Published in final edited form as:

Crit Rev Biochem Mol Biol. 2015 ; 51(4): 268–281. doi:10.3109/10409238.2016.1172554.

The Immunoproteasome in Oxidative Stress, Aging, and Disease

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Abstract

The Immunoproteasome has traditionally been viewed primarily for its role in peptide production for antigen presentation by the Major Histocompatibility Complex (MHC), which is critical for immunity. However, recent research has shown that the Immunoproteasome is also very important for the clearance of oxidatively damaged proteins in homeostasis, and especially during stress and disease. The importance of the Immunoproteasome in protein degradation has become more evident as diseases characterized by protein aggregates have also been linked to deficiencies of the Immunoproteasome. Additionally, there are now diseases defined by mutations or polymorphisms within Immunoproteasome-specific subunit genes, further suggesting its crucial role in cytokine signaling and protein homeostasis (or ‘proteostasis’). The purpose of this review is to highlight our growing understanding of the importance of the Immunoproteasome in the management of protein quality control, and the detrimental impact of its dysregulation during disease and aging.

Keywords

adaptation; proteostasis; 20S core; Nrf2; I κ B α ; IFN γ

1. Discovery of the Immunoproteasome

In the early 1990s, the low-molecular mass polypeptides (LMP’s), specifically *LMP2* and *LMP7*, and eventually the multicatalytic endopeptidase complex 1 (*MECL-1*) genes, were discovered and identified as interferon- γ inducible subunits that are incorporated into a specialized form of the 20S Proteasome called the Immunoproteasome (Brown et al., 1991, Ortiz-Navarrete et al., 1991, DeMars and Spies, 1992, Früh et al., 1992, Zhou et al., 1993, Aki et al., 1994, Akiyama et al., 1994, Groettrup et al., 1996). The *LMP7* and *LMP2* genes are located adjacent to the Major Histocompatibility Complex (MHC) which, in humans, comprises a 4-million base-pair span on chromosome 6, encoding many of the genes involved in the immune response. The *LMP7* and *LMP2* genes, respectively, encode the Immunoproteasome $\beta 5i$ and $\beta 1i$ subunits, while *MECL-1* encodes the $\beta 2i$ subunit (Akiyama

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Declaration of Interest

This work was supported by Grant #ES 003598 from the National Institute of Environmental Health Sciences of the US National Institutes of Health to KJAD, and the National Science Foundation Graduate Research Fellowship #DGE-1418060 to LC-DP.

et al., 1994, Hayashi et al., 1997). It was originally proposed that the main purpose of the Immunoproteasome-specific subunits was to generate peptides for MHC class I antigen presentation, utilized by the immune system to identify self-cells from those under viral infection. These peptides differed from the conventional fragments created by the 20S (or 26S) proteasomes, due to different catalytic activities of the Immunoproteasome. Interestingly, cells under viral attack face elevated oxidative stress, resulting in greater protein oxidation (Schwarz, 1996). Our lab was the first to suggest the “PrOxI hypothesis” which postulates that protein oxidation may actually be used by the Immunoproteasome as a recognition signal to generate peptides for antigen presentation (Teoh and Davies, 2004). In this review, we discuss the roles the Immunoproteasome during oxidative stress, aging, and disease.

1a. The 20S Core Proteasome and the 26S Proteasome

Proteasomes are multi-subunit protein complexes that are responsible for maintaining the proteome. The 20S core Proteasome is a cylindrical structure comprised of four rings; two identical outer α rings (each composed of seven distinct α subunits) and two identical inner β rings (each composed of seven different β subunits) in the order $\alpha \beta \alpha$ (Krüger and Klotzel, 2012, Vilchez et al., 2014). The α rings facilitate substrate recognition and recruitment of regulator proteins, while the β rings contain the catalytically active components of the 20S core (Krüger and Klotzel, 2012, Glickman and Ciechanover, 2002). The $\beta 1$, $\beta 2$, and $\beta 5$ subunits are responsible for proteolysis, (Pickering and Davies, 2012b), with each having a unique catalytic activity: caspase-like, trypsin-like, and chymotrypsin-like, respectively (Figure 1) (Ferrington and Gregerson, 2012).

The 20S core Proteasome maintains the quality of the endogenous proteome by removing oxidatively damaged, disordered, and hydrophobic proteins to prevent their accumulation, aggregation, and cross-linking (Davies, 1993). The 20S Proteasome appears to recognize the surface hydrophobic patches that are created when proteins undergo oxidatively-induced structural rearrangement, with consequent exposure of (normally shielded) interior hydrophobic amino acid residues. (Pacifi et al., 1993, Davies, 1993, Giulivi et al., 1994, Davies, 2001). Such rearrangements are a somewhat random outcome of the charge changes that oxidation produces on amino acid targets, and are common to all proteins, thus providing a simple, efficient, and universal mechanism for the recognition and selective removal of oxidized proteins, before they aggregate and cross-link. The 20S Proteasome α rings recognizes these hydrophobic patches, bind to them, and ‘feeds’ the oxidized proteins into the proteolytic core where they are degraded in the β rings; small peptides and amino acids are then released back out through the α rings (Pacifi et al., 1989, Pacifi et al., 1993, Davies, 1993, Giulivi et al., 1994, Davies, 2001).

As protein oxidation is a normal consequence of metabolic processes, and is often increased by an oxidative insult, it is critical the 20S core has means of enhancing its rate of degradation during periods of oxidative stress. One mechanism is the binding of 11S (Pa28) regulatory complexes to the ends of the α rings (Pickering and Davies, 2012b, Pickering and Davies, 2012a). The α subunits provide binding sites for regulators, such as the 19S or 11S (Pa28), as well as acting as gates that monitor substrate admittance (Bar-Nun and Glickman,

2012). Additionally, the α rings of the 20S Proteasome assist in preferentially processing oxidized proteins in an ATP-independent, and ubiquitin-independent manner (Krüger and Kloetzel, 2012, Shringarpure et al., 2003, Davies and Goldberg, 1987, Pacifici et al., 1989, Reinheckel et al., 1998).

Addition of 19S regulatory complexes to the 20S core generates the 26S Proteasome which preferentially degrades ubiquitinated protein substrates in a process requiring ATP hydrolysis. ATP is utilized by the 19S regulator to de-ubiquitinate protein substrates, unfold them, and introduce them into the 20S core for degradation (Gu and Enenkel, 2014). Ubiquitinylation of endogenous cellular proteins is a highly targeted process, catalyzed by E1, E2, and E3 ubiquitin ligating, conjugating, and polymerizing enzymes. Basically, the primary sequences of cellular proteins contain vital coding that directs their susceptibility to ubiquitinylation by specific E3 ubiquitin ligases. Thus, the rate, amount, and sites of ubiquitinylation determines the breakdown rates of most cellular proteins by the 26S Proteasome.

Despite its high affinity for poly-ubiquitinated proteins we, and others, find that the 26S Proteasome is very poor at degrading oxidized proteins (Pacifici et al., 1989, Giulivi et al., 1994, Reinheckel et al., 1998, Grune et al., 2010). In addition, oxidized proteins do not undergo preferential ubiquitinylation (Fagan et al., 1986, Jung et al., 2014, Kästle et al., 2012, Grune et al., 2010) and an intact ubiquitin activating/conjugating/ligating system is actually not required for the selective degradation of oxidatively modified proteins (Shringarpure et al., 2003, Shang and Taylor, 1995). Furthermore, the 20S and 26S proteasomes generate different patterns of peptides, indicating differences in cleaving preferences likely conferred by the 19S regulator (Huber et al., 2012, Kniepert and Groettrup, 2014).

Finally, during oxidative stress ECM29 and HSP70 disassemble the 26S Proteasome by sequestering away the 19S regulatory caps, in turn providing an additional pool of available 20S Proteasome (Grune et al., 2011, Wang et al., 2010). This immediately increases cellular capacity to degrade oxidized proteins (via the 20S Proteasome) and increases cellular ability to survive an oxidative stress. 11S regulators also shows increased binding 20S Proteasomes, which results in increased capacity to selectively degrade oxidatively damaged proteins following an oxidative stress (Pickering et al., 2010, Pickering and Davies, 2012b). Concurrently, the 19S regulators are segregated and bound by HSP70 for 3–5 hours following an initial stress, allowing for the clearance of oxidized proteins, after which time the 26S Proteasome is re-assembled (Figure 2) (Grune et al., 2011). Phosphorylation can also lead to the dissociation of the 26S Proteasome by increased preferential binding between the phosphorylated 20S core with the 11S (Pa28) regulator instead of the 19S cap (Bose et al., 2001, Rivett et al., 2001).

1b. The Immunoproteasome

The Immunoproteasome resembles the 20S Proteasome in structure, except that three β subunits of the catalytic 20S core are replaced by three different Immunoproteasome β_i subunits, all of which are inducible by interferon- γ stimulation (Aki et al., 1994, Huber et al., 2012) or by oxidative stress (Pickering and Davies, 2012a). The Immunoproteasome β_2

subunit has trypsin-like activity, matching the 20S $\beta 2$ subunit. Similarly, the $\beta 5_i$ subunit, like its $\beta 5$ counterpart in the 20S core, demonstrates chymotrypsin-like activity. However, unlike the 20S $\beta 1$ subunit, which shows caspase-like activity, the Immunoproteasome $\beta 1_i$ subunit exhibits chymotrypsin-like activity. This apparent redundancy of activity in both the $\beta 1_i$ and $\beta 5_i$ may explain the overall increased chymotrypsin-like activity of the Immunoproteasome compared to the 20S catalytic core. This in turn, aids in the generation of peptides with hydrophobic C-termini to fit in the groove of MHC class I molecules (Gomes, 2013). In addition, the Immunoproteasome assembles more quickly than does the 20S Proteasome. However, the Immunoproteasome lacks the ability to cleave peptide bonds after aspartate or glutamate residues, perhaps implying specificity for its role in the immune response (Figure 1) (Gomes, 2013, Huber et al., 2012).

The Immunoproteasome has primarily been studied for its role in generating peptides for antigen presentation by MHC class I molecules in the immune response (*see review by* (Basler et al., 2013)). However, beyond its role in the immune system, the Immunoproteasome is an active participant in the clearance of oxidized proteins (Pickering et al., 2010, Pickering and Davies, 2012b). Although postulated for some time (Teoh and Davies, 2004, Ding et al., 2006, Ding et al., 2003), the first demonstration that the Immunoproteasome can actually preferentially degrade oxidized proteins with an activity and selectivity equal to, or greater than, that of the 20S Proteasome has been shown within the past decade (Pickering et al., 2010, Pickering and Davies, 2012b, Grimm et al., 2012, Yun et al., 2016). In addition, binding of the 11S (Pa28) regulator to the Immunoproteasome clearly improves both its activity and selectivity for oxidized proteins (Pickering et al., 2010, Pickering and Davies, 2012b). As will be discussed in the sections below, it now seems clear that the Immunoproteasome has an expanding biological role due to its involvement in neuronal function, oxidative stress responses, and protein homeostasis (Hussong et al., 2010, Aiken et al., 2011, Seifert et al., 2010).

1c. Regulation of 20S Proteasome and Immunoproteasome Assembly

Proteasome and Immunoproteasome assembly has been extensively studied and discussed, respectively (Griffin et al., 1998, Gu and Enenkel, 2014), and (Ferrington and Gregerson, 2012). The mechanisms for constructing different Proteasome subtypes are relatively similar, except that assembly of the Immunoproteasome is favored over assembly of the 20S Proteasome. This favoritism has been proposed to be due to several factors including: the different order of subunit incorporation, Proteasome maturation protein (POMP) preference for Immunoproteasome subunits, interferon- γ induced upregulation of POMP expression, and the observation that assembly and maturation of the Immunoproteasome is faster than that of the 20S Proteasome (Heink et al., 2005, Griffin et al., 1998). While assembly of the 20S Proteasome begins with the $\beta 2$ subunit, the Immunoproteasome begins with the $\beta 1_i$ subunit (Ferrington and Gregerson, 2012). The incorporation of $\beta 1_i$ aids in the recruitment of $\beta 2_i$. Maturation is assisted by $\beta 5_i$ incorporation and activation of catalytic properties by cleaving the propeptide N-terminals from $\beta 1_i$ and $\beta 2_i$. Because POMP has a greater affinity for $\beta 5_i$ than for $\beta 5$, this occurs preferentially and more quickly than does the assembly and maturation of the 20S Proteasome. Additionally, the Immunoproteasome is expressed at lower basal levels and has a shorter half-life than that of the 20S Proteasome; the half-lives

having been measured at 27 hours for the Immunoproteasome and 133 hours for the 20S Proteasome (Heink et al., 2005, Tanahashi et al., 2000). The rapid turnover of the Immunoproteasome is thought to aid in rapid and effective responses to environmental changes (Heink et al., 2005). A small pool of intermediate proteasomes, which consists of various combinations of catalytic subunits from the different types of Proteasome, are also present in cells (Guillaume et al., 2010), and subunit composition also varies with cell type and tissue location (Kniepert and Groettrup, 2014).

1d. Degradation of Oxidized Proteins by the Immunoproteasome

Oxidation is a normal consequence of life in an oxygen environment, to which all cellular proteins are subject to at low levels. We have previously proposed that the Immunoproteasome might recognize and selectively degrade such mildly oxidized intracellular proteins, thus providing a common mechanism by which all intracellular proteins could be processed for the MHC Class I pathway: the 'PrOxI' Hypothesis (Teoh and Davies, 2004). Despite many experimental studies showing that the 20S Proteasome can selectively degrade oxidized proteins, evidence of such an activity for the Immunoproteasome has been largely circumstantial, or indirect, until recently. In 'head-to-head' assessments we have now measured and compared the proteolytic capacity of purified 20S Proteasome to that of the Immunoproteasome (isolated from erythrocytes, reticulocytes, and mouse embryonic fibroblasts (MEF) pretreated with interferon γ) to degrade native versus oxidized forms of various proteins. We find that the Immunoproteasome is as efficient as and, in certain cases slightly better than, the 20S Proteasome in selectively degrading the oxidized forms of proteins (Pickering et al., 2010, Pickering and Davies, 2012b). Furthermore, binding of the 11S (Pa28) regulator increases both the Immunoproteasome's selectivity and its activity (Pickering et al., 2010, Pickering and Davies, 2012b). Our studies have revealed a crucial role for the Immunoproteasome in degrading oxidized proteins during stress, and also provide an oxidation-linked rationale for its role in antigen processing (Teoh and Davies, 2004).

2. Immunoproteasome, Redox Signaling, and Oxidative Stress

Redox signaling occurs as a result of normal cellular metabolism where molecules such as hydrogen peroxide (H_2O_2), nitric oxide (NO^*), and oxygen itself, are used to control crucial signaling pathways, such as Nrf2, IRF1, HIF-1, and NF- κ B (Pickering et al., 2012, Morgan and Liu, 2011, Lowenstein and Padalko, 2004). In addition, redox signaling is also used to modulate various pathways if oxidant/electrophile levels rise slightly with mild stresses, or during exposures to potentially damaging or toxic levels of oxidants: a condition known as frank oxidative stress. The Immunoproteasome now clearly plays an important role in helping to maintain homeostasis during both mild stresses and frank oxidative stress.

2a. Hydrogen peroxide (H_2O_2)

During oxidative stress there is an increase in oxidized proteins that must be degraded in order to prevent formation of cytotoxic protein aggregates. One contributing factor that causes protein oxidation is the increased generation of H_2O_2 . Our lab uses H_2O_2 to study oxidative stress and the roles of different proteasomes and their regulators in maintaining

protein homeostasis. We find that the Immunoproteasome and the 11S (or Pa28) proteasomal regulator play significant roles, along with the 20S Proteasome, in maintaining homeostasis during H₂O₂-induced frank oxidative stress (Pickering et al., 2010, Pickering and Davies, 2012b). Such positive responses to non-lethal but damaging or toxic insults are often referred to as examples of a process known as ‘hormesis’ (Le Bourg, 2007, Semchyshyn, 2014), but may actually occur independently of any damage as by a mechanism we call ‘Adaptive Homeostasis’ – see below.

We also find that cells respond to extremely low levels of H₂O₂ by increasing Immunoproteasome, 11S (Pa28) regulator, and 20S Proteasome synthesis and overall levels, even in the absence of any protein damage (Pickering et al., 2010, Pickering and Davies, 2012b, Pickering et al., 2013a, Pickering et al., 2013b, Pickering et al., 2012). Thus, it seems clear that a mild and transient stimulus of H₂O₂ activates signal-transduction pathways (including those of the 20S and Immunoproteasome) that prime the cell to withstand future oxidative insults. Clearly, no actual damage is required to activate such pathways, thus suggesting that, rather than hormesis, cells are actually modulating their homeostatic set-points in a process we call ‘Adaptive Homeostasis.’ Should a more severe, oxidative stress occur subsequently, the elevated levels of Immunoproteasome, 20S Proteasome, and Pa28 (11S) regulator are capable of degrading the increased amounts of oxidized proteins, thus contributing to improved cell survival.

Interestingly, although synthesis of the 20S Proteasome and the Pa28 (11S) regulator is accomplished through the Keep1-Nrf2 signal transduction pathway, it appears to have no control over Immunoproteasome synthesis (Pickering et al., 2012). Indeed, examination of the $\beta 1_i$, $\beta 2_i$, and $\beta 5_i$ Immunoproteasome subunit genes reveals no functional Electrophile Responsive Element (EPrE) sites to which Nrf2 can bind. Preliminary evidence points to the IRF-1 signal transduction pathway, the cAMP/cGMP pathway, and the NF- κ B activation pathway, as potential routes for H₂O₂ mediated transcription/translation of the Immunoproteasome (Figure 3) (Takada et al., 2003, Thomas et al., 2007).

2b. Nitric oxide (NO[•])

Nitric oxide, at very low concentrations, is a crucial signaling molecule in vivo that is necessary for the regulation of vascular tone. Conversely, at very high concentrations, nitric oxide can cause oxidative damage, by combining with superoxide to form peroxynitrite (Pacher et al., 2007). In turn, peroxynitrite mediates its effect through two pathways: directly damaging proteins, lipids, and DNA; and indirectly providing a cellular stimulus. Hence, high levels of nitric oxide leads to the upregulation of the Immunoproteasome via the cGMP/cAMP signaling pathway, which interact with the cAMP response element found in the promoter regions of the $\beta 1_i$ and $\beta 5_i$ subunit genes (Kotamraju et al., 2006, Thomas et al., 2007, Ferrington and Gregerson, 2012). In turn, this protective effect ensures an increased pool of Immunoproteasome to help cope with the elevated protein damage. More importantly, removal of the Immunoproteasome, results in apoptosis of NO[•]-stressed cells. This was demonstrated through the work of Kotamraju and colleagues, who showed that inhibiting Immunoproteasome induction results in inactivation of the oxidant-inducible transferrin receptor. The transferrin receptor is necessary for iron homeostasis, and if

inactivated, can lead to apoptosis in endothelial cells (Kotamraju et al., 2005, Kotamraju et al., 2006, Kotamraju et al., 2003). Hence, this makes the Immunoproteasome expression and activity essential for survival of cells exposed to high levels of nitric oxide.

2c. Interferon- γ signaling

Under non-inflammatory conditions, or in the absence of oxidative stress, the Immunoproteasome is only a small portion of the total cellular Proteasome pool (Tanahashi et al., 2000, Hendil et al., 1998). However, upon inflammation, interferon- γ is released and stimulates cells to produce reactive oxygen species such as the H_2O_2 and the superoxide and hydroxyl radicals, which damage the cellular proteome (Pearl-Yafe et al., 2003, Watanabe et al., 2003, Seifert et al., 2010). Pre-existing 20S Proteasome provides immediate triage by degrading the initial pool of oxidized proteins. In turn, this provides a buffer period for the cell to increase its oxidative responses, including transcription and translation of nascent Immunoproteasome subunits (Seifert et al., 2010). It should be noted, however, that cells with an increased production of reactive oxygen species, or those more likely to be stimulated by cytokines such as immune cells, have higher basal levels of Immunoproteasome compared to other cell types (Heink et al., 2005).

3. The Immunoproteasome in Antigen Presentation and Infections

As previously mentioned, the Immunoproteasome plays an important role in both the immune system and protein homeostasis. Since the mechanism by which the Immunoproteasome generates peptides for antigen presentation has been extensively reviewed (Goldberg et al., 2002, Basler et al., 2013, Angeles et al., 2012), we will not focus on that function in this review. We will also not consider the important question of infections any further, since the specific antigen can determine the response (*for a review on viral infection see* (McCarthy and Weinberg, 2015)). Instead, this review will focus more on the growing recognition of the role of the Immunoproteasome in diseases and aging.

3a. The Immunoproteasome and Disease – General Aspects

Alterations in the expression, activity, or function of the Immunoproteasome have been linked to several diseases. These changes may either cause the pathology, or be a symptom of the disease. Alterations in the Immunoproteasome may potentially arise due to genetic changes, polymorphisms or mutations, as will be discussed. Of note, though disease-associated mutations have been identified in two of the Immunoproteasome-specific subunits, genetic alterations in the constitutive 20S Proteasome subunits have not (Maksymowych et al., 1995, Fraile et al., 1998, Chistyakov et al., 2000, Gomes, 2013). In this next section, we will consider the impact of changes in the Immunoproteasome upon various diseases and the aging process.

3b. Inflammatory Diseases

Inflammation can occur during injury, infection, or disease. It is characterized by damage or stress to a tissue and is associated with cytokine signaling pathways as part of the overall immune response. Cytokines can either trigger further damage within cells and/or induce the mechanisms for abrogating such damage, and hence, return the cell to homeostasis

(Belardelli, 1995). Immunoproteasomes are thought to ameliorate inflammation-induced damage to the cell, and as mentioned above, its expression is upregulated by cytokines released during inflammatory responses. Protecting the cell from inflammation-related damage can occur either by degrading damaged proteins or by regulating cytokine production. To accomplish either of these tasks, the Immunoproteasome must first be expressed. One of the most well characterized inducers of the Immunoproteasome is interferon- γ (Aki et al., 1994, Akiyama et al., 1994, Groettrup et al., 1996). Other cytokines, such as TNF- α can also induce Immunoproteasome expression, but interferon- γ appears to be the most robust (Ferrington and Gregerson, 2012, Tanoka and Kasahara, 1998).

Upon interferon- γ signaling, cellular responses include phosphorylation of the 20S Proteasome, and initiation of transcription of the Immunoproteasome-specific β subunits: $\beta 1i$ (*LMP2*), $\beta 2i$ (*MECL-1*), and $\beta 5i$ (*LMP7*) (Aki et al., 1994). This is accomplished via binding of signal transducers and activators of transcription-1 (Stat-1) and interferon regulatory factor-1 (IRF-1) to interferon- γ regulatory elements in the promoter regions of these genes (Foss and Prydz, 1999). *LMP2*, *LMP7*, and *MECL-1* each have multiple interferon- γ response elements, as well as NF- κ B, cAMP, and SP-1 response sequences within their promoters (Ferrington and Gregerson, 2012). Additionally, interferon- γ signaling also increases expression of the 11S regulator. It is thought that the 11S regulator assists the Immunoproteasome in generating peptides for antigen presentation as it is more efficient at antigen production than is the 19S (Gomes, 2013). Following maturation, the Immunoproteasome is also capable of degrading oxidized proteins (Pickering et al., 2010, Pickering and Davies, 2012b, Seifert et al., 2010).

Studies have shown that the Immunoproteasome plays a role in cytokine production in response to inflammation or infection, and cells or animals deficient in Immunoproteasome subunits have decreased cytokine signaling (Muchamuel et al., 2009, Arima et al., 2011, Kitamura et al., 2011, Liu et al., 2012, Rockwell et al., 2012). Cytokines that have been shown to be regulated by the Immunoproteasome include interferon- γ , IL-2, IL-4, IL-10, and IL-23, and cells from *LMP7*^{-/-}*MECL1*^{-/-} knockout mice have been used to show that lack of the Immunoproteasome also causes decreased expression of two cytokine transcription factors, GATA3 and t-bet (Rockwell et al., 2012, Muchamuel et al., 2009). Taken together, these findings suggest that the Immunoproteasome not only plays a role in responding to inflammation, but also participates in activating the inflammatory cytokines, as well.

3c. Cancers

The Immunoproteasome has been suggested to play a role in regulating tumor development. Specifically, loss of the Immunoproteasome $\beta 1i$ subunit in *LMP2*^{-/-} knockout mice results in development of uterine leiomyosarcomas, and these tumors from human patients also show lack of $\beta 1i$ expression (Hayashi et al., 2011, Ferrington and Gregerson, 2012). In addition to lacking $\beta 1i$, these tissues also lack interferon- γ -induced IRF-1 expression, which is necessary in regulation of cell-cycle progression. Another study showed that a specific polymorphism in the *LMP7* gene for the $\beta 5i$ subunit is associated with an increased risk for

colon cancer (Fellerhoff et al., 2011). It has also been shown that Immunoproteasome expression is upregulated in acute promyelocytic leukemia cells (Khan et al., 2004).

However, it is important to highlight that although polymorphisms within *LMP2* and *LMP7* may occur simultaneously, they each exert different genetic effects, which are cancer dependent. For example, polymorphisms within *LMP7* shows a higher prevalence in gastric cancer (GC), whereas *LMP2* polymorphisms, within the same cancer, were not associated with promoting GC (Ma et al., 2015). Conversely, polymorphisms within *LMP2* were found to play a key role in the development of acute myeloid leukemia and multiple myelomas, whereas polymorphisms within *LMP7* were not considered a risk factor (Yu et al., 2013). Taken together, these studies suggest that, depending on the type of cancer, the Immunoproteasome may either be acting as a contributing factor in the development or progression, or may only be a consequence of the disease.

3d. Macular Degeneration

Inflammation and oxidative stress have been shown to play roles in age-related macular degeneration, or AMD (Beatty et al., 2000). Specifically, aging and oxidative stress have been shown to upregulate the expression of the immunoproteasome in murine retinal pigment epithelial cells (RPE) (Hussong et al., 2010). Hence, due to the highly oxidizing environment associated with AMD, it has been suggested that the Immunoproteasome is upregulated in more advanced stages of the disease (Ethen et al., 2007, Ferrington et al., 2008). As well, further studies in cultured retinal pigment epithelial cells (RPE) from mice lacking either one (*Imp7^{-/-}*) or two (*Imp7^{-/-}/mecI-1^{-/-}*) immunoproteasome subunits showed loss of Immunoproteasome induction upon oxidative stress (Hussong et al., 2010). Together, suggesting this increased expression in AMD lends more evidence for nonimmune functions of the Immunoproteasome.

3e. Alzheimer Disease

The subunits of the Immunoproteasome have been shown to have single nucleotide polymorphisms leading to greater risk of certain neurodegenerative diseases. Alzheimer disease is a neurodegenerative disorder characterized by late onset, progressive dementia, loss of neurons, and neurofibrillary tangles and plaques in the brain (Karch and Goate, 2015, Neuman et al., 2015, Goedert et al., 1989, Hardy and Selkoe, 2002, Jansen et al., 2014). These tangles are hyperphosphorylated aggregates of the tau protein, and the plaques are extracellular aggregates of the amyloid β protein. The constitutive Proteasome has been shown to be inhibited by these tau aggregate tangles (Keck et al., 2003, Poppek et al., 2006, Grune et al., 2010). Hyperphosphorylation of the tau protein, and its decreased turnover by the Proteasome, may be mediated by the abnormally high levels of the Regulator of Calcineurin 1 protein (RCAN1) seen in Alzheimer patients, as RCAN1 prevents calcineurin from dephosphorylating tau (Ermak et al., 2001, Lloret et al., 2011): Note that RCAN1 was originally called DSCR1 or Adapt78. Additionally, accumulation of tau aggregates in astrocytes of Alzheimer's patients have also been linked to increased expression of the Immunoproteasome (Mishto et al., 2006, Jansen et al., 2014). This suggests that cells try to cope by using the Immunoproteasome, albeit unsuccessfully, to clear away protein aggregates (Keck et al., 2003, Poppek et al., 2006, Grune et al., 2010).

Furthermore, the accumulation of Advanced Glycation-End Products (AGEs) has been identified as a hallmark of Alzheimer's disease (Vitek et al., 1994). AGEs form insoluble protein aggregates that are not only difficult for the cell to degrade, but have been associated with increased oxidative stress and inflammation (Bierhaus et al., 2005). Interestingly, increased expression of the Immunoproteasome has been identified within amyloid plaques (Mishto et al., 2006), the primary location of AGEs. This finding is further supported by cell culture studies, which suggest that upon the addition of exogenous AGEs, results in a robust increase in the Immunoproteasome expression and activity, and no change in the constitutive proteasome (Grimm et al., 2012). More importantly, the work by Grune and colleagues suggests a novel pathway of Immunoproteasome induction: activation of the AGE-receptor (RAGE), triggers phosphorylation of STAT1 via Jak1/2, resulting in the transcriptional increase of the Immunoproteasome subunits (Grimm et al., 2012). Thus highlighting an additional mechanism of Immunoproteasome activation that extends beyond the gamma-interferon pathway.

3f. Huntington Disease

Another neurodegenerative disease characterized by protein aggregation or inclusion body formation/accumulation is Huntington Disease. The polyglutamine expansion of the huntingtin (HTT) protein is thought to cause protein aggregation. This is a CAG repeat disease characterized by protein aggregates, neuronal dysfunction, and neurodegeneration (Jansen et al., 2014, Whalley, 2015). It has been shown that while there is no change in total Proteasome content, there is an increase in Immunoproteasome subunit expression (Díaz-Hernández et al., 2003). This suggests a switch from the constitutive 20S Proteasome to the Immunoproteasome. It is possible that the increased chymotrypsin-like activity of the Immunoproteasome is more important for degradation of protein aggregates found in Huntington patients than is the caspase-like activity. Importantly, the Huntington protein requires phosphorylation in order to be degraded by the Proteasome (unlike the Tau protein, whose phosphorylation inhibits proteasomal degradation). Thus, it is suggested that an insufficient amount of RCAN1 may cause the Huntingtin protein to evade normal degradation by the 20S Proteasome or the Immunoproteasome, worsening disease symptoms. This is especially apparent in patients with only a medium number of CAG repeats, but who show severe disease symptomology (Ermak et al., 2009).

3g. Parkinson Disease

Parkinson disease is a neurodegenerative disease greatly limiting mobility, and is characterized by the degeneration of the dopaminergic neurons of the substantia nigra and cellular protein aggregations called Lewy Bodies (Leroy et al., 1998). The causes have yet to be fully elucidated as there have been discrepancies about the deleterious impact of mutations on disease development (Jansen et al., 2014, Vilchez et al., 2014). While the Immunoproteasome has not been shown to be directly altered or mutated in Parkinson's disease, changes in the ubiquitinylation pathway most likely will affect the availability of appropriately targeted substrates for Immunoproteasome degradation (Vilchez et al., 2014). However, further research is necessary to properly determine the role the Immunoproteasome in Parkinson's disease.

3h. Amyotrophic Lateral Sclerosis (ALS) and Autoimmune Diseases

Amyotrophic lateral sclerosis (ALS) is an autoimmune disease characterized by late-onset, rapid progression of neurodegeneration that is ultimately fatal. One pathological hallmark of ALS is protein aggregation, resulting from loss of function mutations in the superoxide dismutase (*SOD1*) gene (Beckman et al., 1993, Puttaparthi and Elliott, 2005). Protein aggregates resulting from *SOD1* mutations correlate with the state of the disease, but their exact role in the disease remains unknown (Puttaparthi and Elliott, 2005). These aggregates are only found in the affected tissues, and can only be cleared via Proteasome-mediated degradation. Of note, Immunoproteasome expression was found to increase in astrocytes and microglia in the mouse model for ALS (Puttaparthi and Elliott, 2005). However, the study authors' suggest this elevation is due to an overall change in cellular Proteasome composition, rather than solely a direct increase in the Immunoproteasome. Hence, the upregulation of the Immunoproteasome may represent an attempt to delay disease progression through increased clearance of protein aggregates, and this may offer a potential therapeutic target in the future. While there has been no link shown between induction of the Immunoproteasome and disease progression or severity, Ahtoniemi and colleagues have shown that inhibiting Immunoproteasome induction results in decreased survival in ALS animal models (Ahtoniemi et al., 2007). These data suggest that the Immunoproteasome may actually play a role in limiting the severity of the disease. Additionally, recent reports have shown increased cytokine signaling as part of the ALS pathology (Meissner et al., 2010, Evans et al., 2013).

3i. *PSMB8* Mutations Resulting in Autoimmune Diseases

Recent studies have found that a number of diseases result from mutations in the *PSMB8* gene for the Immunoproteasome $\beta 5i$ subunit (Table 1). Alterations in the $\beta 5i$ function and expression in these diseases are the cause of the phenotype, as opposed to an effect of the condition (e.g. aging). These diseases are classified as autoimmune in nature, and exhibit a chronic inflammatory response without an incipient infection. They also show similar symptoms, which might be expected given that they result from point mutations in the same gene. The most commonly shared feature of these diseases is dysregulation of lipid processing and insulin regulation. Interestingly, *LMP7*^{-/-} ($\beta 5i$) mice do not have the phenotypes associated with the autoimmune diseases that humans with mutations in the gene, *PSMB8*, experience (Ferrington and Gregerson, 2012). Instead, these mice possess clinical signs more reminiscent of Diabetes. In fact, two small nucleotide polymorphisms (SNPs) in *PSMB8* have been associated with autoimmune forms of Diabetes in humans (Deng et al., 1995). As well, transcriptome analysis, shows marked increase of *PSMB8* in pancreatic tissue from Type I Diabetic individuals (Planas et al., 2010). Together, while the mutation in an Immunoproteasome subunit gene is the etiology for these diseases, it remains to be determined if the different phenotypes are the results of protein aggregation, or dysregulation of cytokine signaling.

4. Aging and Lifespan

Recently, Immunoproteasome expression has been linked to species lifespan in a study involving mice and primates. Long-lived species showed higher basal Immunoproteasome

levels and activity compared to short-lived animals (Pickering et al., 2015). This finding is supported by studies showing that although the Immunoproteasome expression increases with age (Husom et al., 2004, Ferrington et al., 2005, Gavilán et al., 2009), its inducibility by γ -interferon is diminished (Stratford et al., 2006). This is accompanied by a concurrent age-related accumulation of oxidized proteins within senescent cells. Thus implying that age-related rises in the Immunoproteasome may be a compensatory mechanism that is insufficient to cope with the overall increase in oxidized proteins. Another plausible explanation is the increased amount of the Immunoproteasome may represent inactive or inhibitor-bound units, as has been found to occur with the 20S Proteasome during aging and various age-associated diseases (Sitte et al., 2000a, Sitte et al., 2000b, Sitte et al., 2000c, Bulteau et al., 2001, Grune et al., 2004, Powell et al., 2005, Fratta et al., 2005, Stadtman, 2006, Aiken et al., 2011, Pickering et al., 2013b).

5. Summary and Conclusions

Considering all the recent publications on the importance of the Immunoproteasome in oxidative stress, diseases, aging, and we suggest that the Immunoproteasome should no longer be thought of only as a mechanism for generating peptides for antigen presentation (as important as this function is). As our understanding of the different roles of the Immunoproteasome expands, so does its importance for the clearance of oxidized proteins. It remains to be seen if the degradation targets of the Immunoproteasome during oxidative stress are used for antigen presentation, or if these peptides are further broken down by other proteases. Importantly, optimal functioning of both the Immunoproteasome and the 20S Proteasome appear to be critical for healthy aging, and dysregulation may can promote disease development and even hasten unhealthy aging and senescence.

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Figure 1.

Panel A Side view of the 20S Proteasome which is comprised of two identical α and β rings, each consisting of seven α and β subunits, respectively. The outer α rings recognize, bind, and feed the protein substrate into the catalytically active inner β rings. The beta rings contain three unique proteolytic subunits: β_1 , β_2 , β_5 , which are sequestered into the internal region of the Proteasome for its catalytic activity. **Panel B.** Side view of the Immunoproteasome. Oxidative stress and inflammation triggers the transcriptional upregulation and formation of the Immunoproteasome. Similar to the 20S core, the Immunoproteasome consists of two alpha and two beta rings, but with the three catalytically active beta subunits substituted with the Immunoproteasome-specific beta-subunits: β_{1i} , β_{2i} , β_{5i} . **Panel C.** Top-views of the 20S proteasome (left) and the Immunoproteasome (right). Similar to the 20S beta ring, which has trypsin-like activity (β_2), chymotrypsin-like activity (β_5), and caspase-like activity (β_1 , which is also known as peptidyl glutamyl-peptide hydrolyzing activity), the Immunoproteasome catalytic subunits consist of two subunits with chymotrypsin-like activity (β_{2i} & β_{5i}), and one with trypsin-like activity (β_{1i}).

Figure 2.

The primary role of the Ubiquitin-Proteasome-System (UPS) is to ensure proper functioning of the cellular proteome. The UPS relies upon the ATP-dependent 26S proteasome to conduct the normal turnover of poly-ubiquitin tagged proteins, such as Nrf2. In contrast, the 20S Proteasome preferentially degrades oxidatively damaged protein substrates, without need for ATP or ubiquitin. During unstressful conditions (left-half of the figure), Nrf2 is polyubiquitinated, disassociates from Keap1, and is targeted for degradation by the 26S proteasome. During oxidative stress, however (bottom right-side of the figure), the Nrf2-Keap1 complex disassociates, and phosphorylated-Nrf2 translocates into the nucleus, where it binds to the Electrophile Responsive Elements (EpRE, which is also called the Antioxidant Response Element or ARE) contained in various stress response genes, including the subunits of the 20S proteasome. This leads to *de novo* synthesis of the 20S Proteasome subunits, and new intact 20S Proteasomes. Although Proteasome transcription and translation are effective in increasing cellular capacity to degrade oxidized proteins and prevent their aggregation and accumulation, this adaptive process takes several hours. Fortunately (as shown in the top right-side of the figure), cells also have an immediate response mechanism to increase the capacity to degrade oxidized proteins, which is disassembly of 26S Proteasomes by ECM 29 and HSP70. Upon exposure to oxidative stress, the 19S regulator is removed (from 26S proteasomes) by ECM29, producing additional free 20S Proteasomes. The 19S regulators are sequestered and protected from degradation by

HSP70. Remarkably, following 3–5 hour recovery period, the 26S Proteasome is reassembled just as newly synthesized 20S Proteasomes (signaled by Nrf2) begin to appear.

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Figure 3.

Unlike the 20S proteasome, the subunits of the Immunoproteasome lack functional EpRE binding domains, and so cannot be regulated by Nrf2. Instead, the Interferon gamma (IFN γ) pathway may be activated. When IFN γ is added to cells it triggers the activation of Jak1 and Jak2, resulting in the dimerization and phosphorylation of Stat1. Activation of Stat1 is also possible through oxidative stress, (without IFN γ addition) as hydrogen peroxide has been found to cause dimerization of Stat1. In turn, Stat1 translocates into the nucleus, where it binds to interferon-1 (IRF-1). Following translation, IRF-1 moves back into the nucleus to increase expression of the immunoproteasome subunits. A potential alternative route for Immunoproteasome regulation is through the NF- κ B pathway. Upon an oxidative insult, Protein Kinase D (PKD) becomes phosphorylated, which acts to disassociate I κ B α from NF- κ B (the DNA binding domain protein dimers p50 and p65). In turn, I κ B α is degraded by the proteasome and NF- κ B can migrate into the nucleus where it may potentially interact with, and regulate the expression of, the Immunoproteasome subunits.

Various autoimmune diseases result from mutations within the *PSMB8* gene of the Immunoproteasome, which encodes the β_{5i} subunit. Mutations result in either truncation or loss of tertiary structure, which leads to decline or complete loss of function of the β_{5i} catalytic subunit.

Table 1

Autoimmune Diseases with <i>PSMB8</i> (β_{5i} subunit) mutation				
Disease	Mutation within <i>PSMB8</i>	Effect upon β_{5i} subunit	Symptoms	
JMP Joint contracture, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy ¹⁻⁴	Gene: 224C>T Peptide: Thr75Met	Change in tertiary structure, leads to decreased chymotrypsin-like activity	<ul style="list-style-type: none"> Joint contractures Mild metabolic disturbances Muscle atrophy Elevated liver enzymes Hypergammaglobulinemia 	
CANDLE Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature ²⁻⁵	Gene: 405C>A Peptide: Thr75Met	Altered tertiary structure leads to decreased chymotrypsin-like activity; In some instances, mutation results in protein truncation.	<ul style="list-style-type: none"> Skin lesions Low grade-fever Progressive lipodystrophy Developmental delay during first year of life 	
NNS Nakajo-Nishimura syndrome ^{2-4, 6}	Gene: 602G>T Peptide: Gly201Val	Conformational change in binding pocket; decreased chymotrypsin-like activity; no autocleavage and cannot incorporate into the β ring	<ul style="list-style-type: none"> Periodic fever Skin rash Joint contractures Lipomuscular atrophy 	
JASL Japanese autoinflammatory syndrome with lipodystrophy ^{2-4, 7}	Gene: 426G>T Peptide: Gly197Val	Missense mutation results in decreased protein levels and accumulation of immature immunoproteasome	<ul style="list-style-type: none"> Auto-inflammation Lipodystrophy 	

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