



*Commentary*

## **Ageing: when the ubiquitin–proteasome machinery collapses**

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**Abstract:** In mammalian cells, protein degradation is an essential and dynamic process that is crucial for survival, growth, differentiation and proliferation of cells. Tellingly, the majority of intracellular proteins are degraded via the ubiquitin–proteasome system (UPS). UPS-mediated protein degradation serves qualitative and quantitative roles within the cellular proteome. For instance, UPS specifically targets misfolded, aggregated, toxic, mutant and otherwise structurally abnormal proteins for destruction and hence prevent aggregation and accumulation of toxic proteins. Furthermore, several cellular regulatory proteins, including cell cycle regulators, transcription factors, DNA replication and DNA repair proteins are selectively targeted for degradation via UPS and thus contribute to maintaining protein homeostasis (proteostasis) and proper functional proteome. Concomitantly, the deregulation of proteostasis may lead to several pathological disorders including aging-associated pathologies. Remarkably, augmenting the proteasomal activity has been linked to longevity in model organisms and protect these organisms from symptoms linked to protein homeostasis disorders. Herein I comment briefly on the recent work revealing the pivotal role of ubiquitin–proteasome-mediated protein degradation with respect to regulating aging process in model organisms.

**Keywords:** ubiquitin; protein degradation; proteasome; protein stability

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### **1. Intracellular protein degradation by the ubiquitin–proteasome system**

Intracellular proteins in living cells have different half-lives that range from seconds to several weeks [1-3]. Intracellular protein degradation plays crucial roles in cellular and physiological regulation such as the elimination of misfolded or any otherwise abnormal proteins, the maintenance

of amino acid pools inside cells affected by stressful conditions such as nutrient deprivation and the generation of proteolytically active protein fragments such as hormones, antigens, or any other effector proteins [4]. Yet, interestingly, another crucial function of intracellular protein degradation pathways is the selective degradation of proteins whose levels must vary with time and the physiological status of the cell, and thus metabolic instability is considered a pivotal functional attribute of several regulatory proteins. Tellingly, a short half-life of a regulatory protein endows a route to allow the generation of its spatial concentration gradient and permit the rapid fine-tuning of its levels through alteration in its synthesis rate. Notably, pivotal biological circuits often deploy conditional unstable proteins (long lived or short-lived based on the physiological status of the cell) as essential components in their functional systems [4-7]. Some poignant examples of such conditional unstable proteins are cyclins, a group of proteins whose ubiquitin–proteasome-dependent degradation at specific stages of cell cycle regulates cell division and growth, transcription factors (as Myc) [8], and checkpoint control proteins (as p53) [9].

UPS-mediated protein degradation relies on two sequential steps: the substrate is first recognized and covalently conjugated to ubiquitin by specific ubiquitin E3 ligases. After initial ubiquitination, further ubiquitin molecules are conjugated in series at lysine 48 of the ubiquitin to form a polyubiquitin structure, which is then recruited to the 26S proteasome for degradation [4,7]. Although the canonical ubiquitination of target substrates of the UPS system proceeds via a three-enzyme cascade: E1 (ubiquitin activating enzyme, using ATP), E2 (ubiquitin conjugating-enzyme or carrier enzyme), and E3 (ubiquitin protein-ligases) [4,7]. It has been shown recently that the bacterial effector protein SdeA, which serves as a bacterial E3 ubiquitin ligase, ubiquitinates several human Rab proteins without engaging any of the canonical cellular ubiquitination machinery that involves E1 and E2 enzymes [10].

## 2. UPS-mediated protein degradation fine-tunes aging process

Aging was thought to be a stochastic and progressive decline in the capacity of physiological, cellular and molecular networks [11,12]. However, this model has been counteracted since the discovery that specific metabolic signaling pathways regulate the rate of aging process in model organisms and thus can delay it. So far, three metabolic signaling pathways have been identified that impact the rate of aging [11,12]. Caloric diet restriction (DR) has been shown to exert longevity-promoting effect in model organisms [5,6,12]. In addition, Mitigation of the mitochondrial electron transport chain (ETC) and the amelioration of the insulin/IGF-1-like signaling axis (IIS) have been shown to extend the life-span of different model laboratory organisms [11-16]. Even though these three longevity-enhancing pathways operate independently, one common downstream mechanism was hypothesized to mediate their lifespan extension effect, which is the modulation of protein homeostasis and particularly enhancing the degradation activity of the ubiquitin–proteasome system [11-21].

Previous work demonstrated that the brain and liver undergo selective changes in proteasome biology, including increases in proteasome biogenesis in response to aging and diet restriction (DR) [17]. Furthermore, DR was shown to alter the interaction of Hsp90 with the 20S proteasome complex in the brain and liver suggesting that cross-talk between proteasome composition/biogenesis and proteasome activity in tissues is extremely complex and may be modulated by physiological cues like diet restriction [17].

A major source of reactive oxygen species (ROS) are mitochondria. Tellingly, augmented

generation of mitochondrial ROS may lead to loss of mitochondrial function and reduction of energy production resulting in progression of aging [18]. Of note, in mitochondria, the electron transport chain (ETC) is considered the major source of ROS [18]. It was shown that abrogation in ETC is associated with elevation levels of ROS and mitochondrial deregulation. Remarkably, many aging-associated disorders, involving mitochondrial dysfunctions, are also known to exhibit significant ablation of proteasome function and activity. For instance, it was revealed that the partial ablation of proteasome reduced dramatically the activities of complex I and II in neural mitochondria [19].

Previous work has revealed that the mitigation of insulin/IGF-1 signaling pathway (IIS) extends lifespan in both invertebrates and vertebrates [22-25]. IIS reduction has been correlated with increased longevity of humans [23,25]. In worms, it has been demonstrated that suppression of IIS triggers enhanced proteasome activity [22,24]. This fine-tuning process is accomplished, at least in part, via DAF-16 transcriptional repression of the proteasome-associated deubiquitinase *ubh-4* [24]. *Uchl5*, the human ortholog of *ubh-4*; mediate the increase of degradation of toxic pro-apoptotic proteins in mammalian cells [24].

Indeed, several lines of evidence support the notion that augmented protein degradation machinery activities, including proteasome activity, promote life span [11-16,20-25]. For instance, elevated proteasomal activity was observed in long-lived organisms, including the long-lived humans or centenarians and the long-lived animal desert mole rat [12]. Furthermore, recent genetic studies demonstrated that the ectopic overexpression of one of the proteasome subunits enhance the longevity of model organisms indicating the longevity-enhancing effect of promoting proteasome degradation activity [12-14]. Although several studies have unveiled that longevity-enhancing metabolic pathways spur protein degradation machinery activity, including proteasomal activity and therefore abrogate age-related disorders [11-16,20-25], further investigations on mammalian cells are needed to study the therapeutic implications of modulation of protein degradation machinery on aging-related disorders [25,27]. Intriguingly, given the importance of proteostasis and protein degradation machinery in delaying the onset of aging process, why some of the protein degradation machinery components are not constitutively present at relatively high concentrations. Two models were suggested to explain this [11], first, the potentiation for development of cancer might account for lacking constitutive upregulation of degradation machinery components. For instance, although it is known that an attenuated protein degradation capacity is associated with neurodegenerative and aging-related disorders [25,27], it has been unveiled recently that augmented protein degradation capacity is associated with oncogenic transformation and mitigating oxidative stress in tumor cells [26]. These findings underpin a role for augmenting the capacity of protein clearance machinery in anti-oxidative stress signaling and suggest that enhanced protein clearance capacity might serve as an intrinsic signaling circuit crucial for tumor initiation and maintenance [26].

The second hypothetical model, which might account for lacking constitutive upregulation of degradation machinery components, dictates that there is an evolutionary trade-off between demands of somatic cells maintenance and reproductive capacity [11-16]. Tellingly, from an evolutionary perspective, constrained with finite biological resources, living organisms must fine-tune the costly demands of reproduction and somatic maintenance, including maintenance of appropriate proteome quality control networks [28-30]. Several lines of evidences suggest that alteration in the protein degradation and protein quality control networks to mimic circumstances that promote longevity, for instance, overexpression of chaperones or proteasomal subunits, induction of stress responses, or mitigation of translation rates, suppresses fertility and extend development time period. In fact, it has

been shown that reduced IIS, DR, or reduced mitochondrial function, have all been demonstrated to mitigate the actual reproductive capacity (fecundity) as well as promote longevity [28-30]. The previous conjecture may help in explanation the restricted expression of several components of the protein degradation machinery in differentiated cells.

### Conflict of interest

None declared.

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