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Mini Review Article

Alteration of Proteasome System in Aging and Aging-Associated Disorders

Qunxing Ding* and Haiyan Zhu

Department of Biological Sciences, Kent State University at East Liverpool, Liverpool, USA

***Corresponding author:** Qunxing Ding, Department of Biological Sciences, Kent State University at East Liverpool, Liverpool, USA, Tel: 330-382-7523; E-mail: qding@kent.edu

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Abstract

The proteasome system is crucial in protein metabolism involving in physiological and pathological developments, especially in aging and aging-related disorders. Here we discussed the relationship of proteasome with other metabolic systems such as lysosome and ribosome as well as the alteration of proteasome system under oxidative stress, aging and other pathological conditions. Due to its essential roles, the proteasome system provides an active target for therapeutic development in many different pathological conditions.

Keywords: Proteasome; Aging; Oxidative stress; Ribosome; Lysosome

Introduction

Proteasome was first identified in 1977 by Etlinger and Goldberg when they worked on reticulocytes [1]. The 20S core complex has 28 subunits and is a 4-ring cylinder structure with 11S and 19S regulatory complexes which can shuttle on one end or both ends of the cylinder [2]. It is the major machinery for protein degradation, especially for oxidized, misfolded, aged and other damaged proteins [3]. This system has multiple protease activities that can digest proteins into short peptides. In fact, the proteasome system plays a major role in quality and quantity control in protein homeostasis. In addition, the system responses to inflammatory signals, oxidative stress, and other signal to alter its structure and catalytic functions. The basic information and updates of the proteasome system has been reviewed elsewhere [2] so this review will focus on the proteasomal alteration in aging and aging related disorders.

Aging

It is reported that the proteasome activities and the expression of its subunits declined along with aging in epidermis cells [4], such functional decline was also found in heart tissue associated with decreased 20S proteasome content [5]. More data has been reported that impaired proteasome function was associated with the process of aging, and the function of proteasome system played the role in modulating aging rate [6]. On the other hand, the declined proteasome function contributes to the development of aging associated disorders. For example, genetic depletion of proteasome induced accumulation of mitochondrial inclusions and neurodegeneration [7], proteasome inhibition is sufficient to induce mitochondrial dysfunction, increased generation of reactive oxygen species (ROS), elevated RNA and DNA oxidation, and promoted protein oxidation [8]. Furthermore, elevated proteasome assembling factor UMP1 exhibited enhanced viability during stationary-phase aging [9], and increased content and activities of proteasome could extend the lifespan of *C. elegans* [10] and mice [11].

The alteration of proteasome system is also associated with aging-related disorders. Alzheimer's disease (AD) is a leading cognitive disorder especially in elder population and β-amyloid (Aβ) is one of the causative factors that have been densely investigated. Growing evidence indicate that dysfunction of proteasome system induces Aβ accumulation and the accumulated Aβ reversely inhibits the activities of proteasome system [12]. Evidence indicated that impaired proteasome function occurred at very young age of AD mouse model (APPswe/PS1dE9) before plaque formation and cognitive problem, revealing the causative role of proteasome system in the development of AD [13]. In MPTP-induced Parkinson's disease (PD) mice model, the proteasomal genes Uchl3, Ubr7, Ube3c, Usp39, Ube2k, Ube2d3, Ube2g1 were reduced at pre-symptomatic stage and Uchl3, Ube3c, Usp39, Ube2k, Ube2m were reduced at early symptomatic stage [14]. Proteasomal dysfunction was also reported in neuroblastoma and kidney cells, in the cortex and striatum of Huntington's disease (HD) transgenic mice [15]. Furthermore, elevated expression level of proteasome subunit gene PMSE3 was found in multiple pathological conditions such as cancer, rheumatoid arthritis, Sjogren's syndrome, and connective-tissue diseases [16].

In summary, the function of proteasome is tightly associated with aging and aging-related disorders; the early occurrence of proteasome dysfunction in these conditions indicates the causal role of proteasome system. Nevertheless, the cause(s) of proteasomal dysfunction is widely investigated and oxidative stress is one of the factors identified. Most likely, proteasomal alteration may be part of the aging process. Therapeutic development focusing on the proteasome system may systematically improve aging and aging associated disorders.

Oxidative stress

Numerous evidence indicate that oxidative stress plays a critical role in aging and aging related disorders. Consequently, the proteasome system is involved in the generation of oxidative stress. Due to cellular respiration, there is constant oxidative damage in cellular proteins and the majority of oxidized proteins are cleaned up by the proteasome system. The inhibition of proteasome function induced oxidative stress and elevated levels of oxidized and ubiquitinated proteins [17]. Reversely, the inhibition of proteasome activity could also be induced by oxidized substrate proteins and oxidative damage in proteasome subunits [18]. The oxidative stress and proteasome inhibition could be synergistic [19]. In pathological condition, inhibition of proteasome sometimes showed protective effects: the cardiac superoxide dismutase 1 and 2 were increased, the autophagic response was triggered and inflammation was delayed [20]. Therefore, the correlation between oxidative stress and proteasome dysfunction might be another chicken-egg paradox. The actual interaction between proteasome inhibition and oxidative stress may vary along with different cellular conditions in aging process.

Aggregated protein

Protein aggregation occurs commonly in aging and aging related

disorders. The senile plaques and tangles in AD, Lewy bodies and Lewy threads in PD and Dementia with Lewy Body, and the mutant htt aggregates in HD are well documented examples of protein aggregation. Inhibition of proteasome and lysosome systems could induce α-synuclein aggregation directly [21], and protein aggregation could induce proteasome dysfunction as well [22]. Nevertheless, proteasomal subunits could also form aggregates [23]. Although the proteasome impairment and protein aggregation mostly occur in pathological conditions [23,24] protein aggregation could form in healthy cells without inhibition of proteasome and may have detoxic function [25]. In summary, dysfunction of proteasome is sufficient to induce protein aggregation even cell death, but may not be necessary; protein aggregation could induce proteasome inhibition in selected conditions. Generally proteasome is responsible to remove protein aggregation but their interaction is not a simple two-element game, other factors including oxidative stress and ubiquitiation might also take part in the interaction.

Ubiquitination

In proteasome system, the proteins are degraded through ubiquitin-independent and ubiquitin-dependent pathways and the latter is the major process. Generally ubiquitination is the process that a protein is marked for degradation. The marking process is conducted by a series of enzymes (E1, E2, E3, DUBs). The alteration of ubiquitin and the related enzymes dramatically affect the proteasome function. For example, ubiquitin, E1, E2 and E3 had increased expression levels after treated with oxidative low density lipoprotein (ox-LDL) [26], overexpression of ubiquitin could reduce the protein aggregates and extend the lifespan of HD transgenic mice [27]. On the contrary, mutation in ubiquitin activating enzyme E1 could significantly reduce the lifespan of drosophila [28]. Mutation of ubiquitin was directly associated with Aβ accumulation and deposition in AD [12]. The mutation in ubiquitin and associated enzymes were involved in the development of multiple diseases such as Angelman syndrome [29], Paget's disease-like disorder [30], and Charcot-Marie-Tooth disease [31]. These data indicated the critical position of ubiquitination in proteasome system as well as in cellular metabolism.

Immunoproteasome

There are three inducible proteasome subunits (PSMB8, 9 and 10) that can replace three regular subunits (PSMB 1, 2 and 5) to form a special form of proteasome, so called immunoproteasome. The immunoproteasome has similar catalytic activities as a regular proteasome. Also, the immunoproteasome is critical in MHC class I antigen presentation, responsible to oxidative stress [32], and regulated by redox state [33]. Mutation in immunoproteasome subunits largely reduced the capacity to deal with oxidative stress [32] and knocking out PSMB8, 9 and 10 dramatically reduced the MHC class I antigen presentation in transgenic mice [34]. Impairment of immunoproteasome also could induce illness such as enterovirus myocarditis [35]. On the other hand, oxidative stress, injury and aging could increase the expression of immunoproteasome [36]. In addition, the accumulation of AGE (advanced glycation end products) could induce immunoproteasome through RAGE (receptor for AGE) signaling [11]. Interestingly, the long-living species had elevated immunoproteasome levels that indicated the possible role of immunoproteasome in longevity of mice [37]. In rat hippocampus region, the content of immunoproteasome was increased along with aging [38] and this observation was confirm in human [39]. It's believed that the elevated immunoproteasome was associated with chronic inflammation during pathological development [38]. It's well documented that immune dysfunction is coupled with aging, so the inducible proteasome subunits (PSMB 8, 9 and 10) are easy targets for genetic engineering and therapeutic development to improve immune function, aging and aging associated disorders.

Lysosomal crosstalk

Lysosome is another system that degrades proteins in cellular metabolism through a process called autophagy especially for aggregated proteins and aged organelles. Lysosomal system and proteasome system are tightly associated. Proteasome inhibitors induced autophagy effects [40] and the dysfunction of both lysosome and proteasome could occur simultaneously: in heart and skeleton muscle the lysosome system was disturbed and in brain, kidney, liver and lung the proteasome system had reduced function in HD transgenic mice [15]. With chronic low level proteasome inhibition, the autophagy was induced in cultured cells [40], might through class III PI3K pathway resulted in apoptosis [41]. Autophagy was significantly elevated along with aging [42] and such lysosomal elevation usually was coupled with decreased proteasomal function. In certain case inhibition of deubiquitination also blocked autophagy [43]. The connection or crosstalk between proteasome and lysosome is based on different signal transduction pathways, for example the fusion protein of glutathionine S-transferase N-terminal to betaine-homocysteine S-methyltransferase reporter may play a role [44] and glycogen synthase kinase 3β may also deliver the signals [38]. Interestingly, such signaling pathways varied along with age [45]. The crosstalk or interplay between proteasome and lysosome systems might be based on the upstream metabolic signaling pathways or the downstream substrate signals.

Ribosome crosstalk

Ribosome as the protein synthesis machinery is on the upstream of protein metabolism. We reported that there is crosstalk between protein synthesis and degradation. Under proteasome inhibition, the capacity of protein synthesis was impaired in cultured neuronal cells. The impairment of protein synthesis was reversible: the protein synthesis capacity recovered after washing out the proteasome inhibitors within three hours after treatment, and the protein synthesis could not recover if the treatment was longer than six hours [46]. More interestingly, the ribosomal impairment by proteasome inhibitors was cell dependent, which means the proteasome inhibitors had no effects on purified ribosomes in *in vitro* translation [47]. Such interaction was also reported in leaf adaxial determination, mutation in proteasomal subunit gene and ribosomal protein gene share similarity in leaf development with an outgrowth formed on the distal part of the leaf abaxial side [48]. Therefore, the cellular signaling pathways involved in the crosstalk between proteasome and ribosome. For example the ribosomal biogenesis factor WBSCR22 is regulated and tightly controlled by proteasome [49], translation initiation factor 3 had direct interaction with both ribosomal subunits and proteasome subunits [50]. Proteasome controls many factors in ribosome biogenesis that may set up the connection between protein synthesis and degradation [51]. In other words, the birth and death of proteins are tightly associated and such association is dynamic. Regulation of one system might affect the other system significantly, which provide potentials and convenience for drug development.

Therapeutic approach

As discussed above, the proteasome system involved in physiological and pathological processes, especially aging and aging related disorders. Therefore, the proteasome system becomes an active therapeutic target for disease, aging and related conditions. With biological and chemical

agents the proteasome system can be activated to extend lifespan or attenuate diseases [51]. As a hormone ghrelin enhanced the activities of proteasome [52] and a receptor agonist baclofen could also elevated proteasome activities to promote cell viability and improve HD symptoms in transgenic mice [53]. Overexpression of one proteasome subunit could enhance the expression of other proteasome subunits to promote the survival rate of culture cells under oxidative stress [54]. In another report upregulation of proteasome catalytic subunits could not only restore the proteasomal activities but also extend the lifespan of skin cells [55]. Upregulation of a chaperone (POMP) that involves in proteasome complex assembling could improve proteasome function and resistance to oxidative stress [56]. Expressing a peptide (proteasome-activating peptide 1, PAP1) in cultured cells could improve the proteasome activity; reduce oxidative damage and protein aggregation [57]. Furthermore, some chemical proteasome inhibitors like MLN9708 could increase antioxidant enzyme transcripts to elevate the cellular antioxidant levels including glutathione, gamma-globin, and Hb F [58]. An algae extract from *Phaeodactylum tricornutum* could preserve proteasome activities and reduce the oxidative damage from ultra violet irradiation [59]. A novel proteasome inhibitor VR23 was evidenced to reduce proteasome activities and selectively kill cancer cells [60]. These studies indicate the proteasome system is an effective target for therapeutic development with multiple approaches.

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