (RQC) (41). Therefore, stress responses are tightly coupled to the translational state of the cell in order to coordinate changes in PN composition with the quality and quantity of protein biogenesis. Although the extent to which stress responses communicate with one another remains unknown, it is clear that they are integrated into a network that enshrouds the PN to influence proteostasis across subcellular compartments.

Organismal Connectivity of the Proteostasis Network and Stress Responses

With the evolution of multicellular organisms, regulation of the PN has acquired additional layers of complexity to ensure optimal proteostasis both within the cell (cell-autonomous control) and between cells and tissues (cell-nonautonomous control) (42). To this end, cells have evolved the ability to communicate local environmental and proteostasis states to distal cells and tissues. This ability has been demonstrated primarily in the nematode *Caenorhabditis elegans*, in which genetic disruption of AFD thermosensory neurons alters the organismal response to acute or chronic stress (43, 44). Subsequent complementary studies investigating the role of the UPR^{ER} and reduced mitochondrial function in *C. elegans* life-span extension revealed that XBP1 overexpression or disruption of mitochondrial homeostasis, specifically in neurons, enhances the PN throughout the organism through activation of the UPR^{ER} or UPR^{mito}, respectively (45, 46).

Cell-nonautonomous control of the PN and stress responses does not occur solely through neuronal signaling. Altered expression of HSP90 in muscle cells, intestinal cells, or neurons influences the folding environment and stress responses in unperturbed tissues through the TF PHA-4/FOXA (47), whereas overexpression of dFOXO in the muscle tissue of flies can influence protein aggregation in neurons and the retina (48). Furthermore, removal of germ-line stem cells (GSCs) enhances the PN and organismal proteostasis, whereas damage of GSC DNA leads to enhanced somatic stress resistance in worms (49–52).

Together, these findings reveal that the PN and stress response pathways are organized to sense and respond to both intercellular and intracellular stress signals in metazoans. Although the extent to which these observations extend to vertebrate biology is unknown, it is tempting to speculate that in mammals, local signals from affected cells could act to galvanize entire tissues against imminent proteostasis threats such as infection or infarction, or that signals from one tissue could prime the PN of a distal tissue in preparation for periods of intense activity and chronic stress.

Differential Regulation of the Proteostasis Network Across Tissues and Cell Types

The preceding section describes the composition of the PN (and its subnetworks) in terms of the major individual components and their function, an approach that has been adopted by previous reviews (1, 9). However, the inconvenient truth is that the PN is unlikely to exist as a single identity across all cell and tissue types. Certain observations support the hypothesis that the PN and stress responses are not equivalent between cell types. For instance, differential requirements for PN components can be inferred from the disease pathology associated with mutations in genes encoding PN components (Table 1).

Microarray profiling across 80 human tissues revealed that the expression of PN genes is highly heterogeneous, even for central chaperones such as HSC70 and HSP90 (1). PN heterogeneity was not restricted to specific components or chaperone families; instead, all classes of chaperone, autophagy mediators, UPS components, and stress response regulators

exhibited profoundly altered expression patterns between tissues. Significantly altered PN profiles were also observed with age and development, as exemplified by the finding that adult liver was more similar to almost every other tissue tested than to its fetal form (1). Differential PN requirements have also been linked to developmental potential through studies in human embryonic stem cells (hESCs), in which maintenance of pluripotency and efficient differentiation require high levels of proteasome activity through increased expression of the 19S subunit PSMD11 (53).

Such differences in the PN are further supported by the Allen Brain Atlas, a catalog of gene expression based on in situ hybridization studies in 17 mouse brain regions (54). HSP70, HSP90, and HSP110 family members were found to be expressed at high levels throughout the brain; however, the expression of DNAJ/HSP40 chaperones and cochaperones was highly heterogeneous, suggesting that differences in the levels of these proteins may tailor HSP70 and HSP90 function to accommodate region-specific clients (54). Although these findings are in keeping with expected differences in the composition of the transcriptome and proteome between tissues, the degree of heterogeneity in the PN remains surprising, given the common folding requirements of proteins (1).

A genetic investigation of HSR regulation in *C. elegans* also supports the hypothesis that different cell types have different PN requirements. A genome-wide RNA interference (RNAi) screen for genes that influence induction of a fluorescent reporter of the HSR [*hsp-70* promoter driving green fluorescent protein (GFP) expression] identified 52 genes whose knockdown resulted in reporter activation, of which 39 genes encode PN components (55). Whereas knockdown of HSC70 or HSP90 resulted in reporter activation in all tissues, knockdown of other PN components resulted in tissue-specific patterns of reporter activation, despite the ubiquitous expression of these genes. For example, knockdown of TRiC subunits activated the HSR exclusively in muscle, whereas knockdown of a mitochondrial HSP70 homolog induced the HSR reporter only in the intestine. Conversely, depletion of proteasomal subunits or an ER HSP70 homolog induced the HSR in muscle and the spermatheca but not in the intestine. These findings indicate that different tissues likely have distinct PN composition and requirements (55).

Studies to elucidate the relationship between chaperone levels, regulation of stress responses, and proteotoxicity have hinted at how PN heterogeneity can influence disease presentation and progression. An investigation of the HSR in cultured spinal cord cells revealed that compared with glial cells, motor neurons do not robustly upregulate HSP70 in response to heat shock due to an inability to activate HSF1 (56). The basis for this is unknown; however, these findings suggest that an inability to activate the HSR in motor neurons may contribute to ALS.

A complementary investigation of the selective pathology associated with polyglutamine (polyQ) disease conducted microarray profiling of primary cortical, striatal, and cerebellar neurons expressing either mutant huntingtin (mHTT) or mutant ataxin-1 (mAtaxin-1). Cerebellar granular neurons were found to express high levels of HSP70 in response to mHTT expression but not mAtaxin-1. This effect was independent of HSF1 and did not occur in striatal and cortical neurons (57). Furthermore, increased levels of HSP70 were

found in the cerebellar cortex of human HD brain samples but not in tissue from unaffected individuals or from brains of PD patients (57). A more recent study investigating mHTT turnover in different neuronal types found that the ability to efficiently degrade mHTT correlates strongly with neuronal health and can vary among individual neurons (58). Turnover of mHTT was faster in cerebellar neurons than in cortical or striatal cells, suggesting that the degradative capacity of the PN can also contribute to the differential toxicity of mHTT associated with neuronal subtypes (58). Although limited in scope, these studies act as a proof of principle that tissue- and cell-specific regulation of the PN is entwined with cellular function, disease presentation, and progression.

Proteostasis Network Disruption and Proteostasis Collapse in Neurodegenerative Diseases

Whether due to the chronic expression of mutant proteins with altered stability or mutations that arise in PN genes, a large number of human disorders can be categorized as PN disruptions. This observation highlights the general importance of the PN in human health (Table 1) (59, 60).

Protein aggregation is recognized as a hallmark of neurodegenerative disease by the consistent appearance of detergent-insoluble inclusions and aggregates in the nucleus and cytoplasm of neurons. These structures contain amyloid, large-ordered fibrils of cross-β-sheet-enriched proteins, and form in HD, PD, AD, and ALS despite the lack of sequence similarity between the respective disease-causing proteins. Similar aggregate structures have also been detected in type II diabetes and a range of amyloid disorders throughout the periphery; some 50 human diseases have been linked to amyloid formation (59). Note that protein aggregates can also take many amyloid-free forms, each of which may have a unique role in disease presentation and progression, with some aggregates proposed to represent active compartmentalization of misfolded species by the PN (59–61).

The commonality of these observations has led to fundamental questions of how and why proteostasis collapse occurs and how this affects disease onset and progression. Does chronic expression of misfolding-prone proteins overwhelm or progressively disrupt the PN, or do age-related changes in the PN compromise its robustness, leading to accelerated misfolding, aggregation, and progression of disease? Intriguingly, there is evidence to support both disease models.

The expression of polyQ fused to yellow fluorescent protein (polyQ: :YFP) in *C. elegans* muscle, intestine, or neurons leads to aggregate formation in a polyQ length- and age-dependent manner (62). In the presence of endogenous metastable proteins, polyQ disrupts the folding capacity of the PN, enhances the misfolding of metastable proteins, and causes cellular dysfunction and specific loss-of-function phenotypes (63). In return, aggregation and toxicity of polyQ: :YFP are further intensified by the presence of metastable proteins, providing support for a “feed-forward” amplification of protein misfolding toxicity (63). These findings suggest that the chronic expression of aggregation-prone proteins reduces the folding capacity of the PN, resulting in the misfolding of metastable proteins across the proteome. Although these observations support PN dysregulation as a pivotal feature of

neurodegenerative disease, these studies did not address which components of the PN are compromised.

Dysregulation of Molecular Chaperones

Studies of chaperone levels in tissue culture and mouse models of polyQ disease showed that the levels of HSP70 (HSPA1A/B) and DNAJ/HSP40 (DNAJB1), as well as some cochaperones, decline with protein aggregation (64, 65). This reduction in chaperone levels can occur through a combination of transcriptional dysregulation and sequestration of chaperones by mHTT or polyQ aggregates (64–66). Sequestration of chaperones by insoluble aggregates also leads to reduced levels of soluble HSP70, HSP40, HSP90, and sHSPs in mouse and *C. elegans* models of AD, tissue culture and *Drosophila* models of PD (67–70), and tissue culture and mouse models of spinocerebellar ataxia 3 [SCA3; also known as Machado–Joseph disease (MJD)] (71). These observations suggest that perturbation of molecular chaperones may be central to global proteostasis collapse in disease. How, then, might dysregulation of molecular chaperones contribute to neuronal dysfunction?

Sequestration of HSC70 by intracellular aggregates interferes with clathrin-mediated endocytosis (CME) in mammalian cells, including neurons (72). These effects were observed in cells expressing aggregation-prone forms of mHTT, mAtaxin-1, and SOD1, suggesting that protein aggregation and chaperone sequestration may contribute to a range of neurodegenerative disease phenotypes (72). These observations haveled to a so-called chaperone competition model, in which the compulsive requirement of misfolded proteins for HSC70/HSP70, and likely other chaper-ones, reduces the chaperone pool available to maintain normal cellular function. This model could explain the pleiotropic effects observed in all neurodegenerative diseases; however, it is unknown whether chaperone sequestration causes a gradual or sudden impairment of cellular pathways, which chaperones are affected, or whether all chaperone-regulated processes are equally affected.

Disruption of Protein Degradation Pathways

One of the principal features of protein folding diseases is the ubiquitination of proteins within aggregates. The presence of ubiquitinated inclusions suggests that disease-related proteins marked for degradation may be inefficiently targeted to proteasomes or are resistant to degradation. Alternatively, investigators have reasoned that impairment of the UPS could underlie the accumulation of ubiquitylated proteins and therefore significantly contribute to multiple neurodegenerative diseases. Experiments examining the effects of Aβ on proteasomal activity in vitro revealed an inhibitory effect on the chymotrypsin-like properties of the 20S core (73), consistent with observations of impaired proteasome function in AD patient brains (74). Further evidence for UPS dysfunction in AD comes from studies showing that a mutant form of ubiquitin (UBB+1) accumulates in AD brain tissue and causes proteasome inhibition and neurotoxicity via the activity of the E2 ubiquitin–conjugating enzyme HIP-2 (75). The expression of mutant SOD1 also causes dys-regulation of the UPS in mammalian cells and in spinal cord motor neurons of mice (76, 77). This effect is proposed to occur through transcriptional dysregulation and sequestration of proteasomal subunits by mutant SOD1 aggregates (76, 77). Similarly, turnover of a

fluorescent proteasome reporter (GFP^U degron) is impaired in mammalian cells expressing mutant α-synuclein, and reduced proteasome activity has been reported in the substantia nigra of PD patients compared with that of unaffected individuals (78). This reduction in activity may be exacerbated in familial forms of PD caused by mutations in the E3 ubiquitin ligase parkin (79).

Although linked to AD, PD, and ALS, UPS dysfunction has been most intensely studied in the context of polyQ disease. Initial biochemical studies suggested that expansions of polyQ may directly inhibit or "choke" the proteasome (80), causing the accumulation of lysine 48– and lysine 63–linked ubiquitin chains in brain tissue from HD patients and mice (81). However, more recent data have shown that the inhibitory effect of mHTT on the proteasome is not associated with increased polyQ length or aggregation state, suggesting that ubiquitin chain accumulation in HD does not occur due to direct negative interactions between mHTT and the proteasome (82). Recent findings in yeast and HEK293 cells support this idea by demonstrating that sequestration of Sis1p (human DNAJB1) by mHTT or mAtaxin-3 aggregates decreases the trafficking of misfolded proteins to nuclear proteasomes for degradation, thus exacerbating proteostasis collapse (83). This finding suggests that UPS impairment arises from a progressive titration of chaperones away from clients, thereby interfering with the movement of ubiquitylated clients to the proteasome (82). Thus, it is the growing "queue" of proteasomal substrates that causes an accumulation of ubiquitin conjugates in HD (82), indicating that, like CME, dysregulation of the UPS is a symptom of chaperone competition in disease. Given that chaperone sequestration is also observed in AD, PD, and ALS models, this mechanism may contribute to proteostasis collapse in multiple neurodegenerative diseases.

In addition to their role in proteasomal impairment, alterations in autophagy have been linked to health and disease progression. Mice deficient for the autophagy-related genes *Atg5* and *Atg7* exhibit severe neurodegeneration (84, 85), and the expression of disease-associated proteins is reported to exert differential inhibitory effects on autophagic pathways. Consistent with a role of autophagy in disease, AD patient tissues exhibit impaired initiation of macroautophagy and an excess of autophagic vacuoles in dystrophic neurites, possibly due to impaired targeting of the vacuolar ATPase to the lysosome (86, 87). In contrast, α-synuclein overexpression impairs autophagy in mammalian cells and mice through reduced expression of RAB1A, thereby inhibiting autophagosome formation (88). In addition to macroautophagy, mutant α-synuclein may impair CMA, suggesting that defects in multiple autophagic arms could contribute to PD (89, 90). In HD, autophagosome formation and lysosomal fusion appear to be unaffected by the expression of mHTT; instead, it has been proposed that the loading of cytosolic cargo, particularly organelles, is inefficient, possibly due to aberrant interactions between p62, ubiquitin chains, and mHTT (91). In contrast to findings in HD, AD, and PD, a recent study has suggested that autophagy is enhanced in ALS mice. Reduced levels of lipofuscin, LC3, and p62 have been observed in motor neurons of $SOD1^{G85R}$ mice (92). Treatment with the autophagy inhibitor chloroquine restored lipofuscin, LC3, and p62 levels in motor neurons, suggesting that mutant SOD1 causes hyperactive autophagy in mice (92). Together, these findings support the idea that impairment of protein degradation pathways is likely fundamental to much of the cellular

disruption observed in neurodegenerative diseases. However, as reported for molecular chaperones, it is clear that PN disruption can have disease-specific components.

Stress Response Pathway Impairment

Dysregulation of the HSR with disease progression is associated with toxicity in tissue culture, *Drosophila melanogaster*, and mouse models of HD, SCA-17, and SCA-3/MJD, as well as in mammalian cells expressing a synthetic amyloid-forming peptide (93–99). Impaired binding of HSF1 to DNA is observed genome wide in HD cells and is reported to affect the expression of many important nonchaperone genes (100). Although the mechanism of HSR impairment is unclear, it is possible that changes in HSF1 activation, reduced HSF1 levels, and altered chromatin architecture underlie transcriptional dysregulation observed at HSP genes (95, 97, 98). Therefore, disease-causing proteins robustly impair the PN by sequestering existing chaperones while simultaneously preventing their replacement through the activation of the HSR.

Surprisingly few studies have investigated the relationship between the UPR and neurodegenerative diseases, although several groups have reported that ER stress is an early feature of AD, PD, HD, ALS, and prion diseases (101). Disruption of the ATF6 arm of the UPR^{ER} is reported to occur in mouse models of HD and a VAPB cell model of ALS, suggesting that differential changes in UPR arms may be a feature of disease progression (102, 103). These observations point to the progressive loss of stress response pathways as a possibly crucial feature of multiple neurodegenerative diseases. The loss of the HSR may leave neurons increasingly vulnerable to transient environmental insults and to the chronic presence of aggregation-prone proteins, thereby exacerbating disease progression.

Spreading of Protein Aggregates

In addition to cell-autonomous disruptions of the PN, several observations indicate that α-synuclein, polyQ, mHTT, and mutant SOD1 aggregates exhibit spreading behavior in tissue culture cells and rodent and patient brains. Postmortem analyses of fetal mesencephalic dopaminergic neurons transplanted into PD patients, and neuronal transplants grafted into the striatum of HD patients, revealed disease-like degeneration of healthy tissues accompanied by Lewy body formation in PD patient grafts (104, 105). Transmission and internalization of α-synuclein and mHTT aggregates can be recapitulated in cell culture and rodent models of PD and HD, respectively, and are also observed in mammalian cells expressing mutant SOD1 and in *C. elegans* expressing a yeast prion domain protein (106–110). Although aggregate spreading appears to be a common feature of these diseases, the mechanism by which internalization and transmission occur may be disease specific and has been proposed to occur through endosomal pathways, secretory vesicles, and macropinocytosis in models of PD, HD, and ALS, respectively. Furthermore, the incorporation of aggregates from culture media or neighboring cells initiates nucleation and aggregation of otherwise-soluble proteins in the cytosol, raising the possibility that proteostasis collapse and PN dysregulation can be propagated between neurons. Collectively, these findings illustrate that the presence of aggregation-prone proteins can disrupt the PN and drive proteostasis collapse both within and between cells in, but not limited to, numerous neurodegenerative diseases (Figure 2).

Could Programmed Changes in the Proteostasis Network Underlie Disease Onset and Progression?

Despite being expressed from birth, disease-associated proteins often trigger disease only later in life. This observation has led to the hypothesis that the pathways necessary to maintain proteostasis and suppress protein misfolding and aggregation are progressively compromised with age, eventually leading to disease onset. In support of this idea, reduced expression of molecular chaperones, altered proteasome activity, and disruption of stress responses have been observed in aged rodent tissues and senescent human cells (36, 111, 112). Additionally, an investigation of chaperone and cochaperone gene expression in young (36±4 years of age) and aged (73 ±4 years of age) human brain tissue revealed that of 332 genes examined, 101 are significantly repressed with age, including HSP70, HSP40, HSP90, and TRiC genes (113). Furthermore, 62 chaperone genes, including several small HSPs, were found to be significantly induced, likely as a result of the cellular response to accumulating protein damage with age (113). Concordant changes were observed in HD and AD brain tissues, and RNAi of genes dysregulated in human aging exacerbated polyglutamine aggregation and toxicity in *C. elegans* muscles and in HeLa cells (113). Together, these data suggest that the PN undergoes significant remodeling in human brain tissue during aging and that these changes have functional consequences for the onset and progression of neurodegenerative diseases. However, these findings did not address whether the age-associated compromise in PN function is late onset, gradual, or abrupt. It has been widely assumed that proteostasis decline with age is gradual; however, studies in invertebrates have begun to challenge this model and suggest that the initiating factors for proteostasis collapse and disease susceptibility may be part of programmed events that occur earlier in adulthood than anticipated (Figure 3).

Changes in Proteostasis Capacity Occur in Early Adulthood

Protein folding capacity during aging was initially assessed using *C. elegans* expressing endogenous metastable temperature-sensitive proteins (myosin, perlecan, dynamin, ras, and acetylcholine receptor subunit) in various tissues (114). The metastability of temperature-sensitive protein folding sensors allows a prediction to be tested: If protein folding capacity declines during aging, then metastable proteins should misfold even in animals grown under permissive temperatures. Therefore, by monitoring the folding state of these proteins through life, one can pinpoint precisely when protein folding capacity declines.

Metastable proteins were found to mislocalize and aggregate between day 2 and day 5 of adulthood, indicating that, relative to the mean life span of *C. elegans* (∼21 days at 15°C), protein folding capacity declines in early adulthood. For example, the misfolding of temperature-sensitive paramyosin at day 4 of adulthood occurs long before the cytological decline of myofilament structure and the appearance of gross motility defects (114). The fact that these observations were made with multiple unrelated metastable proteins expressed in different tissues suggests that the early decline in proteostasis is not limited to one group of proteins or to one tissue or cell type, but rather reflects a general decline in the PN (114).

Complementary studies in *C. elegans* adopted an unbiased proteomics-based approach to characterize the composition of detergent-insoluble protein aggregates collected from worm lysates at different days of life (115, 116). A subset of the proteome was aggregated at day 3 of adulthood; however, little to no aggregation was reported at day 1 of adulthood, matching the observations described above using metastable proteins. Aggregation increased with age, occurred in both the soma and the germ line, and contained proteins with sequence and structural similarities (high β-sheet content), suggesting that protein aggregation in early adulthood is influenced by protein sequence (115). These findings suggest that protein aggregation is an early, nonrandom event and that early adulthood is the critical threshold for proteostasis collapse. However, a large fraction of the proteome is clearly protected against aggregation, and even among proteins that form aggregates the rate may be markedly different. Furthermore, even though all animals displayed aggregation in early adulthood, heterogeneity in the timing of aggregation was observed across the population (115).

Age-associated protein aggregates were consistently found to contain molecular chaperones, translation factors, and ribosomal subunits (115–117), perhaps explaining observations that translation, as measured by polysome profiling, also declines early in *C. elegans* adulthood (117). RNAi knockdown of proteins associated with aggregates was found to increase life span in ∼50% of cases, suggesting that these proteins contribute to normal aging, perhaps due to their propensity to form aggregates. Although informative, the approaches employed by this first wave of studies could not detect oligomers and small aggregates that remain detergent soluble. Therefore, protein misfolding may be even more widespread than suggested. Why, then, does early loss of proteostasis occur in *C. elegans*, and is this mechanism conserved?

Studies on normal aging in *D. melanogaster* indicate that protein aggregation with age is a conserved feature in both muscle and brain tissue (48). However, it is unclear how early in life it occurs. Ubiquitin-positive aggregates are observed in flight muscles, retina, brain, and adipose tissue of adult flies. These aggregates dramatically increase in size and shape between days 7 and 35 of adulthood; however, the precise timing, progression, and consequence of aggregation in flies have not been determined (48). Furthermore, the composition of aggregates in old *Drosophila* is currently unknown, and it will be interesting to determine whether they are also enriched for ribosomal subunits, translation factors, and other abundant proteins, as is observed in aged *C. elegans* (115–117). It will also be important to determine the extent to which protein aggregation contributes to normal aging in mammals.

Requirements of Stress Response Pathways Through Life

Stress response pathways are traditionally regarded as a safeguard against an increase in misfolded proteins due to translational errors, altered pH, inflammation, and fluctuating temperatures. However, stress response pathways should also be considered an important process by which cells can rapidly and transiently alter the composition of the PN and shift the proteostasis boundary to meet acute temporal demands (1). In this context, stress response arms of the PN are essential to all physiological cellular commitments, as

demonstrated by the fact that HSF1 is essential for proper development and growth in yeast, *C. elegans*, *D. melanogaster*, and mice (118–121). However, inducing a fully fledged cell stress response represents a substantial cellular commitment. Constitutive activation of HSF1 is detrimental to cells and increased expression, and activity of HSF1 has been linked to multiple forms of cancer, highlighting the need for appropriate and balanced activation of stress response pathways as and when required throughout life (122).

How, then, are cell stress responses controlled to meet the changing demands of metazoans? Recent studies have shown that when challenged with a toxic insult such as heat shock or the ER stress inducer tunicamycin, the induction levels of HSR- and UPR-regulated genes is reduced throughout the soma by ∼80% by day 2 or 3 of adulthood in *C. elegans* (46, 114). This results in markedly reduced stress resistance and suggests that collapse of the HSR and UPR precedes proteostasis collapse. We do not know how these observations translate to a complex mammalian system with distinct sexes and different parent/progeny requirements following birth; however, a similarly timed collapse of restraint stress–induced *Hsp70* induction occurs in the aging rat adrenal cortex, and both male and female *Drosophila* subjected to hyperthermia exhibit reduced tolerance and *Hsp70* induction early in adulthood (123). These findings support the idea that early transcriptional dysregulation of stress responses may be a conserved event in metazoans, at least in some tissues.

The ability of HSF1 to modify aging and disease also depends on the life stage of the organism. RNAi of the phosphatidylinositol 3-kinase *age-1* or the sole *C. elegans* insulin/insulin-like signaling (IIS) receptor *daf-2* impairs IIS, extends life span, and suppresses the age-dependent aggregation and toxicity of polyQ and Aβ expressed in body wall muscle cells (62, 124). These effects are strictly dependent on HSF1 and DAF-16/FOXO3A, which minimize proteotoxicity by partitioning misfolded proteins into large nontoxic aggregates (DAF-16-regulated pathway) or by suppressing aggregation entirely (HSF1-controlled pathway) (124).

Experiments exploring the temporal requirements of HSF1 and DAF-16/FOXO3A for protection against protein misfolding and toxicity demonstrated that HSF1 and DAF-16/FOXO3A are strongly required early in life, suggesting that molecular events in early adulthood may be critical to disease suppression in later life (125, 126). Furthermore, RNAi of *daf-2* extends life span most effectively when initiated before day 2 of adulthood, with the degree of life span extension progressively decreasing to day 8 of adulthood (127). Collectively, these findings suggest that in *C. elegans*, the PN is in its most robust state early in life and confers protection across the proteome. However, as animals commence reproduction, the proteostasis boundary shifts and protein aggregation accelerates.

Why, then, do stress responses decline in early adulthood, and does this decline represent a random, passive, or programmed event? If stress response collapse is programmed, what are the organismal benefits of such an event? Future experiments to determine the molecular basis of these events, as well as which other stress response pathways also decline early in life, will greatly enhance our understanding of aging and disease onset.

Temporal Requirements of Protein Degradation Pathways

Cells can sculpt proteome composition and functionality through protein degradation pathways; however, as described for neurodegenerative diseases, disruption of these pathways also leads to cellular dysfunction. As such, it is feasible that any reduction in the protein degradation capacity of a cell could contribute to proteostasis collapse and promote aging. Studies in *C. elegans* expressing a photoconvertible proteasomal substrate showed that by day 5 of adulthood, reporter turnover occurred at a much slower rate in dorsorectal neurons than was observed at day 2 of adulthood, suggesting a significant reduction in proteasome activity in these cells. In contrast, no such decline was observed in body wall muscle cells, suggesting that age-related changes in the UPS may be tissue specific (128).

Another study that monitored proteasome activity between day 1 and day 2 of adulthood found a dramatic increase in ubiquitin G76V: :GFP turnover in all somatic tissues as animals began reproducing (129). This phenomenon correlated with a global increase in levels of K48-linked polyubiquitylated proteins, indicating that increased activity of the UPS as a whole occurs in early adulthood, as opposed to a specific increase in the proteolytic properties of the proteasome (129). Together, these findings suggest that the overall activity of the UPS increases substantially in the soma as animals reach reproductive maturity and declines thereafter in a tissue specific manner. Reduced proteasome activity has also been reported in early adulthood in *D. melanogaster* heads (between day 1 and day 5 of adulthood) and in rat spinal cord (between 3 and 12 months of age), indicating that early change in UPS activity may be a conserved feature of aging in some tissues (130, 131).

Pharmacological Enhancement of the Proteostasis Network as a Modifier of Aging and Disease

If the programmed collapse of proteostasis has a role in disease presentation, is it possible to intervene? If so, what are the consequences? Genetically enhancing the expression or activity of individual PN components suppresses disease onset and progression in a multitude of cell and animal models. Overexpression of many PN components can suppress protein folding toxicity, an observation consistent with the importance of all PN nodes for proteostasis. Although genetic studies have been invaluable in developing the paradigm that enhancing the PN is a viable approach to treating neurodegenerative disease, future therapies will require the identification and development of small-molecule enhancers of PN function. In this section, we focus on efforts to develop small molecules that can enhance various aspects of the PN, as well as their effects on disease (Table 2).

One strategy is to directly activate HSF1, thereby increasing the expression of multiple molecular chaperones simultaneously. This approach has been traditionally achieved by inhibition of HSP90 with compounds that bind the N-terminal ATP-binding pocket, such as radicicol, geldanamycin, or 17-AAG (64, 132–134). Treatment with HSP90 inhibitors activates HSF1 and increases chaperone levels, suppressing polyQ aggregation and toxicity in cell, *Drosophila*, *C. elegans*, and mouse models of disease (95, 132, 134–136). Although these studies are an important proof of principle, inhibition of HSP90 is not a viable long-term option given the central role of HSP90 in numerous essential cellular processes (12).

Therefore, we must look beyond these studies to new classes of HSP90-independent HSF1 activators for future therapeutics.

High-throughput screens in yeast and HeLa cells identified HSF1A and F1, respectively, as two small molecules that activate HSF1 independently of HSP90 inhibition (136, 137). HSF1A suppresses toxicity in cell and tissue culture models of HD and SCA-3/MJD and appears to activate HSF1 by impairing the activity of TRiC, a recently discovered negative regulator of HSF1. HSF1A treatment blocks the direct interaction between TRiC and HSF1, thereby eliciting an HSR (137, 138). Although the precise mechanism by which F1 activates HSF1 is unknown, F1 treatment increases the expression of chaperones and antioxidant enzymes and markedly suppresses polyQ toxicity in *C. elegans* and tissue culture models of HD. Despite only modest induction of stress response genes, F1 is able to correct protein misfolding and toxicity in diverse models of protein conformational disease, suggesting that subtle, holistic changes to the PN could be a powerful way to manage protein folding disorders (136). However, sustained activation of the HSR can be detrimental in the context of some protein misfolding diseases. For example, a recent study of the HSR in the context of cell models of α_1-antitrypsin deficiency, Niemann–Pick type C1 disease, and cystic fibrosis revealed that the HSR is hyperactive in these diseases and that reduced HSF1 activity suppresses toxicity (139).

An alternative and complementary approach to the treatment of neurodegenerative disease could be to enhance degradation pathways and thus the turnover of misfolded proteins. Treatment of cell, *Drosophila*, and mouse models of HD, SCA3/MJD, AD, PD, and ALS with the mTOR inhibitor rapamycin (or a derivative) reduces aggregation and suppresses disease (140– 143). However, similar to HSP90 inhibitors, the role of rapamycin as an immunosuppressant means that lifelong treatment of patients may not be practical. As such, small-molecule screens have attempted to identify new classes of autophagy inducers.

An in silico screen based on the structure of 10-NCP, an Akt inhibitor that potently induces autophagy (144), identified the molecules FPZ and MTM as potent activators of autophagic flux and clearance of TDP-43 in mammalian cells (145). Treatment of induced pluripotent stem cell–derived motor neurons and astrocytes with these molecules suppressed mutant TDP-43-dependent cell death (145). A screen for autophagy inducers in yeast identified the molecules SMER-10, -18, and -28 as TOR-independent activators of autophagy (146). Treatment of PC12 cells stably expressing mutantα-synuclein (A53T) with SMER-10, -18, or-28 significantly reduced levels of mutant α-synuclein, an effect that was enhanced by cotreatment with rapamycin (146). In addition, SMER-10, -18, and -28 were effective at suppressing mHTT aggregation and toxicity in COS-7 cells and flies (146). Together, these results suggest that novel small-molecule modifiers of autophagy have promise as future disease therapeutics.

In addition to autophagy activators, small molecules that affect the activity of the proteasome represent an effective means to clear misfolded proteins from cells. The DUB USP14 suppresses turnover of Tau and TDP-43 in mouse embryonic fibroblasts (MEFs) by impairing the protea-some; therefore, small-molecule inhibitors of USP14 could help clear these toxic proteins from cells (147). To identify small-molecule inhibitors of USP14,

investigators set up an in vitro system containing proteasomes, reconstituted USP14, and a 7-amido-4-methylcoumarin (Ub-AMC) fluorogenic degradation substrate. By screening ∼63,000 molecules for their ability to restore proteasomal substrate degradation, these authors identified the potent and selective USP14 inhibitor IU1. Treatment with IU1 reduced the levels of Tau, TDP-43, and ataxin-3 in MEFs in a USP14-dependent manner and independently of changes in proteasome levels or composition (147). These findings suggest that small molecules that target the PN have promise in the fight against age-related disease. Future studies to identify further small-molecule regulators of the PN and to elucidate to what extent existing PN modifiers can act synergistically to suppress proteotoxicity will pave the way for exciting new therapeutic options for largely untreatable diseases.

The Future of the Proteostasis Network in Health and Human Disease

Maintaining proteostasis is a demanding job that must be accomplished efficiently by every cell to avoid dysfunction. Efforts to understand the fundamental components involved in protein synthesis, folding, and degradation, and the extent to which they are connected, have resulted in the concept of the PN and recognition of the high degree of cooperation required to ensure proteome stability (1, 9). Unraveling the complete repertoire of PN function and connectivity will be a demanding endeavor; however, such studies will elucidate the extent to which the PN and auxiliary factors can regulate aging and age-related disease. A more challenging aspect of PN biology is to integrate these findings with an understanding of the extent to which the PN is tailored to individual cells, tissues, and life stages and the potential implications of this understanding to aging and disease. Given the complexity of this scenario, the temporal and spatial particulars of the PN have been only tentatively addressed to date. Nevertheless, we are discovering that many long-held assumptions regarding proteostasis control and decline are incorrect, and that wide-scale changes in the composition and function of the PN are precise early events, likely coordinated with reproduction. Although we do not know how these observations will extend to complex mammalian systems, a complete understanding of the signals and mechanisms responsible for PN reprogramming will undoubtedly provide important new insights into the means and necessity for organismal control of the PN. As we continue to unravel the foundations of proteostasis biology, we predict that future discoveries encompassing spatial and temporal control of the PN will allow us to develop new combinations of small molecules with the potential to provide long-term effective treatment for a range of human diseases.

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The Oxidative Stress Response in Aging and Disease

Increased protein oxidation is strongly linked to aging and disease (148). Reactive oxygen species (ROS) are prevented from causing oxidative protein damage by antioxidant enzymes such as superoxide dismutases (SODs), glutamate cysteine ligases (GCLs), and glutathione S-transferases (GSTs). In response to ROS accumulation in cells, the TF SKN-1/NRF2 is activated and drives the oxidative stress response (OxSR) (149). Mouse striatal cells expressing mutant huntingtin (mHTT) exhibit a reduced OxSR when challenged with *tert*-butylhydroxyquinone (tBHQ), independent of changes in the level of Nrf2 (150). In contrast, mutant SOD1 impairs the OxSR in ALS mice through reduced expression of *Nrf2* messenger RNA (mRNA) in motor neurons (151). Similarly, transcriptional dysregulation of *Nrf2* and sequestration of Nrf2 protein into $A\beta_{1–42}$ aggregates underlie dysregulation of the OxSR in the hippocampus of AD mice (152). During normal aging in flies, the level of carbonylated proteins is increased twofold by middle age (153). These effects were attributed to reduced expression of proteasomal subunits and impaired turnover of damaged proteins; however, it is likely that dysregulation of the OxSR also contributes to increased protein oxidation with age (153, 154). Although not a direct PN component or modifier, protein oxidation and its control are intimately linked to aging and age-related disease.

Summary Points

1. The PN spans multiple cellular compartments and is coordinated to maintain organismal proteostasis.
2. The PN exhibits substantial heterogeneity in composition and capacity between cells and tissues.
3. Loss of proteostasis and dysregulation of the PN are common features of neurodegenerative disease and normal aging.
4. Changes in proteostasis occur earlier in life than anticipated.
5. Small-molecule enhancers of molecular chaperone activity or protein degradation pathways are effective in suppressing protein aggregation and related toxicity in cell and animal disease models.

Future Issues

1. How do cells transmit proteostasis states to one another?
2. What is the mechanism behind the transmission of aggregates between cells?
3. What is the relationship between the PN and the proteome in different tissues?
4. What is the mechanistic basis for proteostasis collapse, and what are the consequences on organismal health if it is prevented?
5. Do all tissues exhibit identical patterns of proteostasis collapse during aging and disease? If not, which tissues are spared and why?

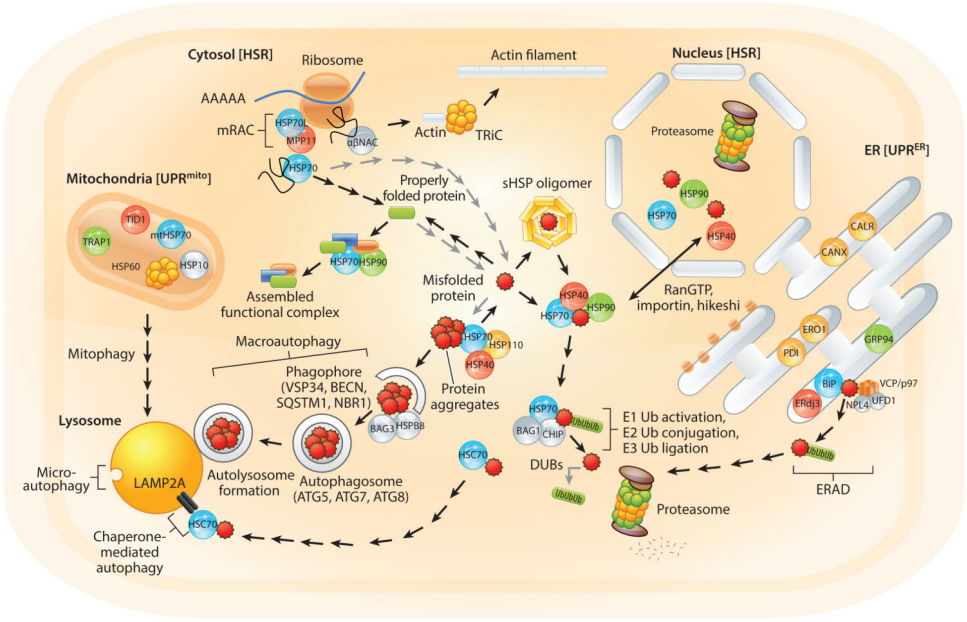

Figure 1.

Overview of the proteostasis network (PN). The human PN must ensure proteome stability across cellular compartments (not drawn to scale). Molecular chaperones of the HSP70 (*blue spheres*), HSP40/DNAJ (*red spheres*), and HSP90 (*green spheres*) families are found in all major cellular compartments and cooperate with cochaperones (*gray spheres*) to promote folding of nascent chains, assembly of protein complexes, refolding of misfolded clients (*serrated red spheres*), or degradation of terminally misfolded substrates by the proteasome. Small heat shock protein (sHSP) homo-oligomers bind misfolded proteins and maintain them in a folding-competent state for the HSP70 machinery. If refolding is unsuccessful, cooperation with the nucleotide exchange factor Bcl2-associated athanogene 1 (BAG1) and the E3 ubiquitin ligase C terminus of HSC70-interacting protein (CHIP) can direct substrates to the proteasome. The HSP60 family of chaperones is crucial for mitochondrial proteostasis (in conjunction with the “lid” cochaperone HSP10) and for folding of cytoskeletal components via the TCP-1 ring complex (TRiC). Certain chaperones and cochaperones perform specialized or compartment-specific functions (*orange spheres*). For example, in the endoplasmic reticulum (ER), protein disulfide isomerase (PDI) and ER oxidoreductin 1 (ERO1) cooperate to promote disulfide bond formation, while calnexin (CANX) and calreticulin (CALR) perform calcium-dependent folding of substrates. Upon protein misfolding, specific stress response pathways such as the heat shock response (HSR) and unfolded protein responses of the ER (UPR^{ER}) and mitochondria (UPR^{mito}) can boost chaperone levels. Occasionally, misfolded proteins can form aggregates that can be deleterious to cells. HSP110 cooperates with HSP70/HSP40 to act as a disaggregase. Alternatively, large aggregates can be degraded by the lysosome through autophagy. A modification of this pathway (mitophagy) can also be used to remove old or damaged mitochondria. Gray arrows indicate pathways that should occur only at low levels in healthy cells. Abbreviations: DUB, deubiquitinating enzyme; ERAD, ER-associated degradation; mRAC, mammalian ribosome-associated complex; NAC, nascent polypeptide chain–associated complex; Ub, ubiquitin.

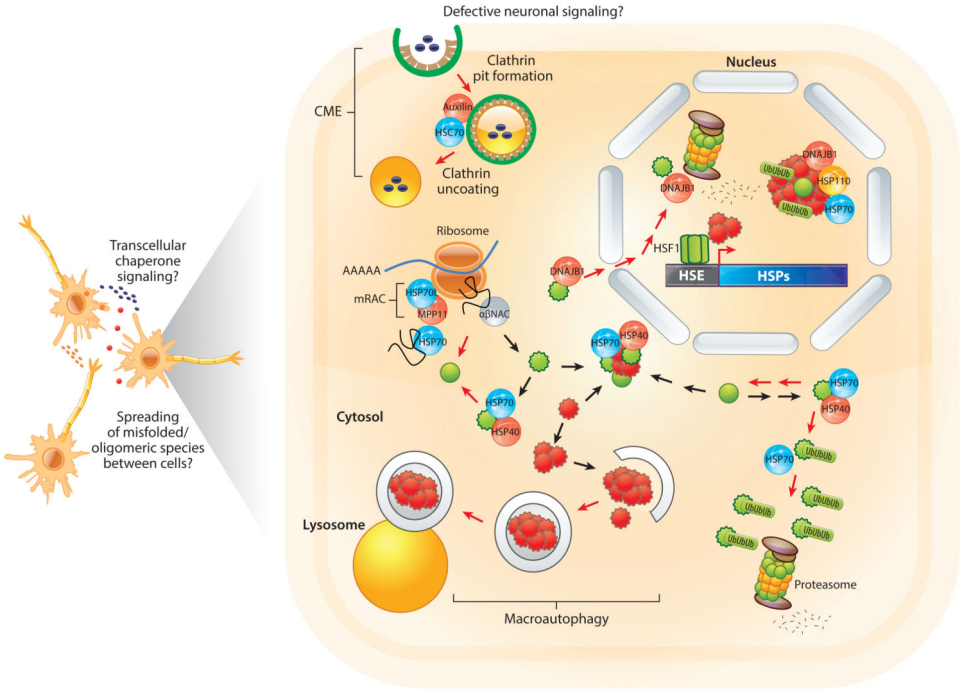

Figure 2.

Disruption of the proteostasis network (PN) in aging and disease. Numerous mechanisms contribute to proteostasis collapse in neurodegenerative disease and aging. Principal among these are reduced levels of soluble chaperones and disruption of protein degradation pathways. The action of HSP70 (*blue spheres*), HSP40/DNAJ (*red spheres*), and cochaperones (*gray spheres*) ensures that newly synthesized proteins fold properly (*green spheres*). Upon protein misfolding (*serrated green spheres*), molecular chaperones can either refold substrates to a functional conformation or direct substrates to the proteasome for degradation in the cytosol or nucleus. The presence of aggregation-prone proteins (*serrated red spheres*) sequesters chaperones and impairs the heat shock response (HSR). Reduced chaperone levels impair clathrin-mediated endocytosis (CME) (actually, HSC70 and auxilin reside within the clathrin cage) and inefficient degradation of ubiquitin (Ub)-conjugated substrates. As chaperone levels become compromised, the likelihood of protein misfolding and aggregation is exacerbated, driving neuronal dysfunction and disease. Protein aggregates can also spread between cells, thereby propagating proteostasis collapse. Red arrows denote pathways dysregulated in aging and/or neurodegenerative disease. Abbreviations: HSF1, heat shock factor 1; HSE, heat shock element; HSP, heat shock protein; mRAC, mammalian ribosome-associated complex; NAC, nascent polypeptide chain–associated complex.

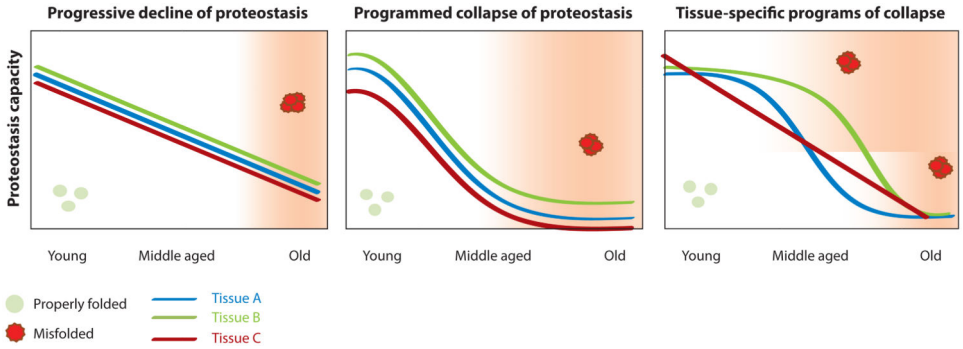

Figure 3.

Proposed models for the relationship between proteostasis collapse, aging, and disease. Proteostasis collapse is associated with aging and disease in multiple tissues. High proteostasis capacity early in life maintains proteome integrity (*green spheres*) and minimizes the risk of disease (*unshaded areas*). The conventional model of aging proposes that proteostasis capacity declines progressively with age, leading to increased incidence of protein misfolding (*red spheres*). Once proteostasis capacity falls below a certain threshold, proteome integrity is widely compromised and leads to disease (*shaded areas*). An alternate model emerging from studies in *Caenorhabditis elegans* is that proteostasis capacity collapses early in adulthood and may be part of a programmed event, thereby resulting in a longer window of disease susceptibility. It is possible that tissues (*colored lines*) exhibit the same or differential patterns of proteostasis collapse during life, which, coupled with specific mutations, result in a specific pattern of disease presentation and progression.

Table 1
Disease-associated mutations of proteostasis network components

Gene	Protein	Function	Disease	Reference
SOD1	SOD1	Superoxide dismutase	ALS	155
UBQLN2	Ubiquilin-2	Ubiquitin-like protein	ALS	156
CRYAA	α-Crystallin	Small HSP	Early-onset cataracts	157
HSPD1	HSP60	Mitochondrial Chaperone	Hereditary spastic paraplegia	158
ATXN3	Ataxin-3	Deubiquitylase	SCA3/MJD	159
PARK1	Parkin	E3 ubiquitin ligase	PD	160
CRYAB	α-Crystallin	Small HSP	Desmin-related myopathy, cardiomyopathy	161
SACS	Sacsin	DNAJ chaperone	Spastic ataxia	162
HSPB1	HSP27	Small HSP	Charcot–Marie–Tooth disease	163
VCP	VCP	AAA ATPase involved in ERAD	Paget disease and FTD	164
SIL1	SIL1	ER-associated nucleotide exchange factor	Marinesco–Sjogren syndrome	165, 166
HSPB8	HSP22	Small HSP	Charcot–Marie–Tooth disease type 2L	167
DNAJC19	TIMM14	Mitochondrial import	DCMA syndrome	168
HSPA9	Mortalin	Mitochondrial HSP70	PD	169
HSPA8	HSC70	Protein folding	Cardiovascular disease	170
PSMB8	PSMB8	Proteasomal subunit	Nakajo–Nishimura syndrome	171
DNAJB2	HSJ1	Neuronal DNAJ chaperone	Distal hereditary motor neuropathy	172
DNAJC6	Auxilin	Clathrin uncoating	Juvenile parkinsonism	173
DNAJB6	DNAJB6	Protein folding	Dominantly inherited myopathy	174
SQSTM1	p62	Autophagy	Paget's disease, ALS	175
DNAJC13	RME8	Receptor-mediated endocytosis	PD	176
P4HB	PDI	Protein disulfide isomerase	ALS	177
UBE3A	UBE3A	E3 ubiquitin ligase	Angelman syndrome	178

Abbreviations: ALS, amyotrophic lateral sclerosis; ERAD, endoplasmic reticulum (ER)-associated degradation; FTD, frontotemporal dementia; HSP, heat shock protein; MJD, Machado–Joseph disease; PD, Parkinson's disease; SCA, spinocerebellar ataxia; VCP, valosine-containing protein.

Table 2

Effects of pharmacological proteostasis network (PN) modifiers on animal models of neurodegenerative disease

Compound	Effect on PN	Disease model	Effect	Reference
Radicicol	Activates HSF1	HD mouse brain slices	Delays aggregation	64
Geldanamycin	Activates HSF1	PD flies	Suppresses loss of dopaminergic neurons	135
17-AAG	Activates HSF1	SCA3/MJD flies	Suppresses compound eye degeneration and SCA3 aggregation, improves survival	134
17-AAG	Activates HSF1	HD flies	Suppresses degeneration of photoreceptor neurons	134
HSP990	Activates HSF1	HD mice	Transiently suppresses aggregation and motor decline	95
Arimoclomol	Coactivates HSF1	ALS mice (G93A)	Suppresses motor neuron death, rescues hind-limb function, and increases life span	179
NG-094	Coactivates HSF1	Worms expressing polyQ in body wall	Reduces aggregation and suppresses motility defects	180
Dexamethasone	Increases HSF1 levels	HD mice	Suppresses aggregation and improves motor performance	97
Dexamethasone	Increases HSF1 levels	HD flies	Suppresses aggregation and improves behavioral phenotypes	97
Geranylgeranyl-acetone	Increases HSP70 levels	SBMA mice	Suppresses aggregation and muscle wasting and improves motor function	181
HSF1A	Activates HSF1	SCA3/MJD flies	Restores eye morphology, size, and pigment color	137
F1	Activates multiple stress responses	Worms expressing polyQ in body wall muscle	Suppresses aggregation and movement defects	136
Rapamycin	Increases autophagy	HD flies	Suppresses photoreceptor neuron death	141
CCI-779 (rapamycin ester)	Increases autophagy	HD mice	Reduces striatal aggregation and improves motor function	141
SMER10	Increases autophagy	HD flies	Suppresses photoreceptor neuron degeneration	146
SMER18	Increases autophagy	HD flies	Suppresses photoreceptor neuron degeneration	146
SMER28	Increases autophagy	HD flies	Suppresses photoreceptor neuron degeneration	146
Verapamil	Increases autophagy	HD zebrafish	Reduces aggregation and restores rhodopsin expression	182
Clonidine	Increases autophagy	HD zebrafish	Reduces aggregation and restores rhodopsin expression	182

Abbreviations: ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; HSF1, heat shock factor 1; PD, Parkinsons disease; SBMA, spinobulbar muscular atrophy; polyQ, polyglutamine; SMER, small-molecule enhancer of rapamycin.