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On the role of the immunoproteasome in transplant rejection

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Abstract
The immunoproteasome is expressed in cells of hematopoietic origin and is induced during inflammation by IFN-γ. Targeting the immunoproteasome with selective inhibitors has been shown to be therapeutically effective in pre-clinical models for autoimmune diseases, colitis-associated cancer formation, and transplantation. Immunoproteasome inhibition prevents activation and proliferation of lymphocytes, lowers MHC class I cell surface expression, reduces the expression of cytokines of activated immune cells, and curtails T helper 1 and 17 cell differentiation. This might explain the in vivo efficacy of immunoproteasome inhibition in different pre-clinical disease models for autoimmunity, cancer, and transplantation. In this review, we summarize the effect of immunoproteasome inhibition in different animal models for transplantation.

Keywords Proteasome · Immunoproteasome · Antigen processing · Antigen presentation · Transplantation

Introduction

The proteasome is responsible for the degradation of proteins in the cytoplasm and nuclei of all eukaryotic cells and exerts numerous essential regulatory functions in nearly all cell biological pathways. The 26S proteasome degrades polyubiquitylated protein substrates and consists of a 19S regulator and a 20S proteolytic core complex. The 19S regulator bears ubiquitin receptors and an ATPase ring in charge of protein unfolding. The 20S core complex has a barrel-shaped structure consisting of four rings with seven subunits each. The outer two rings consist of α subunits; the inner two rings of β subunits forming the central proteolytic chamber (Huber et al. 2012). Depending on the cell type and the presence or absence of the pro-inflammatory cytokine interferon (IFN)-γ, the three inducible β subunits of the immunoproteasome low molecular mass polypeptide (LMP)2 (β1i), multicatalytic endopeptidase complex-like (MECL)-1 (β2i), and LMP7 (β5i), can, in addition to the corresponding constitutive subunits β1c, β2c, and β5c, enrich the cellular assortment of catalytically active β subunits (Fig. 1). These exchanges alter the cleavage specificity of the 20S proteasome. In immunoproteasomes, the caspase-like activity, exerted by β1c in constitutive proteasomes, is strongly reduced, whereas the chymotrypsin-like activity is enhanced. The immunoproteasome-induced changes in the 20S proteasome give rise to more suitable ligands for MHC-I (Basler et al. 2013; Groettrup et al. 2010; Mishto et al. 2014). The altered class I peptidome on immunoproteasome-containing cells influences pathogen-induced cytotoxic T lymphocyte (CTL) responses, pathogen clearance, and shapes the CTL repertoire (Basler et al. 2004, 2006, 2018; Chen et al. 2001; Chou et al. 2008; Ersching et al. 2016; Guimaraes et al. 2018; Hutchinson et al. 2011). Due to the use of immunoproteasome-selective inhibitors in recent years, it became evident that the immunoproteasome has, apart from its role in antigen processing, an important function in T helper cell differentiation (Basler et al. 2018; Guo et al. 2018; Kalim et al. 2012; Muchamuel et al. 2009; Xiao et al. 2017), in macrophage polarization (Chen et al. 2016), in brain inflammation (Kremer et al. 2010; Mundt et al. 2016), in inflammatory cytokine production (Basler et al. 2010, 2014, 2018; Farini

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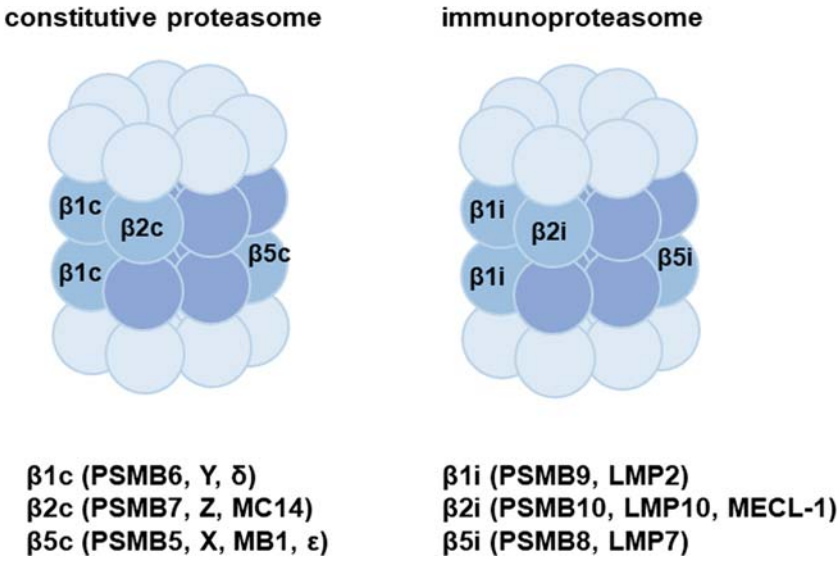

Fig. 1 Localization of the active site bearing subunits in the constitutive proteasome and the immunoproteasome. The proteolytic subunits of the constitutive proteasome are β1c (also known as PSMB6, Y, and δ), β2c (also known as PSMB7, Z, and MC14), and β5c (also known as PSMB5, X, MB1, and ε). The proteolytic immunoproteasome subunits are β1i (also known as PSMB9 and LMP2), β2i (also known as PSMB10, LMP10, and MECL-1), and β5i (also known as PSMB8 and LMP7)

et al. 2016; Guo et al. 2018; Muchamuel et al. 2009), in autoimmune diseases (Basler et al. 2010, 2014, 2018; Ichikawa et al. 2012; Liu et al. 2017, b; Muchamuel et al. 2009; Nagayama et al. 2012; Xiao et al. 2017), in colitis-associated cancers (Koerner et al. 2017; Vachharajani et al. 2017), in angiogenesis (Chen et al. 2018), in viral myocarditis (Althof et al. 2018), in the activation of lymphocytes (Santos et al. 2017; Sula Karreci et al. 2016), and organ transplantation (Li et al. 2018; Sula Karreci et al. 2016).

Over the course of the last century, organ transplantation has overcome major technical limitations to become the success it is today. However, in the absence of pharmacological immunosuppression, allogeneic organs are acutely rejected. In most cases, adaptive immune responses to proteins of the grafted allogenic tissues are the major hindrance to successful transplantation. Both cellular (lymphocyte-mediated) and humoral (antibody-mediated) mechanisms are responsible for transplant rejection. Although other cell types are also involved, T cells have been demonstrated to play the central role in the rejection of grafts (Ingulli 2010). To prevent rejection, current immunosuppressive therapies that target T cells non-specifically have to be taken lifelong, leaving patients more susceptible to infections and tumors, in addition to having toxic off-target effects (Hartono et al. 2013). Hence, there is a strong need to develop alternative treatments to classical immunosuppression to induce donor-specific tolerance. Immunoproteasome inhibition might emerge as such a new treatment option. Immunoproteasome expression is restricted to immune cells and to an inflammatory environment, and therefore, selective inhibitors of the immunoproteasome can be applied below their maximally tolerated dose while still retaining their therapeutic efficacy but lacking untoward toxicity. Immunoproteasome inhibition reduces the generation of the T helper cell subsets Th1 and Th17 which are involved in transplant rejection but spares Th2 and regulatory T cells in vitro and in vivo (Basler et al. 2014; Kalim et al. 2012; Muchamuel et al. 2009; Mundt et al. 2016). This subset preference might contribute to an improved selectivity of immunoproteasome inhibitors as compared to more general immunosuppressants. Furthermore, mice treated with immunoproteasome inhibitors can well control viral infections (Althof et al. 2018; Basler et al. 2011; Muchamuel et al. 2009; Mundt et al. 2016) and immunoproteasome inhibition can even reduce tumor formation (Koerner et al. 2017; Vachharajani et al. 2017). Hence, the immunoproteasome might qualify as a new treatment option to prevent transplant rejection.

Effect of the immunoproteasome-associated MHC-I peptidome on transplant rejection

The use of proteasome inhibitors in vitro demonstrated that the proteasome is responsible for the generation of most ligands presented on major histocompatibility complex class I molecules (MHC-I) (Rock et al. 1994). Although proteasomes are required for MHC class I antigen presentation, they actually destroy many more peptides than they generate (Saric et al. 2001). Only 10–15% of the produced peptides are of the appropriate size for MHC class I antigen presentation while most of them are too short to fit into the binding cleft of MHC class I needing further trimming. Proteasome inhibition in vivo leads to reduced MHC-I antigen presentation resulting in an impaired anti-viral CTL response (Basler et al. 2009). Since LMP2 and LMP7 are encoded in the MHC gene locus and LMP2, LMP7, and MECL-1 are induced by IFN-γ, a role of immunoproteasomes in optimization of MHC class I antigen processing seems obvious. Indeed, early experiments with LMP2- and LMP7-deficient mice demonstrated an involvement of the immunoproteasome in antigen processing (Van Kaer et al. 1994; Fehling et al. 1994). Later, many more studies showed that the

immunoproteasome is responsible for the generation or destruction of MHC-I ligands (summarized in Basler et al. 2013; Groettrup et al. 2010).

Transplantation presents a life-saving therapy and last resort for end-stage organ failure and can be considered among the major accomplishments of the twentieth century in human health. However, a complex series of interactions involving coordination between both the innate and adaptive immune system can result in the rejection of solid organ allografts. Recipient T cells, central to this process, recognize donor-derived antigen (alloantigens) initiating allograft rejection. In two different pathways, major and minor histocompatibility antigens can activate the immune system against the allograft. (1) T cells can either directly recognize intact non-self donor MHC molecules present on the surface of donor cells or (2) donor MHC molecules can be processed and presented as peptides on self-MHC molecules. Using a model substrate, Toes et al. showed that cells expressing immunoproteasomes display a different peptide repertoire compared to cells expressing constitutive proteasomes (Toes et al. 2001). These changes alter the overall cytotoxic T cell specificity as indicated by the observation that LMP7-deficient mice react against cells derived from LMP7-containing wild-type mice. Skin grafting experiments showed that wild-type mice were not able to reject skin from $LMP7^{-/-}$ mice whereas $LMP7^{-/-}$ mice rejected skin transplants from wild-type mice with even greater efficiency than observed for the rejection of male skin by female recipients. Similar results were obtained in mice deficient for all immunoproteasome subunits (TKO) (Kincaid et al. 2012). Mass spectrometry analysis of peptides eluted from $H\text{-}2K^b$ or $H\text{-}2D^b$ derived from splenocytes of wild-type and TKO animals revealed changes in the MHC-I peptide repertoire. Approximately one third of peptides was exclusively presented on wild-type splenocytes, one third of peptides was exclusively presented on TKO splenocytes, and one third was presented on both types. The differences in MHC class I restricted Ag presentation between constitutive and immunoproteasomes is probably due to quantitative and not qualitative differences in the proteasome-generated antigenic peptides (Mishto et al. 2014). The altered peptide presentation in TKO resulted in rejection of wild-type splenocytes in TKO mice, but not vice versa (Kincaid et al. 2012). This indicates that wild-type splenocytes present a markedly different repertoire of peptides than those found in either the thymus or periphery of TKO animals, resulting in recognition of this immunoproteasome-derived repertoire as foreign epitopes. The authors conclude that the TKO host has never seen any of the unique peptides generated by immunoproteasomes and therefore would not be tolerant to them. In contrast, wild-type mice express constitutive proteasomes and immunoproteasomes, so the animals would be expected to be tolerant to the peptides generated by both types of proteolytic complexes. Indeed, apart from its influence on class I antigen presentation in antigen-presenting cells in the periphery, immunoproteasome expression in the thymus has been shown to alter CD8 T cell selection. Different immunoproteasome subunit-deficient mice have an altered T cell repertoire influencing CTL responses (Basler et al. 2006, 2018; Chen et al. 2001; Kincaid et al. 2016; Osterloh et al. 2006). Furthermore, a single amino acid exchange in β2i (G170W) causes severe combined immunodeficiency (SCID) and systemic autoinflammation in G170W mutant mice (Treise et al. 2018). Yeast mutagenesis and crystallographic data suggest that the severe phenotype in G170W mutant mice is due to structural changes in the C-terminal appendage of β2i that prevent the biogenesis of immuno- and thymoproteasomes (a special class of proteasomes in the thymus). Since proteasomes are essential for cell survival, and defective proteasome assembly causes selective death of cells expressing the mutant β2i, this probably leads to death of cells responsible for positive and negative selection in the thymus, and thus most likely causes the severe immunological phenotype observed in G170W mutant mice. Taken together, immunoproteasome expression in the thymus and the periphery influences MHC-I antigen presentation and thereby modulates the cytotoxic T cell repertoire and CTL responses. Hence, due to modulating both the cytotoxic T cells and MHC-I ligands, immunoproteasomes play an important role in transplantation.

The immunoproteasome in graft versus host disease

Hematopoietic stem cell transplantation is used to treat hematologic malignancies. Despite significant advances in tissue typing and donor selection, graft-versus-host disease (GVHD) remains a serious and deadly complication to patients, who undergo hematopoietic stem cell transplantation. GVHD results from donor T lymphocytes activated by host antigen-presenting cells, inducing an inflammatory response against host cells. Bortezomib (also named PS-341, or Velcade; Millennium Pharmaceuticals) is the first clinically approved proteasome inhibitor for relapsed and/or refractory myeloma and mantle cell lymphoma. The boronic acid dipeptide is a reversible broad-spectrum proteasome inhibitor (Adams et al. 1998; Adams et al. 1999). Cells exposed to bortezomib exhibit occupancy of constitutive and immune proteasomal proteolytic subunits, resulting in the rapid accumulation of poly-ubiquitinated proteins, including several regulatory molecules involved in cell signaling and survival pathways. Both T cells and dendritic cells (DCs) are directly affected by bortezomib treatment. Bortezomib has been shown to suppress T cell activation and production of cytokines (Blanco et al. 2006), T cell mobilization (Liu et al. 2012), and T cell proliferation (Berges et al. 2008; Blanco et al. 2006). In DCs, bortezomib suppresses

maturation, induces apoptosis, suppresses function, and inhibits cytokine production (Arpinati et al. 2009; Nencioni et al. 2006; Straube et al. 2007). Since T cells and DCs are crucial players in GVHD, bortezomib treatment seems a promising strategy in preventing GVHD. Indeed, bortezomib has been shown to be effective in acute graft-versus-host disease in mice (Sun et al. 2004). A reduction in GVHD-associated disease parameters was observed but with no adverse effects on long-term donor reconstitution. Some studies in humans suggest that bortezomib-based GVHD prophylaxis and treatment are feasible and may improve efficacy when added to standard regimens (Al-Homsi et al. 2015, 2017; Koreth et al. 2012, 2015). However, recent randomized phase II results indicated that the bortezomib-based regimens evaluated did not improve outcomes compared with tacrolimus/methotrexate therapy (Koreth et al. 2018). The effect of bortezomib and the high expression of immunoproteasomes in immune cells suggest investigating immunoproteasome inhibition in GVHD. Indeed, the LMP7-selective inhibitor ONX 0914 ameliorated GVHD in an MHC-matched minor histocompatibility antigen-disparate murine model (Zilberberg et al. 2015). In mice experiencing GVHD, ONX 0914 treatment in the B10.BR → CBA MHC-matched/minor histocompatibility antigen (miHA)-disparate murine blood and marrow transplant (BMT) model caused a modest but significant improvement in the survival. Stimulator splenocytes, but not responder T cells, treated with ONX 0914 in lymphocyte cultures resulted in decreased IFN-γ production by allogeneic T cells in both MHC-disparate (B10.BR anti-B6) and miHA-mismatched (B10.BR anti-CBA) settings. This indicates that ONX 0914 alters antigen presentation of miHA in this setup.

The immunoproteasome in skin allograft transplantation

Different types of $CD4^+$ T cells play a central role in mediating transplant rejection. Cooperation between $CD4^+$ and $CD8^+$ T cells is thought to be required for maximal graft rejection. Th1 cells have been shown to facilitate $CD8^+$ T cell differentiation by direct cell-to-cell contact or by producing effector cytokines, such as IL-2 and IFN-γ that directly support $CD8^+$ T cell differentiation and killing (Jiang et al. 2004; Shrikant et al. 1999). In recent years, it became evident that, apart from Th1 cells, Th17 cells also mediate acute allograft rejection by recruiting neutrophils and monocytes into the graft promoting transplant inflammation (Gorbacheva et al. 2010; Itoh et al. 2011). LMP7 inhibition was shown to suppress the differentiation of the pro-inflammatory T helper subtypes Th1 and Th17 in vitro (Basler et al. 2018; Kalim et al. 2012; Muchamuel et al. 2009; Mundt et al. 2016) and in vivo (Basler et al. 2014; Mundt et al. 2016). Therefore, the effect of immunoproteasome inhibition was investigated in skin allograft transplantation using the LMP7-selective inhibitor ONX 0914 (Mundt et al. 2017). In vitro, in a mixed-lymphocyte-reaction (MLR), ONX 0914 reduced allo-specific IL-17 production in T cells. However, in vivo allograft survival in an MHC-disparate (C57BL/6 to BALB/c) and a multiple minor histocompatibility antigen (miHA)-disparate (B10.BR to C3H) model of skin transplantation was not altered in recipient mice treated with ONX 0914. It has been shown that mice treated with ONX 0914 can mount a rather normal virus-induced CTL response (Muchamuel et al. 2009). Alterations can only be observed for CTLs specific for LMP7-dependent class I peptides. Thus, the influence of immunoproteasome inhibition on Th cell differentiation appears to be not strong enough to influence skin allograft rejection which is dominated by CTLs in the used skin allograft models (Mundt et al. 2017). Hence, immunoproteasome inhibition does not appear to be a suitable approach to treat acute T cell-mediated skin allograft rejection.

The immunoproteasome in kidney transplantation

Kidney transplantation is the most effective therapeutic approach for end-stage renal disease. Immunosuppressive regimes mainly target T cell-mediated acute kidney rejection. However, in contrast to earlier assumptions, long-term kidney rejection is mainly mediated by alloantibodies. Nevertheless, no FDA-approved medications are available for antibody-mediated kidney rejection. Proteasome inhibitors have been shown to be effective in animal models for humoral diseases. Treatment of two mouse strains with lupus-like disease, NZB/W F1 and MRL/lpr mice, with bortezomib-depleted plasma cells producing antibodies to double-stranded DNA, eliminated autoantibody production, ameliorated glomerulonephritis, and prolonged survival (Neubert et al. 2008). Clinical efficacy was also observed in a small clinical study in patients with active, refractory systemic lupus erythematosus (Alexander et al. 2015). Using bortezomib in experimental renal transplantation in the rat, Vogelbacher et al. could show that bortezomib inhibits the chronic active antibody-mediated rejection (Vogelbacher et al. 2010). The production of alloantibodies against components of glomerular basement membrane was reduced and the humoral response was strongly ameliorated, as shown by decreased numbers of IgG-secreting cells, plasma cells, and partially B cells in bortezomib-treated rats. Furthermore, infiltration of the graft with inflammatory cells like cytotoxic T cells, T helper cells, B cells, and macrophages was efficiently blocked by bortezomib treatment. Several incompletely controlled studies have suggested efficacy of the proteasome inhibitor bortezomib in preventing antibody-mediated kidney transplant rejection in humans (Everly et al. 2008; Pearl et al. 2016; Trivedi et al.

2009; Walsh et al. 2010). However, a recent randomized trial of bortezomib in late antibody-mediated kidney transplant rejection failed to show efficacy (Eskandary et al. 2018).

A limit to the therapeutic application of proteasome inhibitors in kidney transplantation is the ubiquitous expression of the proteasome leading to well-known adverse side effects. For instance, although bortezomib has been shown to be effective in SLE, bortezomib treatment leads to a higher mortality rate in lupus model mice (Ikeda et al. 2017). Hence, a potential benefit in terms of graft survival has to be counterweighed with known adverse effects. In contrast to the constitutive proteasome, immunoproteasomes are expressed in immune cells and in an inflammatory environment, and therefore, selective inhibitors of the immunoproteasome can be applied below their maximally tolerated dose while still retaining their therapeutic efficacy but lacking untoward toxicity. Indeed, immunoproteasome inhibitors have been successfully applied in animal models for humoral immunity. ONX 0914, an LMP7-selective inhibitor, has been shown to have beneficial effect in murine lupus (Ichikawa et al. 2012). Inhibition of the immunoproteasome prevented disease progression by targeting two critical pathways in disease pathogenesis, type I IFN activation, and autoantibody production by plasma cells. Furthermore, in an in vitro humoral alloimmunity model, ONX 0914 was shown to decrease alloantibody production (Eleftheriadis et al. 2017). In a recent study, the effect of immunoproteasome inhibition has been investigated in a rat kidney transplantation model (Li et al. 2018). In this transplantation model, kidneys transplanted from Fischer to allogeneic Lewis rats induce a chronic antibody-mediated allograft rejection. Immunoproteasome inhibition by ONX 0914 ameliorated allograft renal function impairment, prolonged the survival of recipients, and alleviated chronic graft nephropathy. Furthermore, ONX 0914 treatment reduced the numbers of B and plasma cells in the bone marrow and spleen, and suppressed donor-specific alloantibody production. Leukocyte infiltration and the inflammatory response in the renal allografts were strongly reduced in recipient rats treated with ONX 0914. This study was performed at a dose (5 mg/kg) fairly below the maximal tolerated dose but still retained their therapeutic efficacy without obvious side effects. This demonstrates that immunoproteasome inhibitors are promising drugs in kidney transplantation with good tolerability, although ONX 0914 has been shown to induce some apoptosis in primary human renal tubular epithelial cells in vitro (Eleftheriadis et al. 2016).

The immunoproteasome in heart allograft survival

Proteasome inhibitors have been applied in animal models of solid organ transplantation. Recently, Sula Karreci et al. described the development of the novel LMP7-selective inhibitor DPLG3. DPLG3 is a rationally designed, non-covalent reversibly acting N,C-capped dipeptide inhibitor of LMP7 that has a 1000-fold selectivity over the constitutive subunit β5c (Sula Karreci et al. 2016). DPLG3 inhibited β5i competitively with an IC50 of 4.4 nM, with less than 50% inhibition of β1i, β2c, β2i, and β2c at 33.3 μM. No cytotoxic activity of DPLG3 was observed on human PBMCs or mouse bone marrow-derived macrophages. DPLG3 significantly inhibited the production of IFN-α and IP-10 by CpG-activated PBMCs without affecting viability. In the clinic, prevention of graft rejection requires suppression of T cell responses. DPLG3 inhibited proliferation of in vitro TCR-stimulated $CD4^+$ and $CD8^+$ T cells in a concentration-dependent manner. To test whether DPLG3 inhibits T cell responses to alloantigen in vivo, $CD3^+CD25^-$ T cells (C57BL/6 background) were transferred into $RAG^{-/-}$C57BL/6 mice which were grafted with BALB/c skin 1 day in advance. Mice treated daily with 25 mg/kg DPLG3 showed reduced $CD4^+$ and $CD8^+$ effector T cells compared to vehicle-treated mice. Furthermore, exhaustion and co-inhibitory markers PD1, TIM3, and LAG3 on CD4 and CD8 effector cells were enhanced in DPLG3-treated mice. To test the effect of immunoproteasome inhibition on transplantation, Sula Karecci et al. used a stringent, highly reproducible preclinical heart transplant mouse model in which BALB/c hearts are transplanted into fully allogeneic C57BL/6 recipients (Sula Karreci et al. 2016). Effector T cells isolated from the spleen on day 7 post-transplantation showed an upregulation of LMP7 in these cells, indicating that LMP7 is a valuable target in allogenic heart transplantation. Survival of the allograft was significantly prolonged in DPLG3-treated mice compared to vehicle-treated mice (median survival time, day 13 vs. day 7), accompanied by reduced histologic signs of acute allograft rejection. Furthermore, a reduced percentage of effector memory T cells was observed in DPLG3-treated mice. A single-dose of an anti-CTLA4 antibody (sCTLA4-Ig) on day 2 post-transplantation markedly increased the survival of the transplanted heart (median survival time, day 38.5 vs. day 7). Remarkably, mice treated with sCTLA4-Ig (day 2) and DPLG3 (daily for 7 days) significantly prolonged heart survival (median survival time, day 84 vs. day 38.5). Mice receiving sCTLA4-Ig (day 2) and DPLG3 for 14 days even increased the median graft survival time > 100 days. Assessment of alloimmune responses in the periphery also showed a marked reduction in the T cell proliferative response in recipients treated with DPLG3 plus sCTLA4-Ig compared to sCTLA4-Ig alone. Further studies are required to identify the mechanism by which DPLG3 inhibits T cell activation, proliferation, surface marker expression, and secretion of cytokines. Taken together, the results presented in the study by Sula Karecci

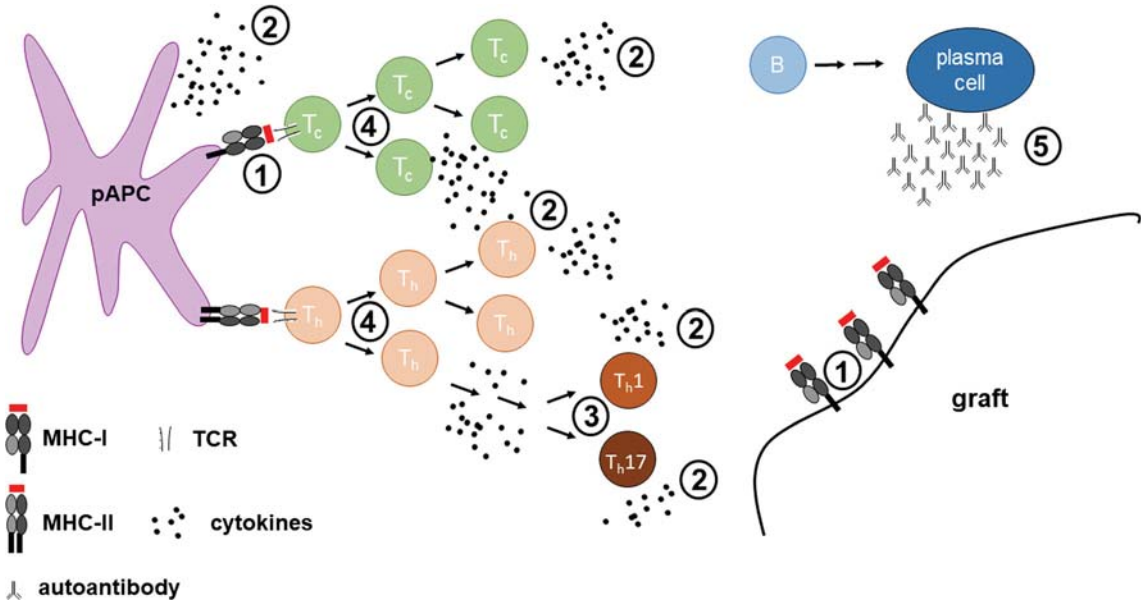

Fig. 2 Immunoproteasome inhibition in transplantation can interfere at multiple levels with transplant rejection affecting different pathways: (1) antigen presentation, (2) cytokine production, (3) T helper cell differentiation, (4) T cell activation and proliferation, and (5) prevention of alloantibody production. pAPC, professional antigen-presenting cell; T_c, cytotoxic T cell; T_h, T helper cell; T_h1, T helper 1 cell; T_h17, T helper 17 cell; B, B cell

et al. show that a brief post-transplant treatment with immunoproteasome inhibitors as part of an immunomodulatory regimen prolongs allograft survival without broadly cytotoxic or immunosuppressive effects.

Conclusion

Immunoproteasome inhibition seems to be a promising approach for preventing transplant rejection. Different studies indicated that immunoproteasome inhibition in transplantation can interfere at different levels affecting different pathways: (1) antigen presentation, (2) cytokine production, (3) T helper cell differentiation, (4) T cell activation and proliferation, and (5) prevention of alloantibody production (Fig. 2).

1. Immunoproteasome inhibition has been shown to affect antigen presentation. Therefore, immunoproteasome inhibition might alter the presentation of donor antigens. Whether these changes influence transplantation efficiency has barely been investigated and remains elusive.
2. Immunoproteasome inhibition has been shown to reduce cytokine secretion of different immune cells. Since cytokines regulate activation and effector functions of all immune cells involved in transplantation, immunoproteasome inhibition will dampen allograft specific immune responses.
3. Depending on the cytokine environment, T helper cells can differentiate into different subsets. While the role of Th17 cell in transplantation is less clear, Th1 cells play a crucial role in the rejection process. Th1 cells are characterized by the production of pro-inflammatory cytokines IFN-γ, IL-2, IL-12, TNF, and GM-CSF. This cytokine profile activates macrophages, natural killer cells, and cytotoxic T cells which are drawn to the graft. Hence, a reduced Th1 differentiation mediated by immunoproteasome inhibition can positively influence graft survival.
4. Both activation and proliferation of $CD4^+$ and $CD8^+$ have been shown to be reduced in immunoproteasome inhibitor-treated mice (Sula Karreci et al. 2016). Since both cell types are crucially involved in rejection, immunoproteasome inhibition will improve graft survival.
5. Alloantibodies are responsible for long-term rejection of allografts. Bortezomib enhances the accumulation of unfolded proteins via the induction of ER stress and the unfolded protein response, eventually leading to apoptotic cell death. Plasma cells that synthesize large amounts of immunoglobulins have a relatively high sensitivity to bortezomib, which partly explains the clinical success of bortezomib in treating plasma cell-derived multiple myelomas. Li et al. showed that immunoproteasome inhibition in rats prevented alloantibody production and reduced the number of plasma cells in an antibody-mediated kidney allograft

rejection model (Li et al. 2018). Hence, it seems likely that immunoproteasome inhibition in plasma cells induces ER stress leading to apoptotic plasma cell death and prevention of alloantibody production.

Taken together, multiple modes of actions on different pathways involved in transplant rejection render the immunoproteasome a highly valuable target. Indeed, the first pre-clinical studies with immunoproteasome inhibitors in animal models of transplantations are encouraging.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Adams J, Behnke M, Chen SW, Cruickshank AA, Dick LR, Grenier L, Klunder JM, Ma YT, Plamondon L, Stein RL (1998) Potent and selective inhibitors of the proteasome: dipeptidyl boronic acids. Bioorg Med Chem Lett 8:333–338

Adams J, Palombella VJ, Sausville EA, Johnson J, Destree A, Lazarus DD, Maas J, Pien CS, Prakash S, Elliott PJ (1999) Proteasome inhibitors: a novel class of potent and effective antitumor agents. Cancer Res 59:2615–2622

Alexander T, Sarfert R, Klotsche J, Kuhl AA, Rubbert-Roth A, Lorenz HM, Rech J, Hoyer BF, Cheng Q, Waka A, Taddeo A, Wiesener M, Schett G, Burmester GR, Radbruch A, Hiepe F, Voll RE (2015) The proteasome inhibitior bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus. Ann Rheum Dis 74:1474–1478

Al-Homsi AS, Cole K, Bogema M, Duffner U, Williams S, Mageed A (2015) Short course of post-transplantation cyclophosphamide and bortezomib for graft-versus-host disease prevention after allogeneic peripheral blood stem cell transplantation is feasible and yields favorable results: a phase I study. Biol Blood Marrow Transplant 21:1315–1320

Al-Homsi AS, Cole K, Muilenburg M, Goodyke A, Abidi M, Duffner U, Williams S, Parker J, Abdel-Mageed A (2017) Calcineurin and mTOR inhibitor-free post-transplantation cyclophosphamide and bortezomib combination for graft-versus-host disease prevention after peripheral blood allogeneic hematopoietic stem cell transplantation: a phase I/II study. Biol Blood Marrow Transplant 23:1651–1657

Althof N, Goetzke CC, Kespohl M, Voss K, Heuser A, Pinkert S, Kaya Z, Klingel K, Beling A (2018) The immunoproteasome-specific inhibitor ONX 0914 reverses susceptibility to acute viral myocarditis. EMBO Mol Med 10:200–218

Arpinati M, Chirumbolo G, Nicolini B, Agostinelli C, Rondelli D (2009) Selective apoptosis of monocytes and monocyte-derived DCs induced by bortezomib (Velcade). Bone Marrow Transplant 43:253–259

Basler M, Beck U, Kirk CJ, Groettrup M (2011) The antiviral immune response in mice devoid of immunoproteasome activity. J Immunol 187:5548–5557

Basler M, Dajee M, Moll C, Groettrup M, Kirk CJ (2010) Prevention of experimental colitis by a selective inhibitor of the immunoproteasome. J Immunol 185:634–641

Basler M, Kirk CJ, Groettrup M (2013) The immunoproteasome in antigen processing and other immunological functions. Curr Opin Immunol 25:74–80

Basler M, Lauer C, Beck U, Groettrup M (2009) The proteasome inhibitor bortezomib enhances the susceptibility to viral infection. J Immunol 183:6145–6150

Basler M, Maurits E, de Bruin G, Koerner J, Overkleeft HS, Groettrup M (2018) Amelioration of autoimmunity with an inhibitor selectively targeting all active centres of the immunoproteasome. Br J Pharmacol 175:38–52

Basler M, Moebius J, Elenich L, Groettrup M, Monaco JJ (2006) An altered T cell repertoire in MECL-1-deficient mice. J Immunol 176:6665–6672

Basler M, Mundt S, Groettrup M (2018) The immunoproteasome subunit LMP7 is required in the murine thymus for filling up a hole in the T cell repertoire. Eur J Immunol 48:419–429

Basler M, Mundt S, Muchamuel T, Moll C, Jiang J, Groettrup M, Kirk CJ (2014) Inhibition of the immunoproteasome ameliorates experimental autoimmune encephalomyelitis. EMBO Mol Med 6:226–238

Basler M, Youhnovski N, Van Den Broek M, Przybylski M, Groettrup M (2004) Immunoproteasomes down-regulate presentation of a subdominant T cell epitope from lymphocytic choriomeningitis virus. J Immunol 173:3925–3934

Berges C, Haberstock H, Fuchs D, Miltz M, Sadeghi M, Opelz G, Daniel V, Naujokat C (2008) Proteasome inhibition suppresses essential immune functions of human CD4+ T cells. Immunology 124:234–246

Blanco B, Perez-Simon JA, Sanchez-Abarca LI, Carvajal-Vergara X, Mateos J, Vidriales B, Lopez-Holgado N, Maiso P, Alberca M, Villaron E, Schenkein D, Pandiella A, San Miguel J (2006) Bortezomib induces selective depletion of alloreactive T lymphocytes and decreases the production of Th1 cytokines. Blood 107:3575–3583

Chen S, Kammerl IE, Vosyka O, Baumann T, Yu Y, Wu Y, Irmler M, Overkleeft HS, Beckers J, Eickelberg O, Meiners S, Stoeger T (2016) Immunoproteasome dysfunction augments alternative polarization of alveolar macrophages. Cell Death Differ 23:1026–1037

Chen WS, Norbury CC, Cho YJ, Yewdell JW, Bennink JR (2001) Immunoproteasomes shape immunodominance hierarchies of antiviral CD8(+) T cells at the levels of T cell repertoire and presentation of viral antigens. J Exp Med 193:1319–1326

Chen X, Zhang X, Chen T, Jiang X, Wang X, Lei H, Wang Y (2018) Inhibition of immunoproteasome promotes angiogenesis via enhancing hypoxia-inducible factor-1alpha abundance in rats following focal cerebral ischaemia. Brain Behav Immun 73:167–179

Chou B, Hisaeda H, Shen J, Duan X, Imai T, Tu L, Murata S, Tanaka K, Himeno K (2008) Critical contribution of immunoproteasomes in the induction of protective immunity against Trypanosoma cruzi in mice vaccinated with a plasmid encoding a CTL epitope fused to green fluorescence protein. Microbes Infect 10:241–250

Eleftheriadis T, Pissas G, Antoniadi G, Liakopoulos V, Stefanidis I (2016) Proteasome or immunoproteasome inhibitors cause apoptosis in human renal tubular epithelial cells under normoxic and hypoxic conditions. Int Urol Nephrol 48:907–915

Eleftheriadis T, Pissas G, Antoniadi G, Liakopoulos V, Stefanidis I (2017) A comparative analysis between proteasome and immunoproteasome

inhibition in cellular and humoral alloimmunity. Int Immunopharmacol 50:48–54

Ersching J, Vasconcelos JR, Ferreira CP, Caetano BC, Machado AV, Bruna-Romero O, Baron MA, Ferreira LR, Cunha-Neto E, Rock KL, Gazzinelli RT, Rodrigues MM (2016) The combined deficiency of immunoproteasome subunits affects both the magnitude and quality of pathogen- and genetic vaccination-induced CD8+ T cell responses to the human protozoan parasite Trypanosoma cruzi. PLoS Pathog 12:e1005593

Eskandary F, Regele H, Baumann L, Bond G, Kozakowski N, Wahrmann M, Hidalgo LG, Haslacher H, Kaltenecker CC, Aretin MB, Oberbauer R, Posch M, Staudenherz A, Handisurya A, Reeve J, Halloran PF, Bohmig GA (2018) A randomized trial of bortezomib in late antibody-mediated kidney transplant rejection. J Am Soc Nephrol 29:591–605

Everly MJ, Everly JJ, Susskind B, Brailey P, Arend LJ, Alloway RR, Roy-Chaudhury P, Govil A, Mogilishetty G, Rike AH, Cardi M, Wadih G, Tevar A, Woodle ES (2008) Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. Transplantation 86:1754–1761

Farini A, Sitzia C, Cassani B, Cassinelli L, Rigoni R, Colleoni F, Fusco N, Gatti S, Bella P, Villa C, Napolitano F, Maiavacca R, Bosari S, Villa A, Torrente Y (2016) Therapeutic potential of immunoproteasome inhibition in Duchenne muscular dystrophy. Mol Ther 24:1898–1912

Fehling HJ, Swat W, Laplace C, Kuehn R, Rajewsky K, Mueller U, von Boehmer H (1994) MHC class I expression in mice lacking proteasome subunit LMP-7. Science 265:1234–1237

Gorbacheva V, Fan R, Li X, Valujskikh A (2010) Interleukin-17 promotes early allograft inflammation. Am J Pathol 177:1265–1273

Groettrup M, Kirk CJ, Basler M (2010) Proteasomes in immune cells: more than peptide producers? Nat Rev Immunol 10:73–78

Guimaraes G, Gomes MTR, Campos PC, Marinho FV, de Assis NRG, Silveira TN, Oliveira SC (2018) Immunoproteasome subunits are required for CD8(+) T cell function and host resistance to Brucella abortus infection in mice. Infect Immun 20;86(3):e00615–17

Guo Y, Chen X, Li D, Liu H, Ding Y, Han R, Shi Y, Ma X (2018) PR-957 mediates neuroprotection by inhibiting Th17 differentiation and modulating cytokine production in a mouse model of ischaemic stroke. Clin Exp Immunol 193(2):194–206.

Hartono C, Muthukumar T, Suthanthiran M (2013) Immunosuppressive drug therapy. Cold Spring Harb Perspect Med 3:a015487

Huber EM, Basler M, Schwab R, Heinemeyer W, Kirk CJ, Groettrup M, Groll M (2012) Immuno- and constitutive proteasome crystal structures reveal differences in substrate and inhibitor specificity. Cell 148:727–738

Hutchinson S, Sims S, O'Hara G, Silk J, Gileadi U, Cerundolo V, Klenerman P (2011) A dominant role for the immunoproteasome in CD8+ T cell responses to murine cytomegalovirus. PLoS One 6:e14646

Ichikawa HT, Conley T, Muchamuel T, Jiang J, Lee S, Owen T, Barnard J, Nevarez S, Goldman BI, Kirk CJ, Looney RJ, Anolik JH (2012) Novel proteasome inhibitors have a beneficial effect in murine lupus via the dual inhibition of type I interferon and autoantibody secreting cells. Arthritis Rheum 64:493–503

Ikeda T, Fujii H, Nose M, Kamogawa Y, Shirai T, Shirota Y, Ishii T, Harigae H (2017) Bortezomib treatment induces a higher mortality rate in lupus model mice with a higher disease activity. Arthritis Res Ther 19:187

Ingulli E (2010) Mechanism of cellular rejection in transplantation. Pediatr Nephrol 25:61–74

Itoh S, Kimura N, Axtell RC, Velotta JB, Gong Y, Wang X, Kajiwara N, Nambu A, Shimura E, Adachi H, Iwakura Y, Saito H, Okumura K, Sudo K, Steinman L, Robbins RC, Nakae S, Fischbein MP (2011) Interleukin-17 accelerates allograft rejection by suppressing regulatory T cell expansion. Circulation 124:S187–S196

Jiang S, Herrera O, Lechler RI (2004) New spectrum of allorecognition pathways: implications for graft rejection and transplantation tolerance. Curr Opin Immunol 16:550–557

Van Kaer L, Ashton-Rickardt PG, Eichelberger M, Gaczynska M, Nagashima K, Rock KL, Goldberg AL, Doherty PC, Tonegawa S (1994) Altered peptidase and viral-specific T cell response in LMP 2 mutant mice. Immunity 1:533–541

Kalim KW, Basler M, Kirk CJ, Groettrup M (2012) Immunoproteasome subunit LMP7 deficiency and inhibition suppresses Th1 and Th17 but enhances regulatory T cell differentiation. J Immunol 189:4182–4193

Kincaid EZ, Che JW, York I, Escobar H, Reyes-Vargas E, Delgado JC, Welsh RM, Karow ML, Murphy AJ, Valenzuela DM, Yancopoulos GD, Rock KL (2012) Mice completely lacking immunoproteasomes show major changes in antigen presentation. Nat Immunol 13:129–135

Kincaid EZ, Murata S, Tanaka K, Rock KL (2016) Specialized proteasome subunits have an essential role in the thymic selection of CD8(+) T cells. Nat Immunol 17:938–945

Koerner J, Brunner T, Groettrup M (2017) Inhibition and deficiency of the immunoproteasome subunit LMP7 suppress the development and progression of colorectal carcinoma in mice. Oncotarget 8: 50873–50888

Koreth J, Kim HT, Lange PB, Bindra B, Reynolds CG, Chammas MJ, Armand P, Cutler CS, Ho VT, Glotzbecker B, Nikiforow S, Ritz J, Blazar BR, Soiffer RJ, Antin JH, Alyea EP 3rd (2015) A bortezomib-based regimen offers promising survival and graft-versus-host disease prophylaxis in myeloablative HLA-mismatched and unrelated donor transplantation: a phase II trial. Biol Blood Marrow Transplant 21:1907–1913

Koreth J, Kim HT, Lange PB, Poryanda SJ, Reynolds CG, Rai SC, Armand P, Cutler CS, Ho VT, Glotzbecker B, Yusuf R, Nikiforow S, Chen YB, Dey B, McMasters M, Ritz J, Blazar BR, Soiffer RJ, Antin JH, Alyea EP 3rd (2018) Bortezomib-based immunosuppression after reduced-intensity conditioning hematopoietic stem cell transplantation: randomized phase II results. Haematologica 103: 522–530

Koreth J, Stevenson KE, Kim HT, McDonough SM, Bindra B, Armand P, Ho VT, Cutler C, Blazar BR, Antin JH, Soiffer RJ, Ritz J, Alyea EP 3rd (2012) Bortezomib-based graft-versus-host disease prophylaxis in HLA-mismatched unrelated donor transplantation. J Clin Oncol 30:3202–3208

Kremer M, Henn A, Kolb C, Basler M, Moebius J, Guillaume B, Leist M, Van den Eynde BJ, Groettrup M (2010) Reduced immunoproteasome formation and accumulation of immunoproteasomal precursors in the brains of lymphocytic choriomeningitis virus-infected mice. J Immunol 185:5549–5560

Li J, Basler M, Alvarez G, Brunner T, Kirk CJ, Groettrup M (2018) Immunoproteasome inhibition prevents chronic antibody-mediated allograft rejection in renal transplantation. Kidney Int 93:670–680

Liu W, Ren HY, Dong YJ, Wang LH, Yin Y, Li Y, Qiu ZX, Cen XN, Shi YJ (2012) Bortezomib regulates the chemotactic characteristics of T cells through downregulation of CXCR3/CXCL9 expression and induction of apoptosis. Int J Hematol 96:764–772

Liu H, Wan C, Ding Y, Han R, He Y, Xiao J, Hao J (2017) PR-957, a selective inhibitor of immunoproteasome subunit low-MW polypeptide 7, attenuates experimental autoimmune neuritis by suppressing Th17 cell differentiation and regulating cytokine production. FASEB J 31(4):1756-1766.

Liu RT, Zhang P, Yang CL, Pang Y, Zhang M, Zhang N, Yue LT, Li XL, Li H, Duan RS (2017) ONX-0914, a selective inhibitor of immunoproteasome, ameliorates experimental autoimmune myasthenia gravis by modulating humoral response. J Neuroimmunol 311:71–78

Mishto M, Liepe J, Textoris-Taube K, Keller C, Henklein P, Weberruss M, Dahlmann B, Enenkel C, Voigt A, Kuckelkorn U, Stumpf MP, Kloetzel PM (2014) Proteasome isoforms exhibit only quantitative differences in cleavage and epitope generation. Eur J Immunol 44: 3508–3521

Muchamuel T, Basler M, Aujay MA, Suzuki E, Kalim KW, Lauer C, Sylvain C, Ring ER, Shields J, Jiang J, Shwonek P, Parlati F, Demo SD, Bennett MK, Kirk CJ, Groettrup M (2009) A selective inhibitor of the immunoproteasome subunit LMP7 blocks cytokine production and attenuates progression of experimental arthritis. Nat Med 15:781–787

Mundt S, Basler M, Buerger S, Engler H, Groettrup M (2016) Inhibiting the immunoproteasome exacerbates the pathogenesis of systemic Candida albicans infection in mice. Sci Rep 6:19434

Mundt S, Basler M, Sawitzki B, Groettrup M (2017) No prolongation of skin allograft survival by immunoproteasome inhibition in mice. Mol Immunol 88:32–37

Mundt S, Engelhardt B, Kirk CJ, Groettrup M, Basler M (2016) Inhibition and deficiency of the immunoproteasome subunit LMP7 attenuates LCMV-induced meningitis. Eur J Immunol 46:104–113

Nagayama Y, Nakahara M, Shimamura M, Horie I, Arima K, Abiru N (2012) Prophylactic and therapeutic efficacies of a selective inhibitor of the immunoproteasome for Hashimoto's thyroiditis, but not for Graves' hyperthyroidism, in mice. Clin Exp Immunol 168:268–273

Nencioni A, Garuti A, Schwarzenberg K, Cirmena G, Dal Bello G, Rocco I, Barbieri E, Brossart P, Patrone F, Ballestrero A (2006) Proteasome inhibitor-induced apoptosis in human monocyte-derived dendritic cells. Eur J Immunol 36:681–689

Neubert K, Meister S, Moser K, Weisel F, Maseda D, Amann K, Wiethe C, Winkler TH, Kalden JR, Manz RA, Voll RE (2008) The proteasome inhibitor bortezomib depletes plasma cells and protects mice with lupus-like disease from nephritis. Nat Med 14:748–755

Osterloh P, Linkemann K, Tenzer S, Rammensee HG, Radsak MP, Busch DH, Schild H (2006) Proteasomes shape the repertoire of T cells participating in antigen-specific immune responses. Proc Natl Acad Sci U S A 103:5042–5047

Pearl MH, Nayak AB, Ettenger RB, Puliyanda D, Palma Diaz MF, Zhang Q, Reed EF, Tsai EW (2016) Bortezomib may stabilize pediatric renal transplant recipients with antibody-mediated rejection. Pediatr Nephrol 31:1341–1348

Rock KL, Gramm C, Rothstein L, Clark K, Stein R, Dick L, Hwang D, Goldberg AL (1994) Inhibitors of the proteasome block the degradation of most cell proteins and the generation of peptides presented on MHC class I molecules. Cell 78:761–771

Santos RLA, Bai L, Singh PK, Murakami N, Fan H, Zhan W, Zhu Y, Jiang X, Zhang K, Assker JP, Nathan CF, Li H, Azzi J, Lin G (2017) Structure of human immunoproteasome with a reversible and noncompetitive inhibitor that selectively inhibits activated lymphocytes. Nat Commun 8:1692

Saric T, Beninga J, Graef CI, Akopian TN, Rock KL, Goldberg AL (2001) Major histocompatibility complex class I-presented antigenic peptides are degraded in cytosolic extracts primarily by thimet oligopeptidase. J Biol Chem 276:36474–36481

Shrikant P, Khoruts A, Mescher MF (1999) CTLA-4 blockade reverses CD8+ T cell tolerance to tumor by a CD4+ T cell- and IL-2-dependent mechanism. Immunity 11:483–493

Straube C, Wehner R, Wendisch M, Bornhauser M, Bachmann M, Rieber EP, Schmitz M (2007) Bortezomib significantly impairs the immunostimulatory capacity of human myeloid blood dendritic cells. Leukemia 21:1464–1471

Sula Karreci E, Fan H, Uehara M, Mihali AB, Singh PK, Kurdi AT, Solhjou Z, Riella LV, Ghobrial I, Laragione T, Routray S, Assaker JP, Wang R, Sukenick G, Shi L, Barrat FJ, Nathan CF, Lin G, Azzi J (2016) Brief treatment with a highly selective immunoproteasome inhibitor promotes long-term cardiac allograft acceptance in mice. Proc Natl Acad Sci U S A 113:E8425–E8432

Sun K, Welniak LA, Panoskaltsis-Mortari A, O'Shaughnessy MJ, Liu H, Barao I, Riordan W, Sitcheran R, Wysocki C, Serody JS, Blazar BR, Sayers TJ, Murphy WJ (2004) Inhibition of acute graft-versus-host disease with retention of graft-versus-tumor effects by the proteasome inhibitor bortezomib. Proc Natl Acad Sci U S A 101:8120–8125

Toes REM, Nussbaum AK, Degermann S, Schirle M, Emmerich NPN, Kraft M, Laplace C, Zwinderman A, Dick TP, Muller J, Schonfisch B, Schmid C, Fehling HJ, Stevanovic S, Rammensee HG, Schild H (2001) Discrete cleavage motifs of constitutive and immunoproteasomes revealed by quantitative analysis of cleavage products. J Exp Med 194:1–12

Treise I, Huber EM, Klein-Rodewald T, Heinemeyer W, Grassmann SA, Basler M, Adler T, Rathkolb B, Helming L, Andres C, Klaften M, Landbrecht C, Wieland T, Strom TM, McCoy KD, Macpherson AJ, Wolf E, Groettrup M, Ollert M, Neff F, Gailus-Durner V, Fuchs H, Hrabe de Angelis M, Groll M, Busch DH (2018) Defective immuno- and thymoproteasome assembly causes severe immunodeficiency. Sci Rep 8:5975

Trivedi HL, Terasaki PI, Feroz A, Everly MJ, Vanikar AV, Shankar V, Trivedi VB, Kaneku H, Idica AK, Modi PR, Khemchandani SI, Dave SD (2009) Abrogation of anti-HLA antibodies via proteasome inhibition. Transplantation 87:1555–1561

Vachharajani N, Joeris T, Luu M, Hartmann S, Pautz S, Jenike E, Pantazis G, Prinz I, Hofer MJ, Steinhoff U, Visekruna A (2017) Prevention of colitis-associated cancer by selective targeting of immunoproteasome subunit LMP7. Oncotarget 8:50447–50459

Vogelbacher R, Meister S, Guckel E, Starke C, Wittmann S, Stief A, Voll R, Daniel C, Hugo C (2010) Bortezomib and sirolimus inhibit the chronic active antibody-mediated rejection in experimental renal transplantation in the rat. Nephrol Dial Transplant 25:3764–3773

Walsh RC, Everly JJ, Brailey P, Rike AH, Arend LJ, Mogilishetty G, Govil A, Roy-Chaudhury P, Alloway RR, Woodle ES (2010) Proteasome inhibitor-based primary therapy for antibody-mediated renal allograft rejection. Transplantation 89:277–284

Xiao F, Lin X, Tian J, Wang X, Chen Q, Rui K, Ma J, Wang S, Wang Q, Wang X, Liu D, Sun L, Lu L (2017) Proteasome inhibition suppresses Th17 cell generation and ameliorates autoimmune development in experimental Sjogren's syndrome. Cell Mol Immunol

Zilberberg J, Matos J, Dziopa E, Dziopa L, Yang Z, Kirk CJ, Assefnia S, Korngold R (2015) Inhibition of the immunoproteasome subunit LMP7 with ONX 0914 ameliorates graft-versus-host disease in an MHC-matched minor histocompatibility antigen-disparate murine model. Biol Blood Marrow Transplant 21:1555–1564