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Activation of the ubiquitin-proteasome system: Implications for neurodegeneration, aging, and tumorigenesis

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ABSTRACT

Since the discovery of the proteasome (1986), many years passed before researchers explored the benefits of its activation. However, its inhibition, which was first observed in the beginning of the 1990s, gained wide acceptance because of its anti-tumor effect, as proteasome inhibition induces apoptosis. Currently, a proteasome inhibitor is utilized as a clinical tool. However, proteasome activation has been shown to either extend the life span of many cellular and animal models or prevent the accumulation of protein aggregates. Later effect might have an important contribution to neurodegenerative diseases with the hallmark of protein aggregation and the impairment of the proteasome. This short review presents prominent data on proteasome activation, focusing on the 20S catalytic proteasome particle. In addition, the benefits and consequences of proteasome activation in tumor development and progression are discussed.

Introduction

The proteasome has been explored as a pharmacological target since its discovery because of the effect of lactacystin on cellular growth[1].The molecular target of lactacystin was identified as the 20S proteasome[2]. As proteasome inhibition promotes apoptosis, the relevance of the proteasome as an important target for anti-tumor therapy was quickly revealed. Currently (July 2017), at least 7,000 publications have been identified in the scientific literature on proteasome inhibition for therapeutic purposes (www.ncbi.nlm.nih.gov/pubmed). Bortezomib, the lead clinical drug, is present in 3,000 results from a literature search (appearance in the title of publications; www.ncbi.nlm.nih.gov/pubmed July 2017). No attempt to explore proteasome activation was made until the overexpression of the β5-catalytic subunit of the proteasome in fibroblast cells, which promoted the extension of the fibroblast life span and increased the degradation of oxidized proteins[3]. Afterward, many achievements on proteasome activation were reported[4]. The most frequently explored effect of proteasome activation has been the extension of life span. The first mechanisms underlying proteasome activation were based on genetic approaches by overexpressing its components and increasing its assembly. Subsequently, compounds allosterically interfering with proteasome activity and metabolic mechanisms promoting proteasome activation have been described[5-8]. The goal of the present review is to highlight proteasome activation from the perspective of clinical applications and to discuss the possible implications of proteasome activation in neurodegeneration, the aging process, and tumorigenesis.

The Ubiquitin-Proteasome System

The proteasome is a multi-catalytic and multimeric protease responsible for the degradation of proteins that are post-translationally modified by a poly-ubiquitin-moiety. The proteasome comprises a central catalytic core named 20S, flanked on one or both sides by regulatory units. The most abundant regulatory unit is the 19S, which is responsible for the recognition of poly-ubiquitinylated substrates. When coupled to the 19S regulatory unit, the proteasome is named 26S. The 19S unit constitutively contains subunits that recognize the poly-ubiquitinylated substrate, subunits to deubiquitylate the substrate and ATPase subunits responsible for the unfolding and translocation of the unfolded protein to the 20S catalytic unit. Protein ubiquitinylation comprises three steps of reactions involving three classes of ubiquitinylating proteins (E1-E3). E3 proteins are the most selective regarding substrate recognition, and thus they are considered important targets for regulating protein degradation[9].

The 20S proteasome

The catalytic unit of the proteasome comprises 28 subunits present in four heptamers, where two central heptameric rings called β-rings are centrally located and flanked by heptameric rings called α-rings. The architecture of the 20S proteasome has a cylinder shape (αββα). The catalytic sites are located in the β-rings. The α-rings are responsible for regulating the gating of the 20S core particle[9].

Substrates of the proteasome

The proteasome is the main protease responsible for the degradation of intracellular proteins. Eighty percent of total intracellular proteins are degraded by the proteasome. Many of these proteins are degraded when they are post-translationally modified by a poly-ubiquitin chain. However, a substantial pool of proteins is degraded by the 20S proteasome independent of the poly-ubiquitin chain[10-12].

Degradation of oxidized proteins

Oxidized proteins are some of the proteins degraded by the proteasome independent of the poly-ubiquitin chain addition. No enzymatic system is available to repair oxidized proteins, except very few cases, such as methionine and cysteine residues, depending on the extent of oxidation[13]. In the middle of the 1980s, the cellular defense mechanism against protein oxidation was proposed to be degradation and was subsequently revealed to be preferentially accomplished by the 20S proteasome through a ubiquitin- and ATP-independent mechanism[14]. Therefore, cells remove oxidized proteins without any energy consumption, avoiding the formation of aggregates. Protein aggregation is involved in degenerative processes, of which neurodegeneration and aging are the most frequently explored. From that perspective, one easily concludes that proteasome activation is important.

Mechanisms of proteasome activation

The physiological proteasome regulators 19S and 11S are natural activators, as their coupling to the 20S core particle promotes its gate opening. Progress toward the discovery of exogenous proteasome agonists has been slow. Proteasome activation was first achieved by inducing the overexpression of its catalytic units or the chaperone involved in its assembly[4]. Afterwards, some drugs acting by stimulating Keap1-Nrf2 signaling also indirectly induced the overexpression of proteasome subunits[15,16]. Very few drugs have been described to directly activate proteasomal catalytic activity. SDS and many hydrophobic compounds, *e.g.,* phospholipids, are known as activators of the catalytic activity of the proteasome *in vitro* and cellular extracts[17]. Oleuropein, a phenolic compound extracted from olive leaves, was shown to activate the 20S proteasome *in vitro* and to promote an extended life span in cellular models[5,16,18]. *Naked Mole* rats that possess an amazing life span of 31 years show increased proteasome activity that is attributed to an as yet unidentified cytosolic protein[19]. A peptide named PAP1 was shown to activate 20S proteasome activity *in vitro* and in cellular extracts of two assayed cell lines (mouse fibroblasts and human neuroblastoma cells) by opening its catalytic chamber[6,20]. In a cellular model (human neuroblastoma cells carrying a mutated SOD1 gene) of Amyotrophic Lateral Sclerosis, PAP1 prevented the aggregation of the mutated SOD1 protein and increased the viability of fibroblasts and neuroblastoma cells upon challenge with the pro-oxidant hydrogen peroxide. Direct activation by small organic compounds was also described[21,22]. Other drugs were described to act on intracellular targets that indirectly modify the catalytic activity of the proteasome, *e.g.,* by promoting or inhibiting post-translational modifications of the proteasome or by inhibiting a deubiquitylase enzyme[23,24].

Consequences of proteasome activation

Although the consequences of proteasome activation are yet not completely predictable, the currently known consequences are the extension of the life span in many species and cellular models[4] and the prevention of protein aggregation, as reported in a few publications[6,8,24]. Both effects are greatly stimulating research in the field, considering the potentially high impact of the prevention of aggregation on degenerative processes. The ubiquitin-proteasome system is a major mechanism to maintain normal functions of the central nervous system as well as plays a decisive role in the malfunction of the brain in several neurodegenerative diseases[25]. Protein aggregation,

a hallmark in those processes, is partway consequence of the ubiquitin-proteasome system malfunction. Therefore, there is a great clinical expectation that the prevention of aggregates upon proteasome activation might improve clinical manifestations in those pathologies.

The mechanism underlying the extension of life span through proteasome activation has not been explored, although it might shed light on the particular mechanisms involved in the aging process and proteostasis.

Notably, epidemiologic data collected by combining studies of neurodegeneration and cancer[26,27] revealed an inverse association between both processes throughout life. Based on genetic and proteomic studies of cancer and neurodegeneration, both studies above concluded that the ubiquitin-proteasome system is one of the central metabolic pathways, as the 20S proteasome catalytic core presents decreased activity in neurodegeneration and, in turn, is increased in tumor cells. Indeed, the half-lives of tumor suppressor proteins, many DNA repair proteins and anti-apoptotic proteins, which are key regulators of tumor cell fate and neuron loss, are regulated by the ubiquitin-proteasome system. Tumor cells present increased expression of many components of the ubiquitin-proteasome system that is related to the increased proteasome activity observed in those cells[28,29]. On the other hand, proteasome activity is decreased in cancer stem cells (CSCs), probably due to the low metabolic activity of CSCs[30]. As already described, low proteasome activity predisposes tumor-initiating cells to form spheres in osteosarcoma, increasing tumorigenesis. Therefore, one would expect that the increased proteasome activity in CSCs would prevent tumorigenesis[31]. In conclusion, researchers have not yet clearly identified the role of the ubiquitin-proteasome system in either tumor development or its progression.

Future perspectives

Although proteasome activation is an important tool for examining degenerative processes that rely on the loss of proteostasis, one should be aware of the possible long-term toxic effects underlying proteasomal activation. As the ubiquitin-proteasome system is a complex system that regulates the half-life of proteins, other components of the system might be more reliable targets for intervention for future studies. Among those components, E3 proteins are undoubtedly important targets. These proteins are highly specific in the recognition of their targets to promote poly-ubiquitylation of the substrate. Therefore, a better comprehension of their mechanisms of action and the regulation of their expression could direct target proteins for degradation. As in the case of drugs that increase the translation of proteasome subunits, a more comprehensive approach to examining the mechanisms of E3 ligase expression might be beneficial to induce the degradation of key proteins without promoting widespread protein degradation. Furthermore, direct proteasome activation is a powerful tool for preventing protein aggregation.

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