

Review Article

The Emerging Role of Immunoproteasome in Vision

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Abstract

The 26S proteasome is a proteolytic complex that degrades damaged and misfolded proteins in cells. Not only is the proteasome essential for maintaining protein homeostasis and cell survival, but it also plays pivotal roles in regulating cell cycle, signal transduction, and gene expression. There is more evidence indicating that the immunoproteasome (i-proteasome), a subtype of proteasome previously known for its role in antigen presentation in immune cells, participates in the stress and injury response in cells. Human patients with genetic mutations in the i-proteasome subunits display phenotypes of chronic inflammation, lipid metabolism defect, diabetes and certain autoimmune diseases. Recent studies from our group and others further revealed that the i-proteasome is required for the stress response, wound healing, differentiation and apoptosis in various ocular tissues. This article aims to provide an overview of our current knowledge of the i-proteasome in the eye and its link to visual function.

INTRODUCTION

Proteasome general review

The proteasome is a multi-subunit proteolytic complex that helps maintain cellular homeostasis through the selective removal of damaged proteins and the degradation of proteins that regulate pathways critical for cell survival. The 20S proteasome, which is the catalytic core, is composed of four stacked rings of seven subunits each (Figure 1). The two outer rings contain the constitutively-expressed α subunits. The inner two rings contain the β subunits. Three of the β subunits ($\beta 1$, $\beta 2$, $\beta 5$) contain the catalytic sites that perform distinct proteolytic activities referred

to as caspase-, trypsin-, and chymotrypsin-like, respectively [1-3] (Table 1). The catalytic subunits $\beta 1$, $\beta 2$, and $\beta 5$ that form the standard proteasome can be replaced in nascent proteasomes by the subunits LMP2 ($\beta 1i$), MECL-1 ($\beta 2i$), and LMP7 ($\beta 5i$) [4-6]. These subunits form the core of the immunoproteasome (i-proteasome). The catalytic core can also contain a mixture of both the standard and i-proteasome catalytic subunits [7,8] and is referred to as the intermediate-type 20S. A thymus-specific $\beta 5t$ subunit ($\beta 5t$) has been discovered recently that further increases the complexity of proteasome's composition [9].

Analysis of the three core subtypes has shown that they differ substantially in their enzymatic activity and cleavage of model protein substrates [7,8], suggesting cell proteasome content could have an impact on cell function. Additionally, all three 20S core subtypes can co-associate with the regulatory complexes PA28 and PA700 to form either symmetric (26S, immunoproteasome) or asymmetric (hybrid) mega-complexes. Distinct functions have been attributed to each proteasome subtype. For example, the ATP-independent degradation of proteins by the 20S core proteasome has been suggested as the primary mechanism for degrading oxidized proteins following an oxidative insult [10,11]. The 26S proteasome requires ATP for activation and is responsible for the degradation of many ubiquitinated [12], and some non-ubiquitinated proteins [13]. One well-described role for i-proteasome is in the generation of immunogenic peptides for antigen presentation by MHC class I molecules on the cell surface. The chymotrypsin-like activity of the LMP2 subunit (Table 1) facilitates production of peptides for antigen presentation, which

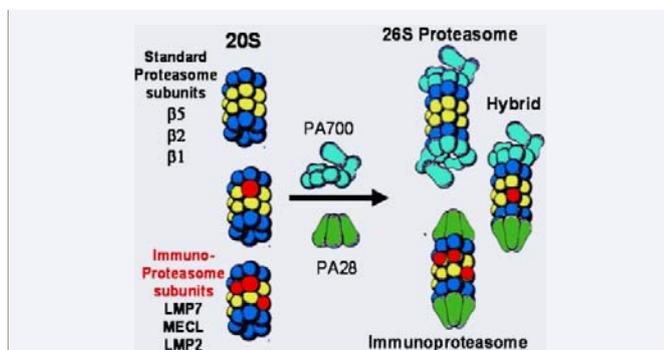


Figure 1 Proteasome subtypes. 20S associates with PA700 and PA28 to form the 26S proteasome, hybrid proteasome and immunoproteasome (i-proteasome subunits, red circles).

requires hydrophobic amino acids at the C-terminal position. In addition to its role in immune surveillance, recent publications from our lab and others suggest i-proteasome's involvement in additional roles, such as regulation of cell signaling [14,15] and protection from stress-induced injury [16,17]. This review will focus on recent novel information regarding i-proteasome's emerging role in ocular tissue.

Immuoproteasome in human diseases

While up-regulation of i-proteasome was previously reported in CNS diseases, such as Alzheimer's and Huntington's diseases [18,19], a direct link between i-proteasome and human diseases has been established only recently (shown in Table 2) [20-25]. Missense and nonsense mutations in the LMP7 subunit, resulting in a truncated or non-functional protein, have been identified in various diseases characterized by auto-inflammation, muscle dystrophy and/or lipodystrophy phenotypes [21-25]. Patients

with single nucleotide polymorphisms (SNPs) in i-proteasome subunits (LMP7 and LMP2) bear higher risks for diabetes and ankylosing spondylitis [24,25]. (To date, no phenotypes related to the eye have been reported in patients with these known genetic modifications in i-proteasome). Notably, the disease phenotypes in these patients are closely replicated in the KO mice. As the list for i-proteasome-related human diseases continues to grow, a greater understanding of the extent to which i-proteasome contributes to key cell process will become evident.

Non-Immune functions of the immunoproteasome

A growing body of literature suggests neither the expression nor the function of i-proteasome is restricted to immune cells or tissues. For example, i-proteasome expression has been reported under steady-state conditions in multiple non-immune tissues, such as skeletal muscle [27], fibroblasts [28], human embryonic stem cells [29] neurons of the retina and brain, and epithelial cells of the retina [17,27] and cornea [30]. Specific non-immune functions attributed to immunoproteasome include regulation of the (1) stress response, potentially via NFkB or PTEN signaling [14,15], (2) cell cycle [31,32], (3) lipid metabolism and adipocyte differentiation [22], and (4) proteolysis of oxidized and misfolded proteins [28,33].

Knock-out (KO) mice with either one (LMP2; LMP7; MECL) or two (LMP7 and MECL) i-proteasome subunits genetically ablated were originally developed by immunologists to determine the role of specific subunits in immune function and antigenic peptide generation [34-36]. Recent studies characterizing the distinct phenotypes for these KO mice have provided important insights into i-proteasome's alternative functions that are unrelated to antigen presentation. While all i-proteasome-deficient mice exhibit increased levels of oxidized proteins, mice lacking the LMP7 subunit exhibit an increased preponderance for autoimmune disorders, chronic inflammation, and diabetes [24,37]. Mice devoid of LMP2 subunit exhibit cardiomyopathy and increased uterine tumor development [15,32,33]. As discussed below, these KO mice have been invaluable in furthering our understanding of i-proteasome's role in the immune privileged ocular tissues.

IMMUNOPROTEASOME AND RETINA

The harsh environment of the retina under normal conditions (bright light, high content of oxidizable lipids, high oxygen, outer segment regeneration) requires extraordinary efforts to maintain cellular homeostasis. As outlined in the previous section, significant experimental evidence supports a role for i-proteasome in maintaining cellular homeostasis and in responding to stress. The presence of i-proteasome in the retina was first reported in rat retina [38] and later confirmed in murine and human retina [17,39] under basal conditions. Immunostaining with anti-LMP7 antibody of retinal sections from mice showed LMP7 was present in the photoreceptor cell inner segment, the inner/outer plexiform layers and retinal pigment epithelium (RPE) [17]. These results imply that i-proteasome plays a role in normal neuronal functions of the retina. In support of this idea, mice singly- or doubly-deficient in the LMP7 or LMP7/MECL1 subunits (L7M1) exhibited a compromised response in both light- and dark-adapted electroretinography (ERG) indicative of

Table 1: Proteasome catalytic subunits.

Proteasome Subunit	Gene	Accession # (Mouse)	Enzymatic Activity
β1	PSMB6	Q60692	Caspase-like
β2	PSMB7	P70195	Trypsin-like
β5	PSMB5	O55234	Chymotrypsin-like
β1i/LMP2	PSMB9	P28076	Chymotrypsin-like
β2i/MECL1	PSMB10	O35955	Trypsin-like
β5i/LMP7	PSMB8	P28063	Chymotrypsin-like
β5t	PSMB11	Q8BG41	Chymotrypsin-like

Table 2: Linkage of human diseases with i-proteasome genetic mutations.

Disease	Mutation	Protein defect/ Disease characterization
JMP ¹	LMP7, Thr75Met (224C → T) [20]	Disruption tertiary structure; decreased CTL activity, hypertriglycerides, low HDL, muscle dystrophy, hypergammaglobulinemia, joint contractures, and elevated liver enzymes.
CANDLE syndrome ²	LMP7, Cys135X (405C → A) [26]	Truncation of protein, loss of function; Fever, skin rash, progressive lipodystrophy, delayed development.
Nakajo-Nishimura syndrome	LMP7, Gly201Val (602G → T) [22]	Disruption of β-sheet, LMP7 not incorporated into mature 20S; Inflammatory & wasting disease, periodic fever, skin rash, lipomuscular dystrophy, joint contractures.
JASL ³	LMP7, Gly197Val [23]	Increased proteasome assembly intermediates and decreased i-proteasome, p38 activation, increased ubiquitination; Disturbed adipocyte maturation, autoinflammation.
Type I Diabetes	LMP7, SNPs [24]	SNP rs3763365 and rs9276810.
Others	LMP2, codon 60 polymorphism (Arg60His) [25]	Higher risk for ankylosing spondylitis.

1: Joint contractures, muscle atrophy, Microcytic anemia, Panniculitis-induced lipodystrophy syndrome.

2: Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated temperature Syndrome.

3: Japanese Autoinflammatory Syndrome with Lipodystrophy.

defects in the transduction of secondary neurons, particularly the bipolar cells [40]. The impact of i-proteasome deficiency on the synaptic junction morphology and/or the expression profile of visual transduction proteins in these KO mice await further investigation to clarify i-proteasome's role in visual function.

I-proteasome is also upregulated with retinal stress and injury. In the retina, increased i-proteasome content was reported in human donor retina with AMD [39], in aged mice [16], and in response to injury induced by cytotoxic T-Lymphocytes [17]. In cultured RPE, conditions that increase i-proteasome content includes exposure to cytokines IFN γ and TNF α [41] or chronic oxidative stress. In support of i-proteasome's protective role, RPE cells deficient in LMP7 and MECL1 were more susceptible to oxidative stress induced by exposure to peroxide [16].

It has been proposed that immunoproteasome has an enhanced ability to process oxidized proteins more effectively [29,33], and thus i-proteasome deficient cells cannot effectively combat the oxidative milieu. Another possible explanation for the observed higher mortality in i-proteasome-deficient cells may be due to dysregulated signaling associated with the stress response. Signaling via NF κ B is the main pathway for responding to stress and injury and culminates in the upregulation of molecules that increases cell survival. Our recent study demonstrated that i-proteasome-deficiency affected the alternative pathway but not the canonical pathway in NF κ B signaling in RPE cell cultures from KO mice. Furthermore, knocking out individual i-proteasome subunit seemed to have differential effects on the NF κ B-responsive genes [14]. Thus, it is possible that i-proteasome response to stress and injury involves regulation of cell signaling that is critical for cell survival, including the NF κ B pathway.

IMMUNOPROTEASOME AND THE CORNEA

The cornea is under constant insult from the environment (i. e. , UV light, exposure to pathogens) and mechanical stress. To maintain corneal avascularity and transparency, efficient coping strategies that maintain cellular homeostasis are needed. The i-proteasome may be actively involved in this process since abundant expression of i-proteasome in the corneal epithelium was detected in corneal superficial and suprabasal layers [30]. Consistent with the distribution of i-proteasomes, high levels of oxidized proteins were observed in the superficial and suprabasal layers of the mouse cornea [42]. As immunoproteasome has been postulated to more effectively degrade oxidized proteins, the elevated content of immunoproteasome in these corneal layers may be a compensatory response to the increased demands to degrade oxidized proteins.

Recent data from our lab supports an essential role for immunoproteasome in the corneal response to stress and injuries. Significant cell death and higher caspase-3 activity of corneal explant cultures from L7M1 double knockout mice was noted compared to WT [30]. In vivo data from L7M1 KO mice also showed higher apoptosis in the corneal epithelium. Additionally, corneal injury induced by mechanical debridement revealed defective wound healing in the i-proteasome-deficient cornea. The L7M1 KO mice had significantly delayed epithelial regrowth accompanied by corneal edema, disrupted tight junctions and altered cytokine production (IL-1 α and IL-6).

Of note, the abnormally high IL-6 level measured in L7M1 KO mice was also observed in the blood and cells of human patients with defects in the LMP7 subunits [23,30]. In mouse cornea, the aberrant production of IL-6 may be responsible for the observed slower epithelial regrowth and re-establishment of the epithelial barrier function post-injury. These negative consequences may be caused by dysregulated NF κ B or hyperactive p38 signaling, which was also a mechanistic explanation suggested in human patients [22,43].

IMMUNOPROTEASOME AND LENS

Wagner and colleagues were the first to report that i-proteasome is expressed in vivo at low levels under basal conditions in lens epithelial cells [44]. They also showed that expression of i-proteasome subunits in a lens epithelial cell line, α TN4-1, could be induced by IFN- γ , a potent inflammatory cytokine [44]. The induction of i-proteasome by IFN γ was demonstrated in vivo in transgenic mice where constitutive production of IFN γ in the lens was accomplished using an α A-crystallin promoter to drive IFN γ expression. In these mice, the high endogenous IFN γ increased i-proteasome subunit expression in the lens epithelial cells two orders of magnitude higher than WT mice. These observations implicate the upregulation of i-proteasome as a cytoprotective mechanism to cope with the interferon-induced oxidative stress, as suggest by a recent study in LMP2-deficient fibroblasts [28].

The constitutive production of lens IFN γ also disrupted lens differentiation and caused increased cataract formation [44]. Investigations in the murine lens epithelial cell line, α TN4-1, showed that incubation with IFN γ at levels required to induce i-proteasome expression caused apoptosis in ~20% of the cells and that proteasome inhibition reversed this effect [45]. Taken together, these studies suggest a potential functional role for i-proteasome in apoptosis [45] or the differentiation [43] of lens cells.

SUMMARY

The expression of i-proteasome under basal conditions in the retina, lens, and cornea suggests a key role in maintaining cellular homeostasis. I-proteasome upregulation in response to challenges that induce stress and injury implies i-proteasome is also an essential component of the stress response. Recent evidence from human patients with mutations in i-proteasome genes and i-proteasome KO mice are providing insight into i-proteasome's ever-expanding role in cellular function that goes beyond simply generating antigenic peptides. More research is needed to clearly define the function of different proteasome subtypes and determine the therapeutic potential of inhibitors that target the functionally relevant subtype. This more refined approach would reduce the toxicity of proteasome inhibitors, which has been a major problem with broad-spectrum inhibitors currently used in cancer therapy.

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