Mechanisms of Ageing and Development 177 (2019) 80–87

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

To adapt or not to adapt: Consequences of declining Adaptive Homeostasis and Proteostasis with age

Laura C.D. Pomatto[a,1], Patrick Y. Sun[a,1], Kelvin J.A. Davies[a,b,c,*]

[a] Leonard Davis School of Gerontology of the Ethel Percy Andrus Gerontology Center, the University of Southern California, Los Angeles, CA, 00089-0191, USA
[b] Molecular & Computational Biology Program of the Department of Biological Sciences, Dornsife College of Letters, Arts, and sciences, the University of Southern California, Los Angeles, CA, 90089-0191, USA
[c] Department of Biochemistry & Molecular Medicine, Keck School of Medicine of USC, the University of Southern California, Los Angeles, CA, USA

ARTICLE INFO

Keywords:
Aging
Protein aggregates
Physiological ceiling
Proteasome
Immunoproteasome
Lon protease
Nrf2
longevity

ABSTRACT

Many consequences of ageing can be broadly attributed to the inability to maintain homeostasis. Multiple markers of ageing have been identified, including loss of protein homeostasis, increased inflammation, and declining metabolism. Although much effort has been focused on characterization of the ageing phenotype, much less is understood about the underlying causes of ageing. To address this gap, we outline the age-associated consequences of dysregulation of 'Adaptive Homeostasis' and its proposed contributing role as an accelerator of the ageing phenotype. Adaptive Homeostasis is a phenomenon, shared across cells and tissues of both simple and complex organisms, that enables the transient plastic expansion or contraction of the homeostatic range to modulate stress-protective systems (such as the Proteasome, the Immunoproteasome, and the Lon protease) in response to varying internal and external environments. The age-related rise in the baseline of stress-protective systems and the inability to increase beyond a physiological ceiling is likely a contributor to the reduction and loss of Adaptive Homeostasis. We propose that dysregulation of Adaptive Homeostasis in the final third of lifespan is a significant factor in the ageing process, while successful maintenance of Adaptive Homeostasis below a physiological ceiling results in extended longevity.

1. Adaptive Homeostasis is not hormesis

To survive an ever-changing environment, organisms from bacteria to mammals rely upon transient and reversible changes, which enable successful coping with external and internal perturbations. These adjustments result in a plethora of temporary cellular adaptations, including modulation of signaling cascades, gene transcription and translation, and protein post-translational modifications. Together, these short-term adjustments allow for successful survival. Adaptive Homeostasis has been defined as follows:

"The transient expansion or contraction of the homeostatic range in response to exposure to sub-toxic, non-damageing, signaling molecules or events, or the removal or cessation of such molecules or events" (Davies, 2016).

Moreover, evidence of adaptive homeostasis as a universal process has been tested across multiple species, including bacteria (Hassett and Cohen, 1989; Russell, 1984), yeast (Davies et al., 1995a), mammalian cells (Wiese et al., 1995; Pickering et al., 2012; Ngo and Davies, 2009; G and rune et al., 2002; Shringarpure et al., 2003), nematode worms (Raynes et al., 2017; Pickering et al., 2013), fruit flies (Pickering et al., 2013; Pomatto et al., 2017a, b), and mice (Zhang et al., 2012) and under various environmental and internal conditions (Pomatto and Davies, 2017). In addition, sex-specific differences are evident. Indeed, the sexually dimorphic response, evident starting at the mammalian cell culture level and extending into mice (Pomatto et al., 2017c), and potentially humans, highlights the importance of further exploration of the adaptive homeostatic response within this sexually dimorphic context.

One crucial distinction we must make is that adaptive homeostasis is not hormesis (Fig. 1). Hormesis requires damage in order to stimulate repair and protective cellular response pathways. Or more aptly described in the words of Nietzsche, 'what does not kill us, makes us

Abbreviations: Nrf2, nuclear factor (erythroid-derived 2)-like 2; LonP1, mitochondrial Lon protease; LonP2, peroxisomal Lon protease; EpRE, Electrophile Response elements; ARE, antioxidant response elements; HO-1, heme oxygenase-1; GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, glutamate-cysteine ligase regulatory subunit; NQO1, NAD(P)H dehydrogenase [quinone] 1

* Corresponding author at: Leonard Davis School of Gerontology, the University of Southern California, 3715 McClintock Avenue, Los Angeles, CA, 00089-0191, USA.
E-mail address: kelvin@usc.edu (K.J.A. Davies).

[1] co-first authors.

https://doi.org/10.1016/j.mad.2018.05.006
Received 26 March 2018; Received in revised form 15 May 2018; Accepted 16 May 2018
Available online 17 May 2018
0047-6374/

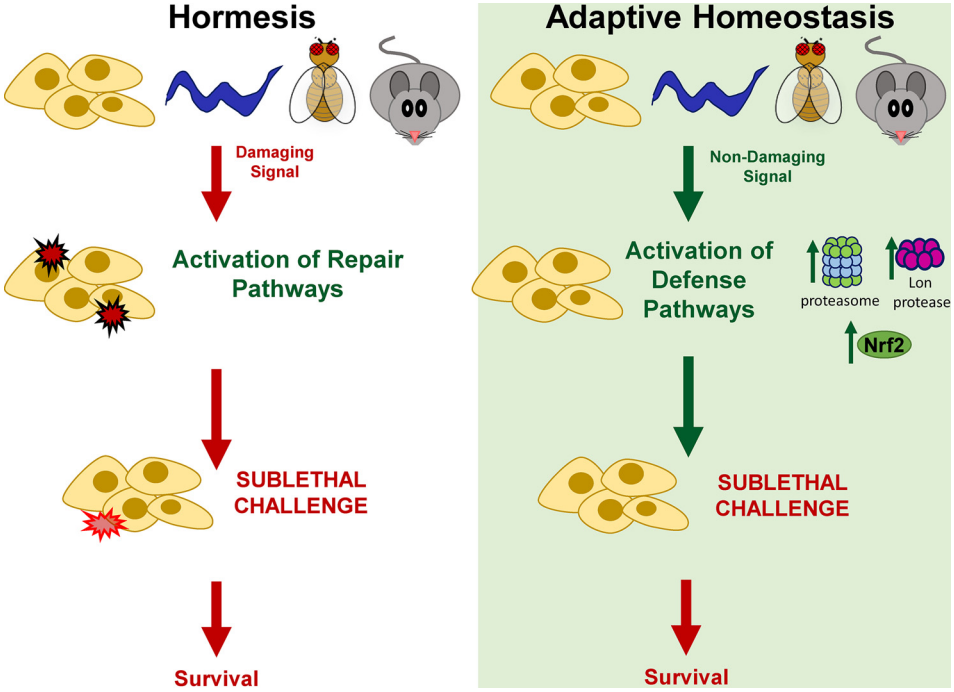

Fig. 1. Adaptive Homeostasis is not Hormesis - Hormesis results following the initial exposure of a cell or organism to a damaging, non-lethal toxin, chemical or environmental condition. Exposure leads to cellular damage, which as long as it is not lethal, causes activation of stress-protective pathways, enabling the cell or organism to remove and repair the damage and preparing the organism or cell to better withstand a future, potentially more damaging oxidative insult, increasing the likelihood of survival. Some DNA repair mechanisms appear to be activated by small amounts of DNA damage. In contrast, adaptive homeostasis relies upon exposure to non-damaging amounts of an internal or external signaling molecule or condition, which does not cause damage, but is enough to activate specific signal-transduction pathways (such as Nrf2 and IRF1) that ensure the increased expression of downstream protective and repair enzymes, such as the 20S Proteasome, the Immunoproteasome, and the Lon protease. In turn, the upregulation of such protective enzymes protects cells and organisms against potentially future toxic insults, increasing their likelihood of survival.

stronger,' and indeed, this is true during the hormetic response in biological systems. First described by Southam and Ehrlich, hormesis is a phenomenon wherein sub-lethal damage, arising from a toxin or poison, results in an exaggerated repair response, which leads to an organism appearing 'stronger' or more resilient than previously (Southam, 1943). Indeed, exposure to toxic amounts of chemicals, agents or damaging environmental conditions is associated with activation of repair pathways, most clearly characterized in conditions promoting DNA damage and resultant induction of DNA repair pathways (Jackson and Bartek, 2009). In contrast, adaptive homeostasis relies upon non-damaging, signaling molecules to induce transient changes, which ensure organisms can activate multiple cellular defense and antioxidant pathways to cope against potential future oxidative insults. Thus, whereas hormesis requires damage for signaling initiation, adaptive homeostasis is continually utilized by cells and organisms to adapt to physiologically-relevant internal and external changes.

2. Cellular proteases: the 20S Proteasome, the immunoproteasome, and the Lon Protease

Protein turnover is a major cellular process critical for the maintenance of protein homeostasis (or 'proteostasis'). Two particular enzymes that play major roles in intracellular proteostasis are the (cytoplasmic, nuclear, and endoplasmic reticulum) Proteasome and the (mitochondrial) LonP1 and the (peroxisomal) LonP2 proteases, which serve to remove damaged, dysfunctional, and aggregation-prone proteins, such as oxidized proteins. The Proteasome is a ubiquitous multisubunit protease that has great plasticity and flexibility with multiple regulators and conformations that selectively degrade different types of proteins (Raynes et al., 2016). The most well-studied conformation of the Proteasome is the 26S Proteasome which has ATP-ubiquitin dependent activity arising from the presence of two 19S regulatory caps, which recognize, bind and unfold ubiquitin-tagged proteins in preparation for degradation (Raynes et al., 2016). The Immunoproteasome is a special form of the 20S Proteasome that contains two substituted subunits encoded by Immunoproteasome-specific genes

Recent work has found that the 19S regulatory caps, so crucial for degradation of ubiquitin-tagged substrates, are themselves, highly vulnerable to oxidation and resultant inactivation. Fortunately, other conformations are highly adept during transient activation of the adaptive response, mainly the 20S Proteasome and the Immunoproteasome both of which have ATP-ubiquitin independent activity (Raynes et al., 2016). The core unit of the Proteasome consists of a proteolytic chamber that has 3 types of catalytic activity: caspase-like activity exhibited by the β1 subunit, trypsin-like activity exhibited by the β2 subunit, and chymotrypsin-like activity exhibited by the β5 subunit (Raynes et al., 2016). While the 26S conformation is responsible for a large portion of protein degradation during normal homeostatic conditions (Raynes et al., 2016), it is very clear that the 20S Proteasome is recruited in response to acute stress and selectively degrades oxidized proteins (Grune et al., 2011; Reeg et al., 2016). Studies have shown that the bulk of oxidatively damaged proteins in the cell are degraded by the 20S Proteasome and the Immunoproteasome (Shringarpure et al., 2003; Chondrogianni et al., 2003) with the exception of mitochondria where the LonP1 protease preferentially degrades oxidized proteins (Bota and Davies, 2002); whether the LonP2 protease performs a similar function in peroxisomes is not yet clear. Recent work in fruit flies further cements the important role of the 20S Proteasome for survival, as suppression of either the β1 or β2 subunits leads to dramatically shortened lifespan in both male and female fruit flies (Pomatto et al., 2017b).

The mitochondrial Lon protease is a key enzyme for protein turnover and regulation, with its function conserved from bacteria to the eukaryotic mitochondrion. Its role as a stress-responsive protease was first characterized in *E. coli* (Goldberg and Waxman, 1985) and later in yeast (Wagner et al., 1994), wherein the conserved activity of its ability to rapidly remove oxidatively-modified proteins was confirmed (Teichmann et al., 1996). Later studies identified Lon as a highly adept and inducible enzyme in mammalian cell culture (Ngo and Davies, 2009) and fruit flies (Pomatto et al., 2017d). Lon has also been found to serve as a crucial enzyme in mitochondrial transcription (Lu et al., 2013), metabolism (Quirós et al., 2014), cellular resilience (Ngo et al., 2011; Bota et al., 2005; Lomeli et al., 2017), and possibly age-dependent sex-differences (Pomatto et al., 2017d). Additionally, LonP2, an enzyme located in peroxisomes, has been found to have similar chaperone functions as that of the mitochondrial Lon protease (LonP1) and, like LonP1, LonP2 is also a stress-inducible enzyme (Walker et al., 2017; Pomatto et al., 2017e). As a single ringed homo-oligomeric enzyme,

which binds to the hydrophobic patches on oxidized proteins, LonP1 is critical in the prevention of accumulation of mitochondrial protein aggregates (Ngo et al., 2011). It should be no surprise then, that with age and chronic diseases (Bulteau et al., 2017), mitochondrial protein aggregates become evident (Dai et al., 2014), and this is accompanied by a parallel decline in Lon activity (König et al., 2017).

3. Consequences of the age-dependent loss of Adaptive Homeostasis

In young animals the synthesis and cellular levels of the 20S Proteasome, the Immunoproteasome, and the Lon protease, all transiently increase in response to pre-stressful levels of appropriate signaling agents such as free radicals, oxidants, quinones, etc. (all of which would be toxic at much higher levels). Following activation of the adaptive homeostasis response, young animals are transiently much better protected against any toxic insult they may encounter. Moreover, the adaptive homeostatic response of different enzymes, including the Proteasome and Lon, is conserved in organisms ranging from yeast (Davies et al., 1995b), invertebrates (Raynes et al., 2017; Pomatto et al., 2017a), to mammals (Pickering et al., 2013). During ageing the loss of proteostasis is accompanied by a decline in the adaptive homeostatic response and its loss is linked to chronic stress and increased disease susceptibility. Decline in an organism's ability to activate the adaptive homeostatic response with age, across multiple forms of internal and external perturbations, appears to be a universal biological phenomenon (Pomatto and Davies, 2017).

The adaptive homeostatic response of the 20S Proteasome occurs through the increase in amount and activity of the Proteasome. This is generally observed as two phases of increased proteolytic capacity. The first phase immediately follows a transient signal indicating a forthcoming and potentially damaging stress event, and involves removal of the 19S regulators from each end of 26S Proteasomes, in a process catalyzed by Ecm29 (Wang et al., 2017, 2010) and hsp70 (Grune et al., 2011). This in turn, provides an immediately available pool of 20S Proteasome to degrade oxidized proteins, eliminating them before they form toxic aggregates. The second phase of increasing proteolytic capacity is due to de novo synthesis of 20S Proteasomes, transcriptionally controlled by the master antioxidant regulator Nrf2 (Pickering et al., 2012). Upon an oxidative signal, Nrf2 quickly translocates to the nucleus, wherein it transcriptionally activates a suite of Phase II detoxification and stress-protective genes including those that code for the 20S Proteasome (Velichkova and Hasson, 2005). Recent work has shed light on the highly conserved relationship between Nrf2 and 20S Proteasome in higher eukaryotic organisms. Age-related decrease in Nrf2 or its orthologs (e.g. SKN-1 in *C. elegans* or Cnc-C in *Drosophila*), contributes to the loss of adaptive capacity of the 20S Proteasome (Raynes et al., 2017; Pomatto et al., 2017a). Unfortunately, forcing the chronic overexpression of SKN-1 (Raynes et al., 2017) or decreasing the levels of its cytosolic inhibitor, Keap1 (Pomatto et al., 2017b), does not restore the adaptive homeostatic response in ageing animals, suggesting a much more nuanced approach will be necessary to restore the age-dependent adaptive decline.

4. Protein aggregates: a consequence of the age-associated loss of Adaptive Homeostasis

Protein aggregation is a process by which modified, oxidized, misfolded or damaged proteins bind together and coalesce into a larger mass which no longer possesses the original function(s) of its component parts. In many cases, protein aggregates can become even more tightly joined amalgams through the formation of intermolecular covalent cross-links, and such cross-linked aggregates often acquire even more toxic characteristics. Protein aggregates are a common phenotype in neurological diseases, many of which have an age-related component, such as Alzheimer disease, Parkinson disease, Huntington disease, and amyotrophic lateral sclerosis (Ross and Poirier, 2004). However, aggregates not associated with neurological diseases are also cytotoxic (Bucciantini et al., 2002). Because of the generality of protein aggregation, there are many different mechanisms that can contribute to their formation, but the dominant mechanism appears to be aggregation of conformationally-altered substrates (Philo and Arakawa, 2009). An example of such interactions is the attraction of hydrophobic regions of misfolded, oxidized, or otherwise damaged proteins that would normally be sequestered within a properly folded protein. Hydrophobic and electrostatic interactions typically initiate aggregate formations (Grune et al., 2004). Upon additional stressors, such as extreme temperatures or oxidation, the formation of cross-linking covalent bonds within the aggregates can occur, which further stabilizes the aggregate and hinders proper degradation. However, the rate limiting step in stable aggregate formation are still the initial non-covalent bonds (Bartkowski et al., 2002) indicating that aggregates can form rather quickly if damaged proteins are not quickly degraded.

The incidence of protein aggregates has been found to increase with age (Strehler et al., 1959). The imbalance between accumulation and removal of damaged proteins becomes highly evident during the last one third of life (Levine and Stadtman, 2001) (Fig. 2). The increase in the concentration of Proteasome protein with age while Proteasome enzymatic activity actually decreases simultaneously (Raynes et al., 2017; Pomatto et al., 2017b; Raynes et al., 2016) lends further support to the idea that Proteasomes can become sequestered in/on protein aggregates and deactivated as they attempt to degrade the damaged components. This, in turn, leads to a further decrease in proteolysis and a subsequent further increase in the formation and size of protein aggregates (Fig. 3) (Höhn et al., 2011). Indeed, evidence from *C. elegans* suggests that, with age, insoluble protein aggregates, termed the 'insolubolome,' exhibit accumulation of 20S Proteasomes in/on the aggregates (Reis-Rodrigues et al., 2012). Studies using senescent fibroblasts showed a similar trend of increased Proteasome accumulation in/on protein aggregates (Grune et al., 2004; Sitte et al., 2000a, b). This positive feedback (with negative biological effects) fits well into the observations of exponential expansion of detrimental outcomes later in life (Fig. 3).

Of course, any exposed lysine residues on the surface of protein aggregates will continue to undergo ubiquitinylation such that increasing polyubiquitin levels actually become a marker for non-

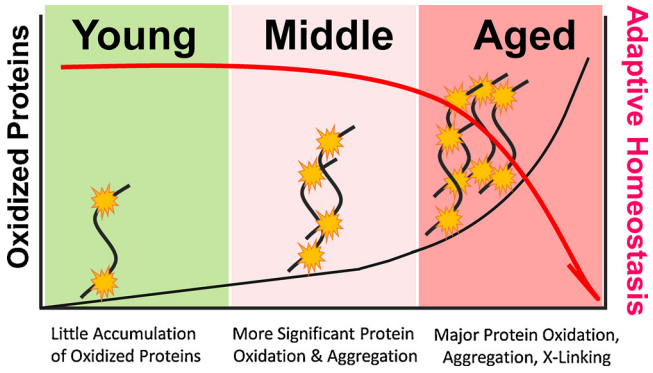

Fig. 2. Protein Accumulation is Evident only during the Final Third, or End-Stage of Life - According to the Free Radical Theory of Aging (Harman, 1956), protein accumulation goes hand-in-hand with cellular homeostasis. However, work measuring protein oxidation has shown that (in the absence of disease) protein aggregates do not really accrue to any great extent until the final third of life. The ability to appropriately regulate protective systems, however, shows minor evidence of decline as soon as late middle-life. These findings suggest that loss of inducibility of the adaptive homeostatic response may contribute to protein oxidation, aggregation, and cross-linking. Furthermore, measurement of changes in the adaptive homeostatic response may be a better indicator of ageing processes before physiological manifestations of many classical ageing markers occurs.

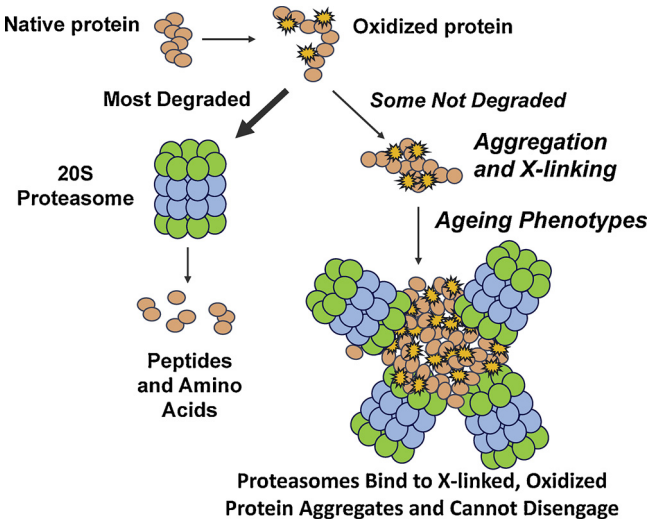

Fig. 3. The Imperfect System: Age-Dependent Protein Aggregation - The cell relies upon the 20S Proteasome to remove damaged proteins from the cytoplasm, nucleus and endoplasmic reticulum. Throughout an organism's life, the majority of damaged proteins are degraded predominantly by the 20S Proteasome, which recognizes its target substrates through the exposure of (normally internalized) hydrophobic patches. In turn, its role as a protease ensures that the majority of oxidized proteins are cleared away. However, as no system is perfect, a small percentage escapes the 20S Proteasome turnover machinery. With time (including the ageing process), the small percentage of oxidized proteins begin to accumulate, aggregate, and crosslink, making it extremely difficult for removal. However, the 20S Proteasome still tries to remove these protein aggregates by attaching to clumps of them. Unfortunately, these clumps of proteins are no longer the ideal size to progress through the barrel-shaped opening of the Proteasome. This leads to multiple Proteasomes latching onto protein aggregates, in an attempt (though futile) to try and degrade these oxidized masses. Unfortunately, the increased accumulation of 20S Proteasomes further exacerbates the aggregation, rather than staunches it, and accelerates the loss of proteostasis with age.

degradable protein aggregates. Further evidence also suggests components of the ubiquitin-Proteasome system are found in protein aggregates, indicating that the Proteasome does attempt to remove these clumps of non-functional proteins, but with limited success (Alves-Rodrigues et al., 1998; Cummings et al., 1998). Protein aggregates have been directly demonstrated to inhibit Proteasome activity (Sitte et al., 2000a, b; Venkatraman et al., 2004; Bennett et al., 2005) and they even seem to have greater inhibitory properties in postmitotic cells (Sitte et al., 2000b). This then leads to greater accumulation of oxidized proteins, which further contributes to the formation of more aggregates in a feed forward manner. It is believed that aggregates beyond a certain size can clog and block the proteolytic barrel of the Proteasome, inhibiting its ability to degrade other proteins (Grune et al., 2004). Conversely, direct inhibition of Proteasome activity leads to increased aggregate formation (Demasi and Davies, 2003; Hyun et al., 2003).

Another mode of degradation is through the mitochondria. Protein aggregates are imported into the mitochondria to be degraded. The aggregates are transported through the outer membrane through the TOM complex pore and through the inner membrane TIM complex and inhibition of TIM subunits have resulted in delay in the degradation of aggregates (Ruan et al., 2017). Once aggregates are in the mitochondria, the Lon protease is responsible for their degradation (Ngo and Davies, 2009; Bota and Davies, 2002; Bayot et al., 2014). However, Lon protease activity has been shown to significantly decline with age as well (Bota and Davies, 2016), which likely contributes to the observed accumulation of aggregates with age (Hamon et al., 2015). Moreover, loss of the Lon protease is associated with accelerated senescence (Ngo et al., 2011; Bota et al., 2005; Ngo and Davies, 2007) and ageing phenotypes (Pomatto et al., 2017d; Quirós et al., 2014; Folgueras et al., 2018; Bota et al., 2002).

5. The physiological ceiling of Adaptive Homeostasis

The Adaptive Homeostatic response is highly transient. Proper homeostasis requires the ability to rapidly turn on a broad-range of transcriptionally targeted genes. One of the most-well characterized transcriptional regulators of the adaptive homeostatic response is Nrf2. It has been identified as the main transcriptional activator of hundreds of detoxification and stress-protective enzymes (Jaiswal, 2004; Zhang et al., 2015). Initiation of the adaptive homeostatic response follows exposure to non-damaging, signaling amounts of an oxidant that trigger the rapid movement of Nrf2 into the nucleus where it binds to the promoter regions of antioxidant response elements (ARE) that are probably better called Electrophile Response Elements (EpRE) and activate the transcription and translation of multiple protective and repair genes (Pickering et al., 2012; Itoh et al., 1997; Tebay et al., 2015). Following the initial transcriptional reprogramming, led by Nrf2, the amplification of multiple stress-protective enzymes occurs (Pickering et al., 2012; Ngo and Davies, 2009; Pickering et al., 2013). However, no signal continues indefinitely and cells must have a means of turning 'off' Nrf2-mediated activation. To do this, cells rely on multiple transcriptional Nrf2-competitors, such as Bach1 (Niture et al., 2014; Chang et al., 2017; Piras et al., 2017) and c-Myc (Zhang et al., 2015; Zhou et al., 2018). These Nrf2 antagonists also bind to the promoter region of ARE/EpRE elements (Oyake et al., 1996), thereby suppressing ARE/EpRE-mediated gene expression (Suzuki et al., 2003). Preliminary evidence indicates that although both Bach1 and Nrf2 accumulate in the nucleus, they do so at different rates, with Nrf2 showing immediate (minutes) translocation, whereas Bach1 accumulation is much slower (hours) (Dhakshinamoorthy et al., 2005), suggesting Bach1 may act as a homeostatic 'off-switch' to Nrf2 activation, imposing a physiological ceiling. Thus the transient and temporal harmony between Nrf2 (transcriptional activator) and its cellular transcriptional inhibitors Bach1 and c-Myc may ensure appropriate modulation of the adaptive homeostatic response in young organisms (Fig. 4A). However, much more work is necessary to fully understand this relationship.

The significance of determining an ecologically-relevant physiological ceiling is well illustrated in organisms living in extreme habitats. Cold stress such as that found in Polar regions has been documented to cause cellular damage through mechanisms such as oxidative stress (Todgham et al., 2007). Cold acclimation is shown to induce activities of both the 20S Proteasome and ubiquitin-26S Proteasome system (Gracey et al., 2004; Buckley et al., 2006; Podrabsky and Somero, 2004; Yen et al., 2008; Lamarre et al., 2009). Protein damage and turnover is generally higher in organisms that inhabit polar-regions, where the temperature remains very low and stable, in comparison with organisms that inhabit more temperate regions of the world (Todgham et al., 2007). As a result, the Proteasomes of Antarctic species have evolved temperature compensations such that their proteolytic activities remain similar to those of their more temperate 'cousins' at ecologically relevant temperatures (Drake et al., 2017). When Proteasome activity was measured at warmer temperatures the Proteasome activity of Antarctic species was significantly higher. Intracellular Proteasome levels, as well as those of Proteasome associated proteins, were elevated in Antarctic fish which is likely responsible for their greater Proteasome activity.

These studies on polar organisms indicate that they were successful in adapting the existing physiological architecture of Proteasome activity that is cold-stress responsive and have it constitutively upregulated to compensate for the low environmental temperature. Yet, further increases in Proteasome activity of these species may be limited by an adaptive ceiling. Organisms that have evolved to inhabit extreme environments may be living close to, or at, their physiological limits. This pattern has been found, for example, in high temperature habitats such as intertidal zones where organisms regularly experience maximal temperatures very close to their respective lethal temperature (Somero,

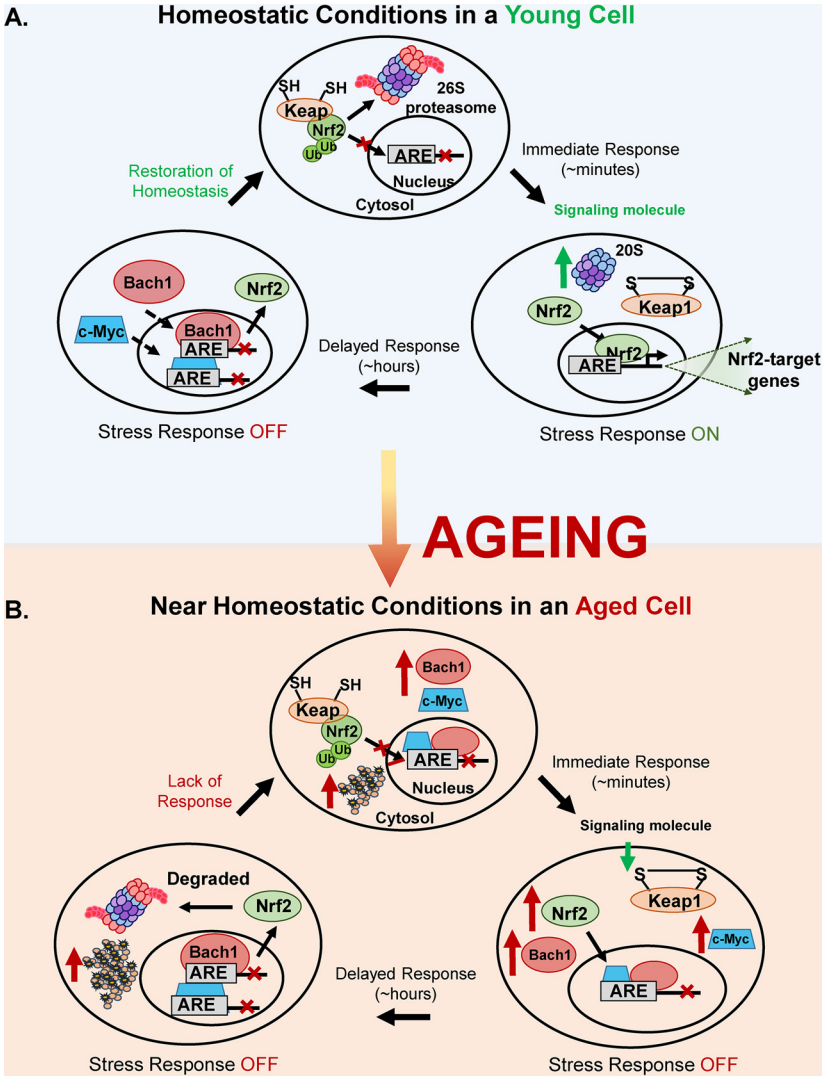

Fig. 4. Age-Dependent Decline in the Nrf2-Mediated Adaptive Homeostatic Response.
A. During homeostatic conditions in young organisms, Nrf2 is sequestered by Keap1 in the cytosol, wherein it is ubiquitin-tagged and targeted for degradation by the 26S Proteasome. Upon activation of the adaptive homeostatic response, Nrf2 rapidly dissociates from Keap1 and translocates into the nucleus (typically within minutes), where it binds to antioxidant-response elements (ARE), leading to activation of Nrf2-regulated genes. Simultaneously, the 19S regulatory caps dissociate from the Proteasome, leading an immediate pool of 20S Proteasome and loss of Nrf2 degradation. After time (typically within hours) the adaptive response is turned off. Though much work is still needed in this area, one mechanism that has been explored is that Nrf2 competitors (such as Bach1 and c-Myc) move into the nucleus, wherein they bind to Nrf2-target genes, turning off their activation. Thus the temporal balance between the adaptive response activator (Nrf2) and its inhibitors (potentially c-Myc and Bach1) is crucial in allowing the transient and coordinated response necessary for maintenance of homeostasis. **B.** With age this temporal response may become dysregulated. Basal amounts of Nrf2 and its transcriptional inhibitors (Bach1 and c-Myc) show an age-dependent rise, along with increased accumulation of protein damage. With age, Nrf2 and Bach1 may have similar rates of nuclear translocation following exposure to signaling molecules or events. This can lead to an abbreviated or truncated Nrf2 response and inadequate Nrf2 signal activation. As a result, dysregulation of adaptive homeostasis leads to greater accumulation of damaged protein aggregates, and loss of cellular proteostasis and homeostasis.

2002).

Whatever the ecological niche an organism inhabits, homeostasis can be maintained as long as damaging effects on proteins, lipids, and nucleic acids can be minimized, repaired, removed, and replaced. Adaptive homeostasis allows an organism to transiently increase its ability to minimize, repair, remove, and replace damaged cellular constituents in response to 'unexpected' changes in internal or external environments, and thus survive. In essence, this is an example of transiently increasing the 'physiological ceiling.' Thus, rapid and transient (adaptive homeostatic) increases in the synthesis of 20S Proteasome, Immunoproteasome, and PA28 Proteasome regulator, mediated by the Keap1-Nrf2 signal transduction pathway, are able to minimize the formation of toxic protein aggregates during a stressful 'event' and maintain organismal fitness by temporarily increasing the ceiling for surviving in an adverse (internal or external) environment.

6. Staying below the physiological ceiling

Mechanisms that promote Proteasome activity have been shown to extend lifespan and delay the onset of detrimental age-related phenotypes (Schmidt and Finley, 2014). Sufficient Proteasome activity is maintained if demand does not exceed the supply set by a physiological ceiling. Once the ceiling is reached, then further insults will accrue a large pool of damaged protein leading to protein aggregate formation. A key to staying below the ceiling is a robust maintenance of proteolytic capacity, which permits an organism to extend its residency in the young and mid zones (Fig. 2), further delaying its entry into the final third zone where rapid growth of detrimental loads, such as the accumulation of protein aggregates, typically occurs. The ability to stay below the physiological ceiling indicates that not only are these organisms successfully maintaining homeostasis, but also that they have further capacity (adaptability) to address additional assaults. As the basal activity rises with age (Fig. 5), the adaptive response decreases, restricted by a physiological ceiling. Ultimately, physiological demands will require a baseline proteolytic activity that exceeds the maximal response. At this point, further challenges will then result in damaged proteins that no longer can be quickly removed, allowing protein aggregates to form and thus catapulting the system into a feed forward mechanism that characterizes the last third of life (Fig. 2). In order to extend lifespan, organisms must be able to stave off entry into this final third zone by maintaining a low baseline to preserve adaptive homeostasis.

Evolution has created many novel strategies for lifespan extension, several of which seem to increase lifespan through the maintenance of stable proteolytic activity. In the longest lived non-colonial animal, the Mahogany Clam (*Arctica islandica*) (Sosnowska et al., 2014), proteasome activity exhibits no age-induced changes (Sosnowska et al., 2014). The Mahogany Clam may have evolved innovations that preserve Proteasome activity so that it can maintain a relatively low baseline of activity for a considerable amount of its lifespan and thus delay its entry

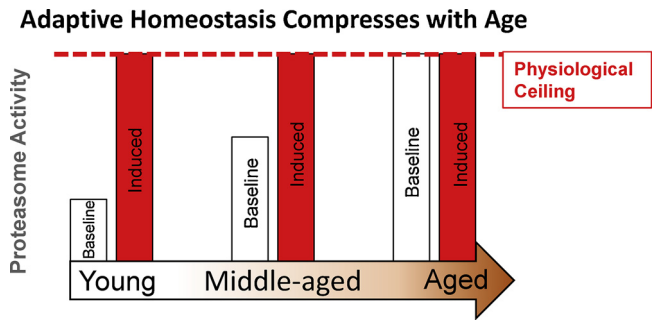

Fig. 5. Compression of the Adaptive Homeostatic Response with Age - Young organisms exhibit low basal amounts of multiple protective proteins/enzymes (such as Nrf2, Proteasome, Immunoproteasome, and Lon protease). Exposure to a non-damaging signaling level of agents, such as oxidants, leads to rapid transcription and translation of protective and repair enzymes, and transient increases in their overall cellular levels. With age, however, basal levels of protective/repair enzymes increase (although activity may be compromised) but adaptive increases (induction) no longer occurs. This results in an age-dependent physiological ceiling to adaptive homeostasis.

into the final aged zone. Similarly, a study of Proteasome activity in centenarians did not reveal the expected age-dependent decrease in activity, but instead found Proteasome activities similar to those of younger individuals (Chondrogianni et al., 2000).

Maintaining a low baseline can also be attributed to evolutionary novelties in translation. The longest-lived rodent, the naked mole rat has greater translational fidelity relative to shorter-lived mice (Azpurua et al., 2013), which results in a lower protein turnover rate. In theory, the decreased number of degradation targets lowers the overall baseline of proteolysis required to maintain homeostasis, so that there is a greater distance between the baseline and a physiological ceiling. When there is a greater need for proteolysis, organisms with a lower baseline requirement of proteolysis have a greater inducible capacity to meet acute and chronic needs before reaching a physiological ceiling.

A lower baseline can also be effective in preserving the adaptive response. Sea Urchin species with different lifespans were found to maintain Proteasome activity similarly with age, without large differences in concentrations of protein carbonyls. Of the three species studied, shorter-lived sea urchins exhibited higher Proteasome activity and the longest-lived urchin species exhibited some of the lowest Proteasome activities (Du et al., 2013). These longer-lived urchins exhibited a more effective protein regulation because they could maintain a similar level of damaged proteins while using less of their proteolytic capacity. The same relationship has been seen in another ageing model, the Giant Clam *Tridacna Derasa*, Proteasome activity in the Giant Clam is elevated compared to shorter-lived clam species (Ungvari et al., 2013). Assuming the physiological ceiling in Proteasome activity is relatively similar in species comparisons, a lower baseline of Proteasome activity in theory grants the longer-lived species a greater adaptive capacity.

The long lifespans in these examples are attributed, in part, to a robust maintenance of protein homeostasis. A major component of this success is staying below the physiological ceiling of proteolytic activity, which in turn preserves the adaptive capacity. This greater adaptive capacity delays entry into the aged zone, and may thus contribute to a longer lifespan. These results indicate that long-lived organisms have evolved strategies that keep the required baseline of activity either incredibly stable or lowered relative to shorter-lived species.

7. Increasing the physiological ceiling

Growing evidence suggests that the baseline levels of stress-protective enzymes increase with age. This trend towards a basal rise in cellular defenses, mirrors trends seen in other physiological markers, including increased inflammation (Miquel, 2009; Baylis et al., 2013), increased protein oxidation (Levine and Stadtman, 2001), and declines in metabolic function (Sies, 2014), most likely attributed to mitochondrial dysregulation (Hill and Van Remmen, 2014). Studies of senescent mammalian cell models show that the ability to induce stress protective enzymes diminishes with increasing population doublings (Ngo et al., 2011; Zhou et al., 2018). Inability to compensate for increased basal oxidation, leads to inadequate protein turnover, which is evident from studies of cells (Ngo et al., 2011; Grune et al., 2004; Zhou et al., 2018), worms (Raynes et al., 2017; Reis-Rodrigues et al., 2012), fruit flies (Pomatto et al., 2017b; Tsakiri et al., 2013a, b), and mice (Dubey et al., 1996; Pickering et al., 2014). Indeed, one recent study assessing age-associated changes in mice showed that multiple protective enzymes, including HO-1, GCLC/GCLM, NQO1, and Nrf2 show an age-dependent rise that is even evident starting as early as middle age (Zhang et al., 2012). Studies assessing changes in model organisms, including nematode worms (Raynes et al., 2017) and fruit flies (Pomatto et al., 2017b), show a similar trend. More interestingly, though the amounts of these different protective enzymes increase, their enzymatic activity often declines, suggesting a (albeit insufficient) compensatory mechanism (Pomatto and Davies, 2017).

In an apparent attempt to compensate for the gradual, but continual increase in cellular damage, multiple defense pathways are chronically activated, leading to a gradual upward shift of the baseline towards the physiologically-relevant ceiling and a compression of the adaptive potential (Fig. 5). Moreover, the temporal interplay between different transcriptional regulators, such as Nrf2 and Bach1 may go awry. Unlike young organisms that show a time-dependent delay between Nrf2 and Bach1 nuclear accumulation (Fig. 4A), aged organisms appear to loose the difference. Potentially, this time between Nrf2, first accumulating in the nucleus to activate down-stream targets, may either be shortened and/or never occur. At the same time, Bach1 and c-Myc may inappropriately move into the nucleus too quickly, thus turning off the adaptive homeostatic response before enough time enables activation (Fig. 4B). However, more work is needed to tease apart this relationship in order to understand the physiological switch that causes the detrimental acceleration of aged phenotypes.

The longest-lived rodent, the naked mole rat has greater Proteasome activity and content (20S and 26S) than shorter lived mice (Rodriguez et al., 2012). The Proteasome from the naked mole rat has also greater resistance to Proteasome inhibitors, which is attributed to a protein factor within the naked mole rat's cytosol (Rodriguez et al., 2014). When other mammalian Proteasomes were exposed to the naked mole rat cytosol, they also exhibited greater proteolytic activity and resistance to inhibitors. A survey across 8 rodent species found that Proteasome activity is positively correlated with maximal lifespan potential (Rodriguez et al., 2016). A comparison between long-lived and short-lived mammals showed that fibroblasts from long-lived rodents and marsupials had a significantly higher adaptive response of the Proteasome when faced with a stressful condition, serum starvation (Pride et al., 2015). Overall, long-lived mammals were characterized with having enhanced proteostasis relative to their shorter-lived counterparts (Lewis et al., 2015). The enhanced proteostasis was based on higher levels of Nrf2 due to lower levels of Nrf2 inhibitors such as Keap1.

An examination of the longest-living mammal, the bowhead whale *Balaena mysticetus* revealed duplications of 26S Proteasome genes (Keane et al., 2015) and higher expression of Proteasome associated genes (Seim et al., 2014). Gene can be a driver of evolutionary phenotypic innovation, giving rise to expanded or novel functions (Long et al., 2003; Kaessmann, 2010). Gene duplications can also provide redundancy and increase expression diversity, providing a means by which organisms can adapt to new environments or physiological conditions (Gu et al., 2004). In the case of the *B. mysticetus*, for example, these evolved modifications, such as redundancy and novelty of function in core protein homeostasis elements, may allow these whales to

successfully maintain protein homeostasis beyond what is observed in other mammals. As a result, these whales have greater ability to remain below the physiological ceiling and significantly postpone the onset of detrimental phenotypes, such as rapid accumulation of protein aggregates, thus resulting in a remarkable lifespan.

8. Conclusions

Adaptive homeostasis is a key attribute in maintaining healthy and responsive biological systems. However, the ability to activate adaptive homeostasis begins to decrease gradually somewhere around middle-age until the final third of lifespan, where it then declines precipitously. The loss of adaptive homeostasis is likely due to the confluence of several factors, but clearly involves an imbalance between Nrf2 and its inhibitors that leads to a drop in proteolytic activity that then results in the rapid accumulation of protein aggregates. Evolutionary innovations of long-lived organisms reveal that maintaining proteolytic activity is one key element in extending lifespan. Specifically the maintenance of adaptive homeostasis appears to be or great importance. This could be achieved through a number of mechanisms including, through lower basal proteolytic activity that creates a greater distance between the baseline and physiological ceiling, through potential extensions of the physiological ceiling due to greater resistance of the Proteasome to inhibitors, through greater expression of the Proteasome activator Nrf2 or diminished expression of Nrf2 inhibitors such as Bach1 and c-Myc, or through duplications of core Proteasome genes. There remains a need to fully characterize the physiological ceiling of proteolytic activity and the molecular mechanisms that constrain and define this ceiling.

Acknowledgements

LCD Pomatto was supported by grant #DGE-1418060 of the USA National Science Foundation. KJA Davies was supported by grant #ES003598 from the National Institute of Environmental Health Sciences of the US National Institutes of Health. KJA Davies and PY Sun were supported by grant #AG052374 from the National Institute on Aging of the US National Institutes of Health.

References

Davies, K.J., 2016. Adaptive homeostasis. Mol. Aspects Med. 49, 1–7.
Hassett, D.J., Cohen, M.S., 1989. Bacterial adaptation to oxidative stress: implications for pathogenesis and interaction with phagocytic cells. FASEB J. 3 (14), 2574–2582.
Russell, N.J., 1984. Mechanisms of thermal adaptation in bacteria: blueprints for survival. Trends Biochem. Sci. 9 (3), 108–112.
Davies, J.M., Lowry, C.V., Davies, K.J., 1995a. Transient adaptation to oxidative stress in yeast. Arch. Biochem. Biophys. 317 (1), 1–6.
Wiese, A.G., Pacifici, R.E., Davies, K.J., 1995. Transient adaptation to oxidative stress in mammalian cells. Arch. Biochem. Biophys. 318 (1), 231–240.
Pickering, A.M., et al., 2012. Nrf2-dependent induction of proteasome and Pa28αβ regulator are required for adaptation to oxidative stress. J. Biol. Chem. 287 (13), 10021–10031.
Ngo, J.K., Davies, K.J., 2009. Mitochondrial Lon protease is a human stress protein. Free Radic. Biol. Med. 46 (8), 1042–1048.
Grune, T., et al., 2002. Ezrin turnover and cell shape changes catalyzed by proteasome in oxidatively stressed cells. FASEB J. 16 (12), 1602–1610.
Shringarpure, R., et al., 2003. Ubiquitin conjugation is not required for the degradation of oxidized proteins by proteasome. J. Biol. Chem. 278 (1), 311–318.
Raynes, R., et al., 2017. Aging and SKN-1-dependent loss of 20S Proteasome adaptation to oxidative stress in C. elegans. J. Gerontol. A Biol Sci. Med. Sci. 72 (2), 143–151.
Pickering, A.M., et al., 2013. A conserved role for the 20S proteasome and Nrf2 transcription factor in oxidative stress adaptation in mammals, caenorhabditis elegans and drosophila melanogaster. J. Exp. Biol 216 (Pt 4), 543–553.
Pomatto, L.C.D., et al., 2017a. The age- and sex-specific decline of the 20s proteasome and the Nrf2/CncC signal transduction pathway in adaption and resistance to oxidative stress in Drosophila melanogaster. Aging (Albany N. Y.) 9 (4), 1153–1185.
Pomatto, L.C., et al., 2017b. The age-and sex-specific decline of the 20s proteasome and the Nrf2/CncC signal transduction pathway in adaption and resistance to oxidative stress in Drosophila melanogaster. Aging (Albany N. Y.) 9 (4), 1153.
Zhang, H., et al., 2012. Nrf2-regulated phase II enzymes are induced by chronic ambient nanoparticle exposure in young mice with age-related impairments. Free Radic. Biol. Med. 52 (9), 2038–2046.
Pomatto, L.C., Davies, K.J., 2017. The role of declining adaptive homeostasis in ageing. J. Physiol. 595 (24), 7275–7309. http://dx.doi.org/10.1113/JP275072.
Pomatto, L.C., Tower, J., Davies, K.J., 2017c. Sexual dimorphism and aging differentially regulate adaptive homeostasis. J. Gerontol. Ser. A 73 (2), 141–149.
Southam, C.M., 1943. Effects of Extract of Western Red-Cedar Heartwood on Certain Wood-Decaying Fungi in Culture.
Jackson, S.P., Bartek, J., 2009. The DNA-damage response in human biology and disease. Nature 461 (7267), 1071.
Raynes, R., Pomatto, L.C., Davies, K.J., 2016. Degradation of oxidized proteins by the proteasome: distinguishing between the 20S, 26S, and immunoproteasome proteolytic pathways. Mol. Aspects Med. 50, 41–55.
Grune, T., et al., 2011. HSP70 mediates dissociation and reassociation of the 26S proteasome during adaptation to oxidative stress. Free Radic. Biol. Med. 51 (7), 1355–1364.
Reeg, S., et al., 2016. The molecular chaperone Hsp70 promotes the proteolytic removal of oxidatively damaged proteins by the proteasome. Free Radic. Biol. Med. 99, 153–166.
Chondrogianni, N., et al., 2003. Central role of the proteasome in senescence and survival of human fibroblasts: induction of a senescence-like phenotype upon its inhibition and resistance to stress upon its activation. J. Biol. Chem. 278 (30), 28026–28037.
Bota, D.A., Davies, K.J., 2002. Lon protease preferentially degrades oxidized mitochondrial aconitase by an ATP-stimulated mechanism. Nat. Cell Biol. 4 (9), 674–680.
Goldberg, A.L., Waxman, L., 1985. The role of ATP hydrolysis in the breakdown of proteins and peptides by protease La from Escherichia coli. J. Biol. Chem. 260 (22), 12029–12034.
Wagner, I., et al., 1994. Molecular chaperones cooperate with PIM1 protease in the degradation of misfolded proteins in mitochondria. EMBO J. 13 (21), 5135–5145.
Teichmann, U., et al., 1996. Substitution of PIM1 protease in mitochondria by Escherichia coli Lon protease. J. Biol. Chem. 271 (17), 10137–10142.
Pomatto, L.C., et al., 2017d. The mitochondrial Lon protease is required for age-specific and sex-specific adaptation to oxidative stress. Curr. Biol. 27 (1), 1–15.
Lu, B., et al., 2013. Phosphorylation of human TFAM in mitochondria impairs DNA binding and promotes degradation by the AAA+ + Lon protease. Mol. Cell 49 (1), 121–132.
Quirós, P.M., et al., 2014. ATP-dependent Lon protease controls tumor bioenergetics by reprogramming mitochondrial activity. Cell Rep. 8 (2), 542–556.
Ngo, J.K., et al., 2011. Impairment of lon-induced protection against the accumulation of oxidized proteins in senescent wi-38 fibroblasts. J. Gerontol. Ser. A: Biomed. Sci. Med. Sci. 66 (11), 1178–1185.
Bota, D.A., Ngo, J.K., Davies, K.J., 2005. Downregulation of the human Lon protease impairs mitochondrial structure and function and causes cell death. Free Radic. Biol. Med. 38 (5), 665–677.
Lomeli, N., Bota, D.A., Davies, K.J., 2017. Diminished stress resistance and defective adaptive homeostasis in age-related diseases. Clin. Sci. 131 (21), 2573–2599.
Walker, C.L., et al., 2017. Redox regulation of homeostasis and proteostasis in peroxisomes. Physiol. Rev. 98 (1), 89–115.
Pomatto, L.C., Raynes, R., Davies, K.J., 2017e. The peroxisomal Lon protease LonP2 in aging and disease: functions and comparisons with mitochondrial Lon protease LonP1. Biol. Rev. 92 (2), 739–753.
Bulteau, A.-L., et al., 2017. Dysfunction of mitochondrial Lon protease and identification of oxidized protein in mouse brain following exposure to MPTP: implications for Parkinson disease. Free Radic. Biol. Med. 108, 236–246.
Dai, D.-F., et al., 2014. Mitochondrial oxidative stress in aging and healthspan. Longev. Healthspan 3 (1) p.6.
König, J., et al., 2017. Mitochondrial contribution to lipofuscin formation. Redox Biol. 11, 673–681.
Davies, J.M., Lowry, C.V., Davies, K.J., 1995b. Transient adaptation to oxidative stress in yeast. Arch. Biochem. Biophys. 317 (1), 1–6.
Wang, X., et al., 2017. The proteasome-interacting Ecm29 protein disassembles the 26S proteasome in response to oxidative stress. J. Biol Chem. 292 (39), 16310–16320.
Wang, X., et al., 2010. Regulation of the 26S proteasome complex during oxidative stress. Sci. Signal 3 (151), ra88.
Velichkova, M., Hasson, T., 2005. Keap1 regulates the oxidation-sensitive shuttling of Nrf2 into and out of the nucleus via a Crm1-dependent nuclear export mechanism. Mol. Cell Biol 25 (11), 4501–4513.
Ross, C.A., Poirier, M.A., 2004. Protein aggregation and neurodegenerative disease. Nat. Med. 10 (Suppl), S10–7.
Bucciantini, M., et al., 2002. Inherent toxicity of aggregates implies a common mechanism for protein misfolding diseases. Nature 416 (6880), 507–511.
Philo, J.S., Arakawa, T., 2009. Mechanisms of protein aggregation. Curr. Pharm. Biotechnol. 10 (4), 348–351.
Grune, T., et al., 2004. Decreased proteolysis caused by protein aggregates, inclusion bodies, plaques, lipofuscin, ceroid, and 'aggresomes' during oxidative stress, aging, and disease. Int. J. Biochem. Cell Biol. 36 (12), 2519–2530.
Bartkowski, R., et al., 2002. Aggregation of recombinant bovine granulocyte colony stimulating factor in solution. J. Protein Chem. 21 (3), 137–143.
Strehler, B.L., et al., 1959. Rate and magnitude of age pigment accumulation in the human myocardium. J. Gerontol. 14, 430–439.
Levine, R.L., Stadtman, E.R., 2001. Oxidative modification of proteins during aging. Exp. Gerontol. 36 (9), 1495–1502.
Höhn, A., et al., 2011. Lipofuscin inhibits the proteasome by binding to surface motifs. Free Radic. Biol. Med. 50 (5), 585–591.
Reis-Rodrigues, P., et al., 2012. Proteomic analysis of age-dependent changes in protein solubility identifies genes that modulate lifespan. Aging Cell 11 (1), 120–127.
Sitte, N., et al., 2000a. Protein oxidation and degradation during cellular senescence of human BJ fibroblasts: part I—effects of proliferative senescence. FASEB J. 14 (15), 2495–2502.

Sitte, N., et al., 2000b. Protein oxidation and degradation during cellular senescence of human BJ fibroblasts: part II—aging of nondividing cells. FASEB J. 14 (15), 2503–2510.
Alves-Rodrigues, A., Gregori, L., Figueiredo-Pereira, M.E., 1998. Ubiquitin, cellular inclusions and their role in neurodegeneration. Trends Neurosci. 21 (12), 516–520.
Cummings, C.J., et al., 1998. Chaperone suppression of aggregation and altered subcellular proteasome localization imply protein misfolding in SCA1. Nat. Genet. 19 (2), 148–154.
Venkatraman, P., et al., 2004. Eukaryotic proteasomes cannot digest polyglutamine sequences and release them during degradation of polyglutamine-containing proteins. Mol. Cell 14 (1), 95–104.
Bennett, E.J., et al., 2005. Global impairment of the ubiquitin-proteasome system by nuclear or cytoplasmic protein aggregates precedes inclusion body formation. Mol. Cell 17 (3), 351–365.
Demasi, M., Davies, K.J., 2003. Proteasome inhibitors induce intracellular protein aggregation and cell death by an oxygen-dependent mechanism. FEBS Lett. 542 (1-3), 89–94.
Hyun, D.H., et al., 2003. Proteasomal inhibition causes the formation of protein aggregates containing a wide range of proteins, including nitrated proteins. J. Neurochem. 86 (2), 363–373.
Ruan, L., et al., 2017. Cytosolic proteostasis through importing of misfolded proteins into mitochondria. Nature 543 (7645), 443.
Bayot, A., et al., 2014. Effect of Lon protease knockdown on mitochondrial function in HeLa cells. Biochimie 100, 38–47.
Bota, D.A., Davies, K.J., 2016. Mitochondrial Lon protease in human disease and aging: including an etiologic classification of Lon-related diseases and disorders. Free Radic. Biol. Med. 100, 188–198.
Hamon, M.-P., Bulteau, A.-L., Friguet, B., 2015. Mitochondrial proteases and protein quality control in ageing and longevity. Ageing Res. Rev. 23, 56–66.
Ngo, J.K., Davies, K.J., 2007. Importance of the lon protease in mitochondrial maintenance and the significance of declining lon in aging. Ann. N. Y. Acad. Sci. 1119 (1), 78–87.
Folgueras, A.R., et al., 2018. Cancer susceptibility models in protease-deficient mice. Proteases and Cancer. Springer, pp. 235–245.
Bota, D.A., Van Remmen, H., Davies, K.J., 2002. Modulation of Lon protease activity and aconitase turnover during aging and oxidative stress. FEBS Lett. 532 (1-2), 103–106.
Jaiswal, A.K., 2004. Nrf2 signaling in coordinated activation of antioxidant gene expression. Free Radic. Biol. Med. 36 (10), 1199–1207.
Zhang, H., Davies, K.J., Forman, H.J., 2015. Oxidative stress response and Nrf2 signaling in aging. Free Radic. Biol. Med. 88, 314–336.
Itoh, K., et al., 1997. An Nrf2/small Maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. Biochem. Biophys. Res. Commun. 236 (2), 313–322.
Tebay, L.E., et al., 2015. Mechanisms of activation of the transcription factor Nrf2 by redox stressors, nutrient cues, and energy status and the pathways through which it attenuates degenerative disease. Free Radic. Biol. Med. 88, 108–146.
Niture, S.K., Khatri, R., Jaiswal, A.K., 2014. Regulation of Nrf2—an update. Free Radic. Biol. Med. 66, 36–44.
Chang, W.-H., et al., 2017. Cigarette smoke regulates the competitive interactions between NRF2 and BACH1 for heme oxygenase-1 induction. Int. J. Mol. Sci. 18 (11), 2386.
Piras, S., et al., 2017. Differentiation modifies Bach1 dependent regulation of HO-1 expression and increases sensitivity to oxidative stress in neuroblastoma cells. Free Radic. Biol. Med. 108, S80.
Zhou, L., et al., 2018. Aging-related decline in the induction of Nrf2-regulated antioxidant genes in human bronchial epithelial cells. Redox Biol. 14, 35–40.
Oyake, T., et al., 1996. Bach proteins belong to a novel family of BTB-basic leucine zipper transcription factors that interact with MafK and regulate transcription through the NF-E2 site. Mol. Cell. Biol. 16 (11), 6083–6095.
Suzuki, H., et al., 2003. Cadmium induces nuclear export of Bach1, a transcriptional repressor of heme oxygenase-1 gene. J. Biol. Chem. 278 (49), 49246–49253.
Dhakshinamoorthy, S., et al., 2005. Bach1 competes with Nrf2 leading to negative regulation of the antioxidant response element (ARE)-mediated NAD(P)H:quinone oxidoreductase 1 Gene expression and induction in response to antioxidants. J. Biol. Chem. 280 (17), 16891–16900.
Todgham, A.E., Hoaglund, E.A., Hofmann, G.E., 2007. Is cold the new hot? Elevated ubiquitin-conjugated protein levels in tissues of Antarctic fish as evidence for cold-denaturation of proteins in vivo. J. Comp. Physiol. B 177 (8), 857–866.
Gracey, A.Y., et al., 2004. Coping with cold: an integrative, multitissue analysis of the transcriptome of a poikilothermic vertebrate. Proc. Natl. Acad. Sci. U. S. A. 101 (48), 16970–16975.
Buckley, B.A., Gracey, A.Y., Somero, G.N., 2006. The cellular response to heat stress in the goby Gillichthys mirabilis: a cDNA microarray and protein-level analysis. J. Exp. Biol. 209 (14), 2660–2677.
Podrabsky, J.E., Somero, G.N., 2004. Changes in gene expression associated with acclimation to constant temperatures and fluctuating daily temperatures in an annual killifish Austrofundulus limnaeus. J. Exp. Biol. 207 (13), 2237–2254.
Yen, H.-C.S., et al., 2008. Global protein stability profiling in mammalian cells. Science 322 (5903), 918–923.
Lamarre, S.G., et al., 2009. Protein synthesis is lowered while 20S proteasome activity is maintained following acclimation to low temperature in juvenile spotted wolffish (Anarhichas minor Olafsen). J. Exp. Biol. 212 (9), 1294–1301.
Drake, M.J., Miller, N.A., Todgham, A.E., 2017. The role of stochastic thermal environments in modulating the thermal physiology of an intertidal limpet, Lottia digitalis. J. Exp. Biol. 220 (17), 3072–3083.
Somero, G.N., 2002. Thermal physiology and vertical zonation of intertidal animals: optima, limits, and costs of living. Integr. Comp. Biol. 42 (4), 780–789.
Schmidt, M., Finley, D., 2014. Regulation of proteasome activity in health and disease. Biochim. Biophys. Acta 1843 (1), 13–25.
Sosnowska, D., et al., 2014. A heart that beats for 500 years: age-related changes in cardiac proteasome activity, oxidative protein damage and expression of heat shock proteins, inflammatory factors, and mitochondrial complexes in Arctica islandica, the longest-living noncolonial animal. J. Gerontol. A Biol. Sci. Med. Sci. 69 (12), 1448–1461.
Chondrogianni, N., et al., 2000. Fibroblast cultures from healthy centenarians have an active proteasome. Exp. Gerontol. 35 (6-7), 721–728.
Azpurua, J., et al., 2013. Naked mole-rat has increased translational fidelity compared with the mouse, as well as a unique 28S ribosomal RNA cleavage. Proc. Natl. Acad. Sci. U. S. A. 110 (43), 17350–17355.
Du, C., et al., 2013. Oxidative damage and cellular defense mechanisms in sea urchin models of aging. Free Radic. Biol. Med. 63, 254–263.
Ungvari, Z., et al., 2013. Testing predictions of the oxidative stress hypothesis of aging using a novel invertebrate model of longevity: the giant clam (Tridacna derasa). J. Gerontol. A Biol. Sci. Med. Sci. 68 (4), 359–367.
Miquel, J., 2009. An update of the oxidation-inflammation theory of aging: the involvement of the immune system in oxi-inflamm-aging. Curr. Pharm. Des. 15 (26), 3003–3026.
Baylis, D., et al., 2013. Understanding how we age: insights into inflammaging. Longev. Healthspan 2 (1), 8.
Sies, H., 2014. Role of metabolic H2O2 generation redox signaling and oxidative stress. J. Biol. Chem. 289 (13), 8735–8741.
Hill, S., Van Remmen, H., 2014. Mitochondrial stress signaling in longevity: a new role for mitochondrial function in aging. Redox Biol. 2, 936–944.
Tsakiri, E.N., et al., 2013a. Proteasome dysfunction in Drosophila signals to an Nrf2-dependent regulatory circuit aiming to restore proteostasis and prevent premature aging. Aging cell 12 (5), 802–813.
Tsakiri, E.N., et al., 2013b. Differential regulation of proteasome functionality in reproductive vs. somatic tissues of Drosophila during aging or oxidative stress. FASEB J. 27 (6), 2407–2420.
Dubey, A., et al., 1996. Effect of age and caloric intake on protein oxidation in different brain regions and on behavioral functions of the mouse. Arch. Biochem. Biophys. 333 (1), 189–197.
Pickering, A.M., et al., 2014. Fibroblasts from longer-lived species of primates, rodents, bats, carnivores, and birds resist protein damage. J. Gerontol. Ser. A: Biomed. Sci. Med. Sci. 70 (7), 791–799.
Rodriguez, K.A., et al., 2012. Altered composition of liver proteasome assemblies contributes to enhanced proteasome activity in the exceptionally long-lived naked mole-rat. PLoS One 7 (5), e35890.
Rodriguez, K.A., et al., 2014. A cytosolic protein factor from the naked mole-rat activates proteasomes of other species and protects these from inhibition. Biochim. Biophys. Acta 1842 (11), 2060–2072.
Rodriguez, K.A., et al., 2016. Determinants of rodent longevity in the chaperone-protein degradation network. Cell Stress Chaperones 21 (3), 453–466.
Pride, H., et al., 2015. Long-lived species have improved proteostasis compared to phylogenetically-related shorter-lived species. Biochem. Biophys. Res. Commun. 457 (4), 669–675.
Lewis, K.N., et al., 2015. Regulation of Nrf2 signaling and longevity in naturally long-lived rodents. Proc. Natl. Acad. Sci. 112 (12), 3722–3727.
Keane, M., et al., 2015. Insights into the evolution of longevity from the bowhead whale genome. Cell Rep. 10 (1), 112–122.
Seim, I., et al., 2014. The transcriptome of the bowhead whale Balaena mysticetus reveals adaptations of the longest-lived mammal. Aging (Albany N. Y.) 6 (10), 879–899.
Long, M., et al., 2003. The origin of new genes: glimpses from the young and old. Nat. Rev. Genet 4 (11), 865–875.
Kaessmann, H., 2010. Origins, evolution, and phenotypic impact of new genes. Genome Res. 20 (10), 1313–1326.
Gu, Z., et al., 2004. Duplicate genes increase gene expression diversity within and between species. Nat. Genet 36 (6), 577–579.
Harman, D., 1956. Aging: a theory based on free radical and radiation chemistry. J. Gerontol 11 (3), 298–300.