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Review

Proteasome activation: An innovative promising approach for delaying aging and retarding age-related diseases

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ABSTRACT

Aging is a natural process accompanied by a progressive accumulation of damage in all constituent macromolecules (nucleic acids, lipids and proteins). Accumulation of damage in proteins leads to failure of proteostasis (or *vice versa*) due to increased levels of unfolded, misfolded or aggregated proteins and, in turn, to aging and/or age-related diseases. The major cellular proteolytic machineries, namely the proteasome and the lysosome, have been shown to dysfunction during aging and age-related diseases. Regarding proteasome it is well established that it can be activated either through genetic manipulation or through treatments with natural or chemical compounds that eventually result to extension of lifespan or deceleration of the progression of age-related diseases. This review article focuses on proteasome activation studies in several species and cellular models and their effects on aging and longevity. Moreover, it summarizes findings regarding proteasome activation in the major age-related diseases as well as in progeroid syndromes.

Contents

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1. Introduction

Proteostasis (protein homeostasis) is a major node that needs to maintain its function in order to retain cellular, tissue and organismal homeostasis (Chondrogianni et al., 2014b). It is now evident that proteostasis represents a major factor affecting various biological processes, including aging (Lopez-Otin et al., 2013) while chronic imbalance of proteostasis has been shown to have negative impact on both cellular and organismal lifespan (Taylor and Dillin, 2011). The proteasome is a major proteolytic machinery being in charge of maintaining proteostasis. As it has been shown to malfunction during aging and age-related diseases (Chondrogianni et al., 2014a) its activation is anticipated to have positive effects not only in longevity but also in the retardation of age-related phenotypes. This review article presents studies demonstrating proteasome activation across different species and various cellular models and reports the effects on aging, longevity and age-related diseases.

2. The proteasome system

The proteasome is a fundamental multicatalytic enzyme complex that facilitates the degradation of normal as well as abnormal, damaged or unnecessary cellular proteins. It is located in various cellular compartments (cytoplasm, nucleus and ER) and represents about up to 1% of the total cellular protein content. The pivotal role of the proteasome is revealed by the fact that it takes part in many and diverse cellular functions including cell cycle, regulation of transcription factors and cell differentiation (Goldberg, 2007).

2.1. 20S core proteasome

The 20S 'core' proteasome is a cylinder-like structure consisted of 28 protein subunits forming a 700 kDa complex. Proteasome subunits are arranged in four heptameric rings with molecular dimensions ranging between 120 Å and 160 Å diameter. The two external rings consist of seven different α subunits and the two internal rings of 7 different β subunits constituting the α_{1-7} β_{1-7} β_{1-7} α_{1-7} conformation. The outer α-rings manage the protein access through a narrow aperture (10–15 Å) to the interior of the proteasome that is formed by the β-rings where the proteolytic sites of the proteasome are located. α-Subunits are additionally responsible for the binding of different regulators in order to alter the activity and the specificity of the core particle. Three out of the seven β subunits, namely β1, β2 and β5, possess proteolytic activities, namely the caspase-like activity (C-L or PGPH), the trypsin-like (T-L) and chymotrypsin-like (CT-L) activity, hydrolyzing proteins after acidic peptide bonds, basic amino acids and hydrophobic amino acids respectively (Kish-Trier and Hill, 2013).

2.2. 26S proteasome

The 26S proteasome is formed by the 20S core particle (CP) and the 19S regulatory particle (RP). Either one or two RPs are bound on the CP. 26S proteasome substrates are recognized through tagging with multiple units of ubiquitin (an 8.5 kDa highly conserved globular protein) that occurs through the ubiquitination machinery. Ubiquitination is a three-step procedure, which demands the action of E1 (ubiquitin-activating enzyme), E2 (ubiquitin-conjugating enzyme) and E3 (ubiquitin-ligase enzyme) ligases. Polymeric ubiquitin chains are produced through the repeated action of E1, E2 and E3 enzymes that results to multiple ubiquitin molecules attached to each other. Poly-ubiquitin chains are the signal for the substrate protein to be recognized and degraded by the proteasome. Once substrate recognition has occurred, poly-ubiquitin chains are disassembled by deubiquitinating enzymes (DUBs) (Groll et al., 2005; Nickell et al., 2009). The above presented proteins constitute the so called ubiquitin–proteasome system (UPS).

2.3. 19S regulatory particle (RP)

The 19S RP is a large complex that consists of 19 different subunits forming two heteromeric subcomplexes that have been termed as the "base" and the "lid" (da Fonseca and Morris, 2008). It is responsible for the protein binding, deubiquitination and translocation of the protein substrate to the 20S core. The base is comprised by 9 subunits of which 6 subunits share an ATPase activity (AAA + ATPases) (Tanaka, 2013). The ATPase subunits (*Rpt1-6*) are arranged in a heterohexameric formation, constructing an ordered ring of *Rpt1-2-6-3-4-5*. *Rpn1*, *Rpn2* and *Rpn13* subunits are the 3 non-ATPases that are indispensable for the appropriate function of the RP complex. *Rpn1* and *Rpn2* share a similar three-dimensional structure and both of them have been revealed to be necessary for the binding and deubiquitination of the proteolytic substrate (Groll et al., 2005; Nickell et al., 2009). The *Rpn13* subunit is found to be more flexible than the other non-ATPases of the "base" subcomplex and together with *Rpn10* (a "bridge" subunit), facilitate the bridging between the "base" and the "lid". Moreover, since they can act as polyubiquitin receptors, they are responsible for the recognition of the ubiquitinated substrates (Groll et al., 2005; Nickell et al., 2009). The "lid" bridges the gap between the two proteasome particles (the 20S and the 19S complexes). It has an evolutionary conserved structure which consists of 9 *Rpn* subunits (*Rpn3*, *5–9*, *11*, *12* and *15*) and six of them (*3*, *5*, *6*, *7*, *9* and *12*) form a heterohexameric arc that caps the base. The overall "lid" structure is very flexible, which is necessary for its positioning that determines the area where the substrate will be placed and deubiquitinated by the non-ATPase *Rpn11* deubiquitinating enzyme (Groll et al., 2005; Nickell et al., 2009). Following the assembly by four chaperones (*Hsm3/S5b*, *Nas2/p27*, *Rpn14/PAAF1* and *Nas6/gankyrin*) (Kish-Trier and Hill, 2013), the 19S regulatory particle acts as a very flexible body that is normally orchestrated in order to provide to the unfolded protein substrate an energy-consuming open access to the 20S core proteasome.

2.4. Immunoproteasome

Immunoproteasomes are specialized forms of proteasomes that are formed when the β1, β2 and β5 constitutive catalytic subunits are *de novo* substituted by the cytokine-inducible β1i, β2i and β5i subunits, respectively. These subunits are up-regulated in response to the major immuno-modulatory cytokine interferon-gamma (IFN-γ) (Ferrington and Gregerson, 2012). Van den Eynde and coworkers have also reported the presence of intermediate

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