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INVITED REVIEW

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Proteasome disorders and inborn errors of immunity

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Summary

Inborn errors of immunity (IEI) or primary immune deficiencies (PIDD) are caused by variants in genes encoding for molecules that are relevant to the innate or adaptive immune response. To date, defects in more than 450 different genes have been identified as causes of IEI, causing a constellation of heterogeneous clinical manifestations ranging from increased susceptibility to infection, to autoimmunity or autoinflammation. IEI that are mainly characterized by autoinflammation are broadly classified according to the inflammatory pathway that they predominantly perturb. Among autoinflammatory IEI are those characterized by the transcriptional upregulation of type I interferon genes and are referred to as interferonopathies. Within the spectrum of interferonopathies, genetic defects that affect the proteasome have been described to cause autoinflammatory disease and represent a growing area of investigation. This review is focused on describing the clinical, genetic, and molecular aspects of IEI associated with mutations that affect the proteasome and how the study of these diseases has contributed to delineate therapeutic interventions.

KEYWORDS
autoinflammatory diseases, interferonopathy, JAK inhibitors, PRAAS, proteasome

1 | INTRODUCTION

1.1 | Systemic autoinflammatory disorders

Inborn errors of immunity (IEI) that are mainly characterized by sterile autoinflammation are referred to as systemic autoinflammatory diseases (SAID). SAID are caused by mutations in different pathways involved in the innate immune response, rendering these to be constitutively active or stay aberrantly active once they have been triggered, leading to systemic autoinflammation.[1,2] Monogenic SAID were initially described in patients who presented with periodic fever syndromes. First identified was familial Mediterranean fever due to autosomal recessive (AR) mutations in *MEFV*, followed by autosomal dominant (AD) mutations in tumor necrosis factor receptor (TNFR, *TNFRSF1A*) causing TNFR-associated periodic fever syndrome (TRAPS). Subsequently, hyperimmunoglobulin D syndrome due to mevalonate kinase deficiency (*MVK*), and cryopyrin-associated periodic syndromes (CAPS) due to gain of function mutations in the NLRP3 inflammasome. Over the last 20 years, a growing number of genes have been uncovered to be underlying SAID, affecting different inflammatory pathways. Although molecular defects leading to SAID may disturb multiple inflammatory pathways; to facilitate understanding and treatment approaches, SAID can be classified according to the inflammatory pathway they predominantly disturb into: inflammasome-opathies, when they affect different types of inflammasomes; relopathies, when they mainly disturb NF-κB pathway and interferonopathies when they are predominantly underlined by an exacerbated type 1 interferon signaling. Molecular defects affecting proteasomes are mainly associated with increased type 1 interferon signaling and have therefore been classified under interferonopathies.

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1.2 | Monogenic interferonopathies

Type I interferons (IFN) are indispensable in antiviral responses; however different mechanisms can lead to sustained pathologic upregulation of type I interferons and cause chronic autoinflammation. SAID molecularly characterized by constitutively increased type I IFN are widely recognized as "interferonopathies." Genetic defects in the nucleic acid sensing pathways or ubiquitinated protein clearance can lead to pathologic upregulation of type I IFN and cause chronic autoinflammation with distinct, but sometimes overlapping clinical phenotypes.[2,3]

Aicardi Goutières is an early-onset neurologic disease caused by different mutations in the DNA and RNA sensing pathways. Clinically, it is characterized by a range of neurologic manifestations including brain calcifications, early-onset encephalopathy with cerebral atrophy and leukoencephalopathy. They can also have some autoimmune features and are widely characterized by an upregulation of type I IFN.[4,5] AD-GOF mutations in *TMEM173*, encoding stimulator of interferon genes (STING), a cytosolic foreign-DNA sensor that triggers an IRF3-dependent interferon response, causes STING-associated vasculopathy with onset in infancy (SAVI) that can present with chilblains, distal necrotizing vasculopathy, and pulmonary hypertension.[6] Although characterized by increased type I IFN signature, SAVI patients only respond partially to JAK inhibition, suggesting other inflammatory pathways contribute to autoinflammation. Recently, STING and C-GAS have been proposed as more precise therapeutic targets.[7,8]

Some monogenic forms of systemic lupus erythematosus (SLE) including those with mutation in *DNASEL1*, *DNASE1L3* are also underlined by increased type I IFNs.[9,10] Furthermore, SLE and other autoimmune diseases, which are widely considered to be polygenic, can also be accompanied by an increased type I IFN response. In these cases, the interferon signature can be related to underlying mechanisms (DNA/RNA signaling, ER stress) that could be targeted specifically to ameliorate disease. Included in this group of autoimmune disorders are non-monogenic forms of SLE and some patients with dermatomyositis, Sjögren syndrome, and arthritis.[11] In these diseases, current evidence suggests that the "interferon signature" may either be a primary driver of disease or a consequence of other disturbed mechanisms that results in induction of autoimmunity and autoinflammation, and dissecting the drivers of an increased type I IFN response can help guide therapeutic strategies.[12,13]

A third group of interferonopathies are those caused by genetic defects in molecules that participate in protein homeostasis, lead to activation of the unfolded protein response (UPR) and subsequent interferon-induced sterile inflammation. Pathogenic variants perturbing proteasome molecules collectively known as proteasome-associated autoinflammatory syndromes (PRAAS) result in proteasome deficiency and subsequent accumulation of ubiquitinated proteins. This pathologic build-up of proteins leads to UPR that induces the expression of interferon genes through different pathways. In addition to PRAAS, the UPR and interferon type I pathways are also up regulated in other protein trafficking IEI including TRAPS, due to intracellular accumulation of misfolded TNFR products. Another protein trafficking disorder recently associated with upregulation of type I IFN genes is COPA syndrome, caused by AD mutations in *COPA*, encoding for a subunit of COPI-complex involved in retrograde ER to Golgi transport, leading to increased ER stress and UPR. COPA is clinically distinct from other interferonopathies and is characterized by early-onset arthritis, pulmonary inflammation, hemoptysis, and variable renal involvement.[14–17] The role of interferons in the pathogenicity of COPA is still unclear and further investigation will determine if they represent a therapeutic target. Herein, we focus on interferonopathies caused by mutations that disturb proteasome function within the spectrum of these subgroup of interferonopathies that disturb proteostasis.

2 | THE UBIQUITIN PROTEASOME SYSTEM AND PROTEASOME ASSEMBLY

The ubiquitin proteasome system (UPS) involves the process by which proteins that are defective or no longer needed are targeted for degradation through ubiquitination of their C-terminal residues to be recognized and subsequently degraded by the proteasome. The UPS plays crucial roles in a variety of cellular processes including the cell cycle (degradation of cyclins), control of apoptosis (anti-apoptotic effects), DNA repair, transcription, signal transduction and antigen presentation.[18,19] The proteasome is the main cellular non-lysosomal proteolytic machinery in the cytosol and the nucleus of all eukaryotic cells, tasked with degrading polyubiquitinated proteins to maintain protein homeostasis. Mammalian tissues contain four subtypes of proteasomes: standard proteasomes with catalytic subunits β1, β2, and β5; immunoproteasomes where the catalytic β subunits are replaced by immuno-subunits that have specific catalytic activity, namely, β1i (LMP2, *PSMB9*), β2i (MECL1, *PSMB10*), and β5i (LMP7, *PSMB8*). Additionally, there are two intermediate proteasomes that consist of a combination of standard and immuno-subunits.[20] The immunoproteasome is present in interferon gamma stimulated cells and is constitutively expressed in most hematopoietic cells including dendritic cells and thymocytes. Furthermore, specific proteasome subtypes have been identified in cortical thymic epithelial cells and testes, known as thymoproteasomes and spermatoproteasomes, respectively.[20]

Proteasomes are the central protein structures of the ubiquitin proteasome system (UPS), they consist of a catalytic 20S core particle and a 19S regulator, together they form the 26S proteasomes. The 20S core particle of the 26S proteasome is a cylindrical structure composed by four stacked rings of α and β subunits.

The assembly of the proteasome is a coordinated process in which different subunits are sequentially incorporated, and this process is assisted by three main chaperone proteins, PAC1/2, PAC3/4 heterodimers, and proteasome maturation protein (POMP). The 20S core particle assembly is initiated in the endoplasmic reticulum (ER), where PAC1/PAC2 heterodimers initiate the formation of the α-ring[21] and PAC3/PAC4 heterodimers

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promote the incorporation of alpha subunits for α-ring formation and repair mismatch α subunit binding. POMP was first identified in yeast (Ump1)[22] and later confirmed in mammalian cells,[23] it assists proteasome assembly after the polymerization of the α-ring by interacting with it to facilitate the sequential incorporation of β subunits into proteasomes.[24] This is achieved by promoting the displacement of PAC3/4 heterodimer and initiating the incorporation of the β subunits into the core particle starting with β2 and subsequently other β subunits. β2 and β5 are known to establish direct contact with POMP and β1 and β7 are the last to be incorporated to complete the β-ring. POMP-deficient cells are unable to associate with β2 and fail to form a β-ring.[25] An α and a β-ring together with POMP and a PAC1/2 heterodimer form a half-proteasome or "half-mer" referred to as the 16S precursor. Although POMP has not been crystalized, it is predicted to dimerize to participate in the formation of a half-mer and further tetramerize when two half-mers join to form a mature 20S proteasome consisting of two outer α-rings and two inner β-rings[26,27] (Figure 1). Upon the completion of proteasome maturation, the catalytic β subunits release their pro-peptides to become active and subsequently degrade POMP and PAC1/2 completing the 20S proteasome assembly process. Thus, degradation of POMP signals for the successful completion of the proteasome biogenesis program.[23,26]

In the cytosol, the 20S catalytic subunit binds to a regulatory 19S subunit on one or both sides of the 20S subunit to form the 26S proteasome.[28–31] The 19S subunit has a base formed by 10 different subunits; 6 ATPase subunits (Rpt1-6 encoded by PSMC1-6) and 4 non-ATPase subunits (Rpn1/PSMD2, Rpn2/PSMD1, Rpn10/PSMD4, and Rpn13/ADRM1) through which it binds to the alpha rings and a lid that contains nine subunits (Rpn) namely, Rpn3 encoded by *PSMD3*, Rpn5/ *PSMD12*, Rpn6/*PSMD11*, Rpn7/*PSMD6*, Rpn8/*PSMD7*, Rpn9/*PSMD13*, Rpn12/*PSMD8*, Rpn15/*SEM1*, and the deubiquitinating enzyme Rpn11/*PSMD14* that regulates the entrance of polyubiquitinated proteins into the 20S proteasome.[32] The 20S proteasome can also bind other regulators including the interferon-inducible activator PA28 constituted by α and β or γ subunits (PA28αβ, PA28γ) or PA200. The incorporation of PA28 changes the conformation of the proteasome increasing its efficiency for proteolytic activity[33,34] (Figure 1). Catalytic β1, β2, and β5 subunits encoded by *PSMB6*, *PSMB7*, and *PSMB5*, confer the proteasome with caspase-like, trypsin-like, and chymotrypsin-like catalytic activity respectively, needed to process cellular proteins.

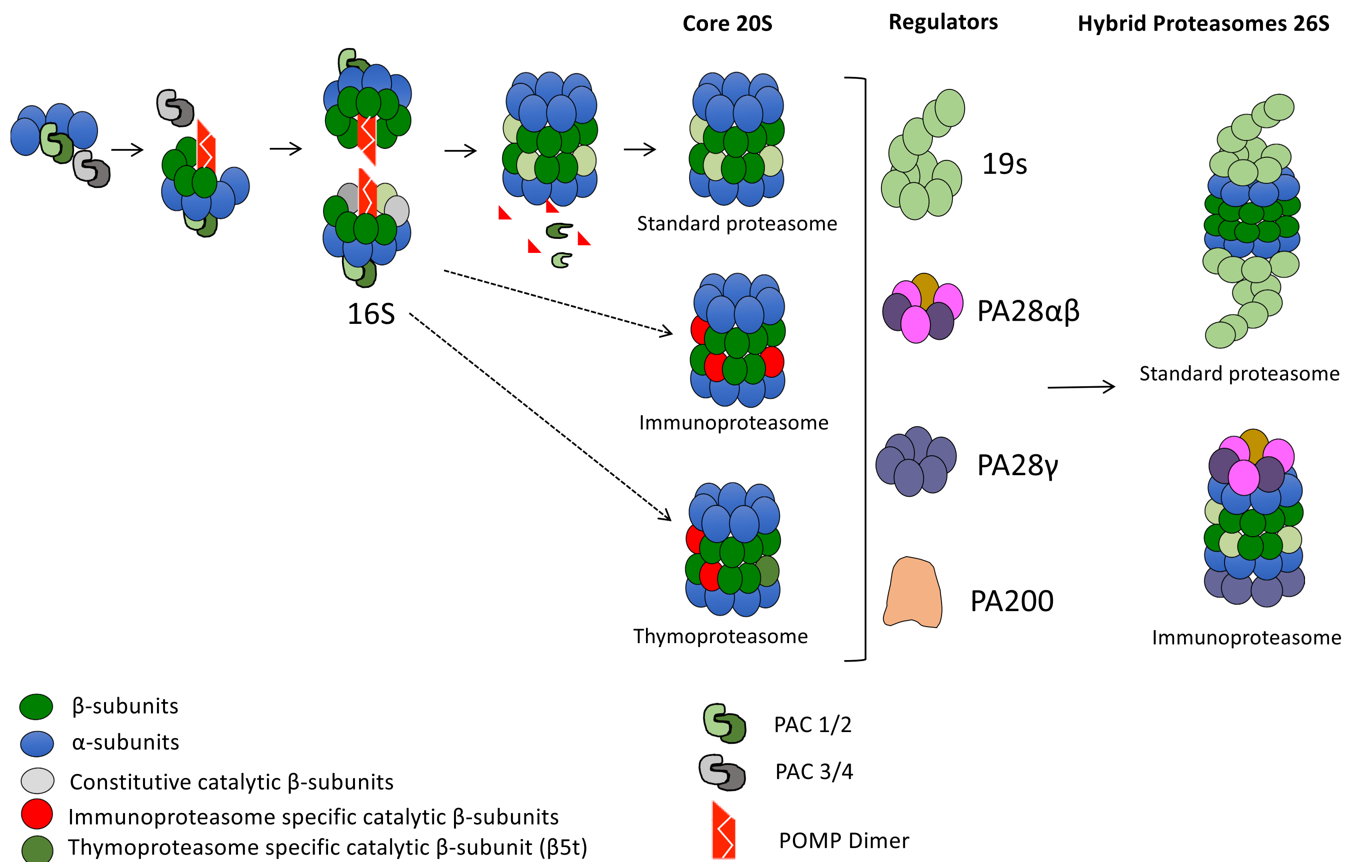

FIGURE 1 Diagram of proteasome assembly. Proteasome assembly is initiated by PAC1/2 and PAC3/4 that associate with α subunits for the assembly of the α-ring. Once the α-ring is assembled, POMP associates with it to start the oligomerization of the β-ring. POMP has been suggested to dimerize before it associates with the α-ring and further tetramerize when two 16S precursors come together to form the 20S core proteasome. Once the 20S proteasome is assembled, its catalytic subunits become active and degrade the remaining chaperones (PAC1/2 and POMP) to complete the assembly process. The 20S proteasome binds to different regulators, namely 19S, PA28, or PA200 to form the 26S proteasomes.

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Vertebrates encode for four additional catalytic β subunits; three of these are inducible by interferon-γ (β1i, β2i, and β5i) and β5t (encoded by *PSMB11*) is specific for thymic cortical epithelial cells and some thymic dendritic cells. These specific subunits will be selectively incorporated into the immunoproteasome and the thymoproteasome respectively.[35] Immune cells constitutively express immunoproteasomes (i20S) that will incorporate these specialized β1i (LMP2), β2i (MECL-1), and β5i (LMP7) catalytic subunits. Mouse and human class-I major histocompatibility (MHC-I or HL-A, -B, -C) molecules do not accept peptide ligands with acidic C-terminal anchor residues; unlike β1, β1i catalytic activity is able to generate peptides with hydrophobic C-terminal peptides that will be able to bind to class-I major histocompatibility (MHC-I) molecules and allow its surface expression.[36] In support of this model, immunoproteasome-deficient mice show a 50% reduction in MHC-I surface expression.[37] During immunological challenge, non-immune cells will be stimulated by cytokines including IFN-γ or tumor necrosis factor TNF-α, to induce the expression of i20S and enhance antigen presentation via MHC-I, allowing for the generation of an appropriate specific T-cell response with subsequent T-cell expansion and survival.[30,34,38] Beyond their role in MHC-I expression, immunoproteasomes are critical for several other processes including gene expression, signal transduction, and cell proliferation.[39] Immunoproteasomes participate in helper T-cell differentiation and survival of T cells in virus-infected mice as demonstrated by adoptive transfer experiments.[38] POMP is also upregulated by IFNs to enhance incorporation of LMP7 catalytic subunits and accelerate i20S assembly. The affinity of POMP to bind processed β5i is greater than its affinity for pro-β5i, favoring the formation of i20s during an immunologic challenge. In addition, the half-life of i20S (27 h) is considerably shorter than that of the standard proteasomes (8–12 days) allowing for a fast but transient and tightly regulated, MHC-I presentation and immunologic response during an immune challenge such as a viral infection.[28,33] POMP silencing results in decreased constitutive 20S and i20S proteasomes, reduced MHC-I antigen presentation and induction of apoptosis.[28,40,41]

A very specific chymotryptic *β* subunit (β5t) is expressed only in the thymus and at high levels in most cortical thymic cells to form thymoproteasomes. Thymoproteasomes are exclusively expressed in cortical thymic epithelial cells (cTECs). β5t is incorporated in thymic proteasomes together with β1i and β2i and confer the thymoproteasome with a unique endopeptidase activity to facilitate the production of specific peptides that bind MHC-I molecules with low affinity and favor positive selection of a repertoire of $CD8^+$ T cells.[42] Thymoproteasomes are required for positive $CD8^+$T-cell selection and mice that lack β5t subunit (*psmb*$^{-/-}$) have a substantial reduction in the development of mature $CD8^+$ T cells.[43–46] While β5t is expressed mainly in the thymic cortex, β5i expressing cells are distributed abundantly in both the thymic cortex and the medulla. In medullary thymic epithelial cells (mTECs), immunoproteasomes contribute to present self-antigens to establish self-tolerance in T cells. Mice lacking immunoproteasomes show reduced CD8 single-positive thymocytes and reduced MHC-I.[47] As a result of the differential expression of immunoproteasomes and thymoproteasomes in the different thymic compartments there is a wide array of peptides presented in the thymus and a reduced overlap between positive and negative selection that is expected to favor $CD8^+$ T-cell clonality.[48–50] As suggested by these experiments in mice, alterations in the incorporation β5i and β5t subunits into the proteasome in humans might result in aberrant T-cell development that could lead to immune dysregulation and autoimmune disease.[35,51]

3 | PROTEASOME-ASSOCIATED AUTOINFLAMMATORY DISORDERS

3.1 | Genetic and clinical aspects

Proteasomes play a critical role in cell viability and the regulation of multiple pathways, including cell cycle progression, cell signaling, immune response, and apoptosis. Imbalances in their regulation or function can be linked to disease. From a historical perspective, Nakajo[52] and Nishimura[53] contributed to the original clinical description of a syndrome in Japanese patients characterized by nodular erythema, elongated thickened fingers, loss of adipose tissue, joint contractures muscular atrophy, microcytic anemia and loss of adipose tissue referred to as Nakajo-Nishimura syndrome. Tanaka et al. and Garg et al. proposed a distinct clinical entity with the description of additional patients identified as JMP syndrome for joint contractures, muscular atrophy, microcytic anemia and panniculitis-induced lypodystrophy.[54] In 2010 Agarwal et al.[55] performed homozygosity mapping of patients described by Garg and identified c.224C>T (p.Thr75Met) mutation in *PSMB8* encoding for β5i subunit, associated with a decrease in chymotryptic-like activity. Torrelo et al.[56] proposed the acronym CANDLE (MIM: 177046) to describe patients with chronic atypical neutrophilic dermatosis, with lypodystrophy and elevated temperature and in 2012, Liu et al.[57] identified the same *PSMB8* AR T75M mutation in these patients. Subsequently, Brehm et al.[58] described that not only biallelic variants can lead to CANDLE, but also when monoallelic mutations in *PSMB8* are combined with deleterious variants in other proteasome subunits, including β7 (encoded by *PSMB4*; MIM: 602177), α3 (encoded by *PSMA3*), β1i (encoded by *PSMB9*, MIM 617591), β2i (*PSMB10*), this can lead to variable defects in proteasome assembly and maturation causing monogenic or digenic forms of CANDLE, respectively. In 2020 Sarrabay et al.[59] described a homozygous AR mutation in PSMB10 causing CANDLE. Collectively, autoinflammatory syndromes associated with proteasome mutations are referred to as proteasome-associated autoinflammatory syndromes (PRAAS).[60] Recently, mutations in *PSMA5* (encoding for α5) and *PSMC5* (encoding for Rpt6), which had not been previously associated with disease, were shown to cause CANDLE in association with the T75M variant in *PSMB8*, confirming an additional combination of digenic PRAAS.[61] Mutations in proteasome chaperones POMP and PAC2 (MIM: 613386) have also been identified within the spectrum of PRAAS; while compound heterozygous mutations in PAC2 cause classical

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AR CANDLE phenotype,[62] AD truncating mutations in POMP cause a distinct phenotype in which autoinflammation is accompanied by severe immune deficiency, delineating a unique disease within the PRAAS spectrum denominated POMP-related autoinflammation and immune dysregulation (PRAID).[58,62–64]

POMP is a widely expressed protein, required for both conventional and immunoproteasome assembly and, as specified above, it participates in multiple steps of proteasome maturation and is known to bind LMP7 (β5i) for its incorporation into the i20S.[28,29,43,58,65,66] Truncating mutations in the penultimate exon of *POMP* result in mRNA transcripts bearing premature termination codons (PTC) that escape nonsense-mediated mRNA decay (NMD). NMD is a conserved mechanism in which transcripts carrying PTC are eliminated to prevent the occurrence of truncated proteins with potential gain of function (GOF) or dominant-negative effects. Mutations identified in *POMP* result in the expression of a truncated protein that perturbs standard and immunoproteasome assembly by a dominant-negative mechanism. Like other forms of PRAAS, in PRAID, proteasome dysfunction leads to accumulation of ubiquitinated proteins and subsequent ER stress, increased unfolded protein response and upregulation of type I IFN-regulated genes. Patients present with neonatal-onset neutrophilic dermatosis, autoinflammation and increased autoantibody production as well as combined immunodeficiency.[64–66] Immunodeficiency distinguishes PRAID from other forms of PRAAS. Patient T cells are skewed toward a naïve $CD4^+$ phenotype and show impaired production of Th1 cytokines (IFN-γ, TNF-α, and IL-2) upon TCR stimulation. Detailed mechanisms underlying immunodeficiency in PRAID remain to be uncovered. We hypothesize that because there is a defect in a molecule that is essential for the incorporation of β subunits, immunoproteasomes, and thymoproteasomes would be less able to compensate with other proteasome subunits resulting an impaired immune response.[67–70] Our recent work demonstrated a reduced T-cell repertoire diversity in POMP patients, supporting the possibility of thymoproteasome impairment contributing to immunodeficiency and immune disregulation.[71] In line with a T-cell defect, patients suffer recurrent viral and bacterial infections and are susceptible to *Pneumocystis jirovecii* and mycobacteria. B cells are skewed toward a memory phenotype with increased circulating plasma cells and autoantibody production. The role of interferons in driving B-cell differentiation is well documented and may account for these findings.[72–75] In contrast to these truncating *POMP* variants, AR deletions in the 5′UTR of an alternative *POMP* transcript give rise to a longer-lived transcript that leads to a keratinization disorder of the skin (KLICK syndrome; MIM: 601952) with no inflammatory component.[76,77]

Currently only two forms of autosomal dominant proteasome IEI have been described. Interestingly, they both present with immunodeficiency in addition to other inflammatory features. In addition to PRAID, Kanazawa et al. recently described a heterozygous missense mutation (G156D) in *PSMB9* encoding for β1i, in two unrelated Japanese patients, impairing 20S proteasome assembly and catalytic activity. This mutation is predicted to disrupt the binding to other β subunits. Patients presented with severe CANDLE/PRAAS features, namely, neonatal-onset systemic inflammation with fever and elevated cytokines /Il-6, IL-18, and IP-10, skin rash, myositis liver dysfunction and basal ganglia calcification. In addition to this inflammatory phenotype, both patients suffered pulmonary hypertension and immunodeficiency which seem to be unique to this *PSMB9*-associated disease. Both patients had low IgG levels with low T and B cell numbers with low T-cell receptor recombination excision circles (TREC) and κ-deleting recombination excision circles (KREC). One of the individuals in this study presented with a profound NK cell defect and hemophagocytic lymphohistiocytosis and both patients acquired polyoma viruses (BK/JC). Like some patients with POMP deficiency, they did not present with lypodystrophy. While mice carrying this heterozygous variant demonstrated a clear thymic development defect, MHC-I processing activity was preserved by immunoproteasomes. In contrast to POMP deficiency, this heterozygous *PSMB9* mutation only seems to compromise the 20S proteasome while POMP deficiency compromises both, 20S and 26S proteasomes.[78] The association of immunodeficiency in *PSMB9* mutation seems to be exclusive to the G156D dominant-negative mutation, since immunodeficiency was not reported in a previously described patient with a *PSMB9* G165D variant inherited in conjunction with a P16Sfs*45 mutation in *PSMB4* causing digenic PRAAS.[60]

3.2 | Immunodeficiency in PRAAS

All forms of PRAAS can have reduced T-cell numbers but this generally not associated with severe immunodeficiency. In line with this observation, mice lacking β1i, β2i, β5i, and β5t show decreased $CD8^+$T-cell numbers and responses however they are not particularly susceptible to infections.[37,47,79,80] Intriguingly, immunodeficiency seems to be unique to the two previously described AD forms of PRAAS; those associated with truncating mutations in *POMP* and G156D *PSMB9* mutation.

As previously mentioned, patients with PRAID showed markedly decreased production of Th1 cytokines in T cells.[64] Immunoproteasomes have been shown to control cytokine production of TNF-α IL-23, IL-6, IFN-γ, and IL-2, as selective LMP7 inhibition reduces the production of these cytokines in human T cells.[81] Interestingly, neither $Lmp7^{-/-}$ nor $Lmp7^{-/-}Mecl1^{-/-}$ knockout mice have a defect in T-cell cytokine production. It has been proposed that this occurs because immunoproteasome-deficient mice are able to compensate by incorporating constitutive β5 subunit into the i20S to facilitate cytokine production.[68] Bearing in mind the critical role of POMP for β5 and LMP7 incorporation into the 20S and i20S proteasome, respectively,[24] it seems plausible that upon infection, PRAID patients are unable to compensate with alternative catalytic subunits and consequently exhibit the observed defect in T-cell cytokine production underlying a combined immunodeficient phenotype, in addition to a reduced $CD8^+$T-cell proportion. Cytokine production recovers after HSCT, in line with restored immunoproteasome function and assembly.[71] Increased infectious

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susceptibility could be further explained by a pan-proteasome defect in POMP-deficient patients affecting not only immunoproteasomes but also thymoproteasomes. Thymoproteasomes are mainly expressed in cTEC, where they are required for thymocyte selection and peripheral homeostasis of $CD8^{+}$T cells.[48] Thymoproteasome defects in mice cause severe immunodeficiency as they are required for positive selection of CD8+T cells.[82,83] In addition, thymoproteasomes confer a broad cytotoxic T-cell repertoire, and are required for an effective antiviral response.[84] As proof of concept to these observations, PRAID patients showed skewed T-cell repertoires in different T-cell subsets with increased clonality, likely contributing to immunodeficiency and immune dysregulation, respectively.[71]

In contrast to β2i/MECL-1 deficient mice, TUB6 mice carrying a heterozygous G170W point mutation in *PSMB10* (encoding for β2i) at the interface of its interaction with β1i (*PSMB9*), has a similar phenotype to *Psmb9*$^{G156D/+}$ mice, showing $T^{-}B^{-}NK^{-}$ severe combined immunodeficiency with systemic sterile inflammation. When TUB6 mice were crossed with MECL-$1^{-/-}$ deficient mice, they resembled the TUB6 mice.[83] Notably, the patient described with AR mutation in *PSMB10* at a different location, results in PRAAS without immunodeficiency.[59] As previously indicated, POMP is also critical in for this β subunit interaction and formation of the β-ring. Interestingly, individuals with heterozygous deletions that include *POMP* do not present with an autoinflammatory phenotype suggesting that only the presence of a truncated protein with a toxic dominant-negative effect can completely disrupt POMP function and cause disease.[64]

These patient descriptions and mouse models underscore the importance of β1i–β2i interaction for immune cell development and function. We speculate that mutations that impair β1i–β2i interaction by toxic dominant-negative mechanisms, underly immunodeficiency in PRAID and G156D *PSMB9* patients as well as in the TUB6 mice, in addition to a thymoproteasome and MHC-I defect. While G156D PSMB9 patients and TUB6 mice had low B cells, PRAID patients showed low B-cell numbers that were skewed toward a memory phenotype, accompanied by overt autoantibody production, the mechanism underlying these features remains to be uncovered.[64] Interestingly the degree of catalytic activity impairment is mild in some patients with the G156D PSMB9 mutation (very low in only one),[85] PSMB10 and POMP mutations, and its impairment does not seem to correlate with the immunodeficient phenotype suggesting other, unexplored roles for β1i and β2i subunits in immune cells.[59,71,78,85]

4 | PROTEASOME DEFECTS IN NEURO DEVELOPMENTAL DISORDERS

The ubiquitin proteasome system serves multiple roles in the central nervous system and disruption of proteostasis is clearly implicated in different forms of neurologic disease. Ubiquitin chain formation relies on the activity of different enzymatic ligases (E1, E2, E3) that catalyze the coordinated assembly of ubiquitin chains that target proteins for proteasomal degradation. Multiple genetic defects in this pathway have been identified in patients with neurodevelopmental disease and recent description of NDD associated with mutations in proteasome components have contributed to conceptualize the possibility of neuroinflammation contributing to NDD.[86] Initially, proteasome mutations leading to NDD were identified only in the 19S regulator.[87] The 19S regulator has six ATPase-associated subunits labeled PSMC1-6, these subunits are critical in the translocation of proteins from the intracellular compartment to the core 20S proteasome for degradation and variants in these particles have been identified to cause predominantly neurodevelopmental disorders. Within the 19S, Rpn5 encoded by *PSMD12*, facilitates deubiquitination of proteins for proteasomal processing. Haploinsufficiency of *PSMD12* was initially described as a NDD with ophthalmic abnormalities and dysmorphic features, with no autoinflammatory manifestations.[88–90] However, subsequent studies described a novel truncating variant in which inflammatory features were present clinically and an interferon signature was demonstrated in patient lymphocytes.[91] In addition to *PSMD12*, Ebstein et al.[92] described 23 unrelated individuals with an AD form of NDD due to mutations in *PSMC3* encoding for another 19S component, Rpt5.These variants led to altered dendrite development in mouse neuronal cultures and the phenotype was recapitulated by introducing these mutants in a fruit fly model. Despite the absence of autoinflammatory symptoms in these patients, they did observe proteasome dysfunction in patient T cells that correlated with an increased expression of type I interferons. In 2021, Ansar et al. described two Pakistani siblings, born to consanguineous parents, that presented with developmental delay, intellectual disability, short stature, mild deafness, and microcephaly, in which a homozygous variant in *PSMB1*, encoding for β6 subunit, was shown to disrupt 20S stability. The phenotype was recapitulated in zebrafish in which they introduced mutations and inserted oligos to decrease *Psmb1* expression, demonstrating *Psmb1* deficiency as the cause of this neurologic phenotype. Interestingly, the patients did not present with inflammatory features, presumably due to the preservation of immunoproteasome function.[93] To our knowledge, there are no other patients reported with *PSMB1*-related NDD, so it is unclear if the phenotype in humans is specific to this genotype or to the global deficiency of the protein. Given some similarities of PSMB1-deficient patients with other patients with mutations in 19S, a disruptive effect in the 20S/19S interaction has been speculated, but this remains to be experimentally evaluated.[93] Altogether, these findings suggest that the 19S regulator plays an important role in central nervous system development and that mutations affecting result mainly in NDD, with variable systemic inflammation.[92,94] The absence of systemic inflammatory features in patients with *PSMB1*-associated disease is intriguing and suggest there may be some compensation at the immunoproteasome level. Conversely, although some patients with mutations in 20S or proteasome chaperones may have some degree of cognitive impairment and show signs of neurologic inflammation including basal ganglia calcifications and aseptic meningitis, these features are not consistent among all

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PRAAS patients and in general, PRAAS patients do not meet NDD criteria and the molecular mechanisms underlying this phenotypic dichotomy remains unclear. Further studies are required to elucidate if tissue-specific inflammation in the SNC contributes to disease and the determinants for the presence or absence of systemic inflammatory features in NDD syndromes associated with proteasome deficiency. Proteasome proteins associated with disease and different clinical manifestations are schematized in Figure 2 and summarized in Table 1.

5 | ASSESSMENT OF PROTEASOME FUNCTION TO DEFINE PROTEASOME DYSFUNCTION

All forms of proteasome-associated autoinflammatory disorders described until now are defined by proteasome loss of function that can be evidenced by assessing proteasome assembly and its catalytic activity. Evaluating proteasome function and assembly is key to assessing the impact of possibly deleterious variants in proteasome subunits. Western blot using native polyacrylamide gel electrophoresis (PAGE) to preserve the protein structure and enzymatic activity is generally used to measure the abundance of individual proteasome subunits and proteasome assembly. Proteasome native complexes can be visualized by in-gel overlay assay by incubating native PAGE gels with suc-LLVY-AMC. Gels can then be transferred onto a membrane and probed with antibodies for the different proteasome components. To evaluate proteasome function, peptidase activity of each catalytic subunit must be assessed individually. This can be done incubating cell lysates with fluorogenic substrates in plates and measuring the fluorescence release overtime. Suc-LLVY-AMC, Bz-GGR-AMC, and Suc-LLE fluorogenic peptides are used to measure chymotrypsin, trypsin- and caspase-like proteasome activity, respectively.[60,71] Mutations in PRAAS affect different immune cells which are often available as this only requires a blood draw, T cells or B cells can then be expanded for the assessment of proteasome assembly and function. When patient samples are not available, mutations can be introduced into tagged proteins and assessed in similar fashion.[61] In any case, this approach is often laborious or requires large quantities of biologic material. To solve this problem and gain further insights into the effects of specific variants in protein interactions, Dafun et al. have recently reported on a combination of mass spectrometry-based methodologies to assess 20S proteasomes. Advantages of this methodology are that it is faster, requires lower amount of biologic material and can be used to assess proteasomes in different tissues which will probably accelerate further insights into tissue-specific consequences of proteasome mutations.[95]

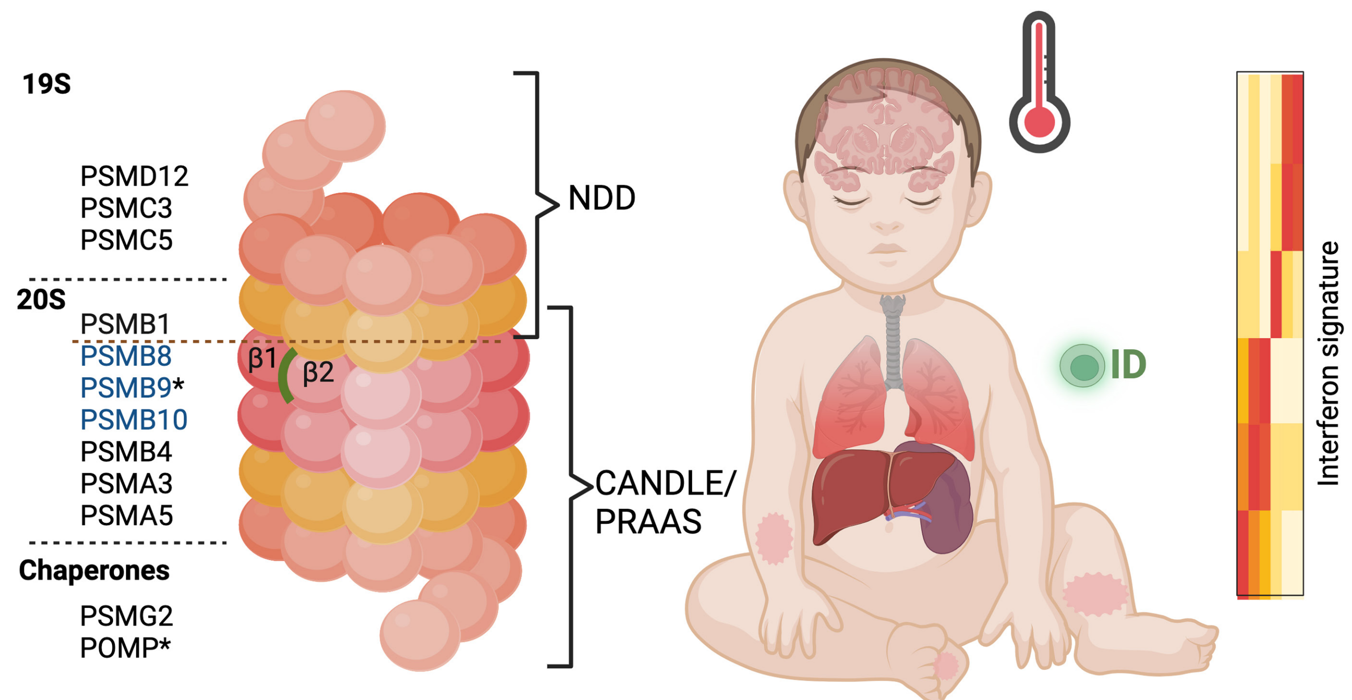

FIGURE 2 Clinical manifestations of proteasome-associated disorders. Mutations in *PSMD12*, *PSMC3*, *PSMC5* in the 19S are associated predominantly with neurodevelopmental disease (NDD). The only core proteasome subunit associated with NDD is caused by mutations in *PSMB1*. All genes associated with NDD are above the dotted brown line. Mutations of 20S core particle subunits and chaperones are associated with chronic neutrophilic dermatosis with lypodystrophy and elevated temperature (CANDLE), proteasome-associated autoinflammatory syndromes (PRASS). Green line between β1 and β1 denotes the notion of this interaction being relevant for the immune system and association with immunodeficiency (ID). Interferon signature scheme at the right denotes that almost all proteasome-associated disorders may present with an increased interferon signature despite not presenting with predominantly autoinflammatory features in the case of NDD. *Cause disease in autosomal dominant form whereas all others are AR.

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TABLE 1 Clinical phenotypes associated with mutations in different proteasome subunits.

Genetic disorder			Clinical manifestations			
Gene	Proteasome subunit	Mode of inheritance	Systemic	Hematologic	Skin and soft tissue	Lungs
PSMB8	B5i/LMP7	AR (homozygous, compound heterozygous or digenic with others[a])	Fever, failure to thrive	Microcytic anemia	Anular rash (neutrophilic dermatosis), lipodystrophy, panniculitis	BOOP -like in one patient, ILD
PSMB4	B7	AR (copound heterozygous or digenic with PSMB8)	Fever, failure to thrive	Anemia, thrombocytopenia	Rash, vasculitis, lypodystrophy	
PSMB9	B1i/LMP2	AD	Fever		Chilblain rash	Pulmonary infiltrates and pulmonary hypertension
PSMB10	B2i/MECL1	AR	Fever, failure to thrive	Microcytic anemia	Periorbital and hands feet anular rash (neutrophilic dermatosis)	ND
POMP	POMP	AD	Fever, failure to thrive	Anemia, thrombocytopenia	Neutrophilic dermatosis	Interstitial lung disease (1 patient)
PSMA3	α3	AR, digenic with *PSMB8*	Fever, failure to thrive	Anemia, thrombocytopenia, lukopenia	Anular rash (neutrophilic dermatosis), lipodystrophy	ND
PSMG2	PAC2	AR	Fever	Autoimmune hemolytic anemia	Edema of extremities, panniculitis, lypodystrophy	ND
PSMD12	Rpn5	AR	ND	ND	Urticarial skin rash	ND
PSMC3	Rpt5	AR	ND	ND	ND	ND

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Musculoskeletal	Liver/spleen	Neurological	Infections	Others	Laboratory
Muscle atrophy, arthritis/ arthralgia	Hepatomegaly, splenomegaly	Asceptic meningitis	Recurrent URT infections		Increased acute phase reactants (CRP, ESR), elevated LFT, anemia, hypertriglyceridemia, intermittently positive autoantibodies (ANA, ANCA)
			URT infections	Conjunctivitis episcleritis	Autoantibodies and low CD8 T cell counts and elevated ferritin in an AR patient
Myositis		Asceptic meningitis, seizures, calcification of basal ganglia	BK (/C viruses)		Increased acute phase reactants, lymphopenia, elevated transaminases, elevated CPK, increased protein in CSF, decreased immunoglobulins and low B cells low TREC and KREC in one patient, low CD8 T cells and absent NK cells in another patient
Long slender fingers	Hepatomegaly, splenomegaly	ND	ND		Increased acute phase reactants, hypertriglyceridemia
	Autoimmune hepatitis		Pneumocystis Jiroveci in 2 patients, mycobacterial infection in 1 patient, recurrent sepsis		CD4 naive T cell skewing, low CD8 T cells. Low B cells skewed to a memory phenotypes. Increased autoantibody titers
Arthritis, arthralgia, myositis	Hepatosplenomegaly	Asceptic meningitis	Recurrent otitis	Lymphadenopathy	Elevated acute phase reactants, elevated LFT
Muscle atrophy, myositis	Hepatosplenomegaly	Mild gross motor and speech delay, basal ganglia calcification	ND	Diffuse lymphadenopathy	Immunodeficiency workup unremarkable, positive Coombs
ND	ND	Intellectual disability, developmental delay	ND	Frontal bossing hypertelorism, nasal bridge depression. Uveitis in one patient	
ND	ND	Developmental delay, speech delay, intellectual disability, motor delay, MRI abnormalities, seizures in 2 patients	ND	Facial dysmorphias	

(Continues)

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TABLE 1 (Continued)

Genetic disorder			Clinical manifestations			
Gene	Proteasome subunit	Mode of inheritance	Systemic	Hematologic	Skin and soft tissue	Lungs
PSMA5	α5	AR Oligogenic with *PSMB8 and PSMC5*	Fever	Anemia, leucocytosis	Generalized nodular rash suggestive of erythema nodosum	ND
PSMC5	Rpt6	AR oligogenic with PSMA5 and PSMB8	Fever	Anemia, leucocytosis	Generalized nodular rash suggestive of erythema nodosum	ND
PSMB1	B6	AR	Short stature	ND	ND	ND

Abbreviations: LFT, Liver function tests; ND, Not described.
[a]PSMA3, PSMB4, PSMB8, PSMB9, PSMA5, PSMC5.

6 | MOLECULAR MECHANISMS LEADING TO INFLAMMATION IN PROTEASOME-ASSOCIATED DISEASES

The upregulation of type I interferons is a relevant biomarker in PRAAS and other inborn errors of proteasomes or "proteasomopathies" as they have been recently classified.[96] However, molecular mechanisms leading to inflammation beyond the upregulation of type I interferons, are not entirely understood, heterogenous and presumably disease- and tissue-specific. This is an area of ongoing investigation that will probably broaden the spectrum of therapeutic targets.

The main consequence of a disruption in the main proteolytic machinery inside cells is the accumulation of ubiquitinated proteins. To ensure protein homeostasis, the ER has an ER stress-associated degradation machinery (ERAD) that can redirect misfolded proteins in the ER lumen back to the cytosol for proteasomal degradation. When ERAD- derived proteins cannot be processed by the proteasome, they accumulate in the ER.[97] In a physiologic scenario, this toxic protein accumulation is perceived as danger signal by multiple sensors and complex signaling cascades collectively known as the unfolded protein response (UPR). Overall, these mechanisms are directed to restore proteostasis by stalling protein synthesis and providing the ER with chaperones for protein folding. However, when these mechanisms are chronically stimulated, they lead to sterile inflammation. As comprehensively reviewed by Pependorf et al., the UPR has been recognized as a major player in the pathogenesis of proteasome deficiency IEI.[87,96] The UPR is initiated through three ER transmembrane proteins: inositol requiring 1 (IRE1) that upregulates sXBP-1, PRK-like ER kinase (PERK) which phosphorylates eIF2α (peIF2α) and activating transcription factor 6 (ATF6).[98] An ER chaperone and ER stress sensor, immunoglobulin-binding protein (BiP, also known as GRP78) is bound to these ER membrane sensors and dissociates from them to activate UPR in turn, GRP78 is further induced by XBP1. In line with an accumulation of proteins in the ER, the upregulation of GRP78 and sXBP1 in the IRE1 pathway, ATF6 and PERK has been demonstrated in PRAAS.[64] Upon ER stress, the PERK pathway activates eIF2α, which leads to shortening the half-life of a subsets of proteins including IκBα and its increased turnover leads to nuclear translocation of NF-κB, contributing to inflammation. In line with these observations increased phosphorylation of eIF2α and upregulation of NF-κB pathway has also been demonstrated in PRAAS.[64] TCF11/Nrf1 is a membrane bound transcription factor that is up regulated during proteotoxic stress to induce compensatory transcriptional programs. However, under chronic stimulation it could contribute to inflammation by increasing mitophagy.[96,99] Proteasome dysfunction is also linked to a decrease in mTORC1 substrates that is thought to contribute to inflammation and metabolic dysregulation observed in PRAAS patients.[87,100] Despite a large body of work describing the concomitant upregulation of the UPR and type I interferons, the precise drivers of the interferon response in this context had remained largely unknown until pivotal work from Davidson et al. which provided robust evidence to link both pathways by identifying protein kinase R (PKR) as a key innate immune sensor of proteotoxic stress.[101] PKR is an intracellular double stranded (ds) mRNA sensor, which is known to upregulate the interferon response via TNF receptor-associated factor 3 (TRAF3) stimulating IRF3 and by promoting the phosphorylation of eIF2α upon viral stimulation.[102,103] At the same time, PKR

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Musculoskeletal	Liver/spleen	Neurological	Infections	Others	Laboratory
ND			ND		Elevated acute phase reactants (CRP, ESR), elevated LDH
ND			ND		Elevated acute phase reactants (CRP, ESR), elevated LDH
ND	ND	Microcephaly, intellectual disability, developmental delay, hypotonia, aggressive behavior, mild deafness			

can upregulate NF-κB activity by directly interacting with TRAF2 and TRAF5.[104] The key role of PKR as a sensor of protein accumulation was demonstrated by studying PKR deficient mice, who failed to mount an interferon and NF-κB-dependent inflammatory response upon proteasome inhibition. Moreover, they identified misfolded IL-24 in the cytosol as the driver of this response and showed that mice lacking IL-24 resembled those lacking PKR after proteasome inhibition. Furthermore, treatment with PKR inhibitor, C16 was able to dampen the interferon response in cells of patients with PRAAS and neuroinflammation in a mouse model for Rpt5-related NDD.[92,101] Importantly, PKR driven inflammation seems to be exclusive to PRAAS, as C16 inhibition was not able to reduce interferon signaling in samples derived from patients with SAVI.[101] The participation of PKR in other forms of protein trafficking disorders remains to be studied. Interestingly, elevation of IL-24 is described for several autoimmune disorders including SLE, rheumatoid arthritis and psoriasis, some of which can also have an upregulation of type I interferons.[105] Davidson's work provides critical clues to link these two observations and provides molecular evidence to consider IL-24 as a potential therapeutic target. Pathways leading to inflammation in proteasome-associated disorders are schematized in Figure 3.

Inflammatory manifestations may be tissue-specific, relying on the disruption of specific proteasome subunits. Lypodystrophy is described in most patients with PRAAS, but some patients with variants in *POMP* and *PSMB9* may be spared from this clinical feature. This clinical observation may be attributable to a differential role of proteasome subunits in different tissues. Arimochi et al.[106] showed that Psmb8 (−/−) mice had slower weight gain underlined by a defect in adipocyte precursors development and maturation. In contrast, Willemsen et al.[107] studied brown pre-adipocytes and showed that *PSMB4*, and not *PSMB8*, is required for adipogenesis, and that the loss of *PSMB4* is associated with ATF3-dependent inflammation. This research highlights the proteasome's role in tissue-specific inflammation and the influence of specific subunits on the development of a particular tissue, supporting the notion that clinical manifestations in proteasome can arise from systemic or tissue-specific inflammation, as well as due to the proteasomes' roles in tissue development and differentiation.

7 | PROTEASOME DYSFUNCTION IN AUTOIMMUNE DISEASE

The proteasome has a central role in apoptosis and immune responses. It has therefore been linked to the pathogenesis of autoimmune diseases such as SLE, autoimmune myositis, and Sjögren syndrome, all of which have also been related to an increased interferon signature as a biomarker of disease and response to therapy.[108–113] Serum levels of IFNα are increased in SLE patients and it associates with disease severity and organ involvement, IFNα may contribute to autoimmunity by induction of auto-reactive lymphocytes, promoting long-term antibody responses and priming myeloid cells.[114] Expression of constitutive and inducible proteasome subunits has been investigated in systemic autoimmune diseases including inflammatory myositis and Sjögren syndrome. The upregulation of specific subunits in some of these diseases is suggestive of prominent role of the proteasome in their pathogenicity.[115,116] However, it is unclear if these findings are a consequence a primary dysfunction of the proteasome or a response

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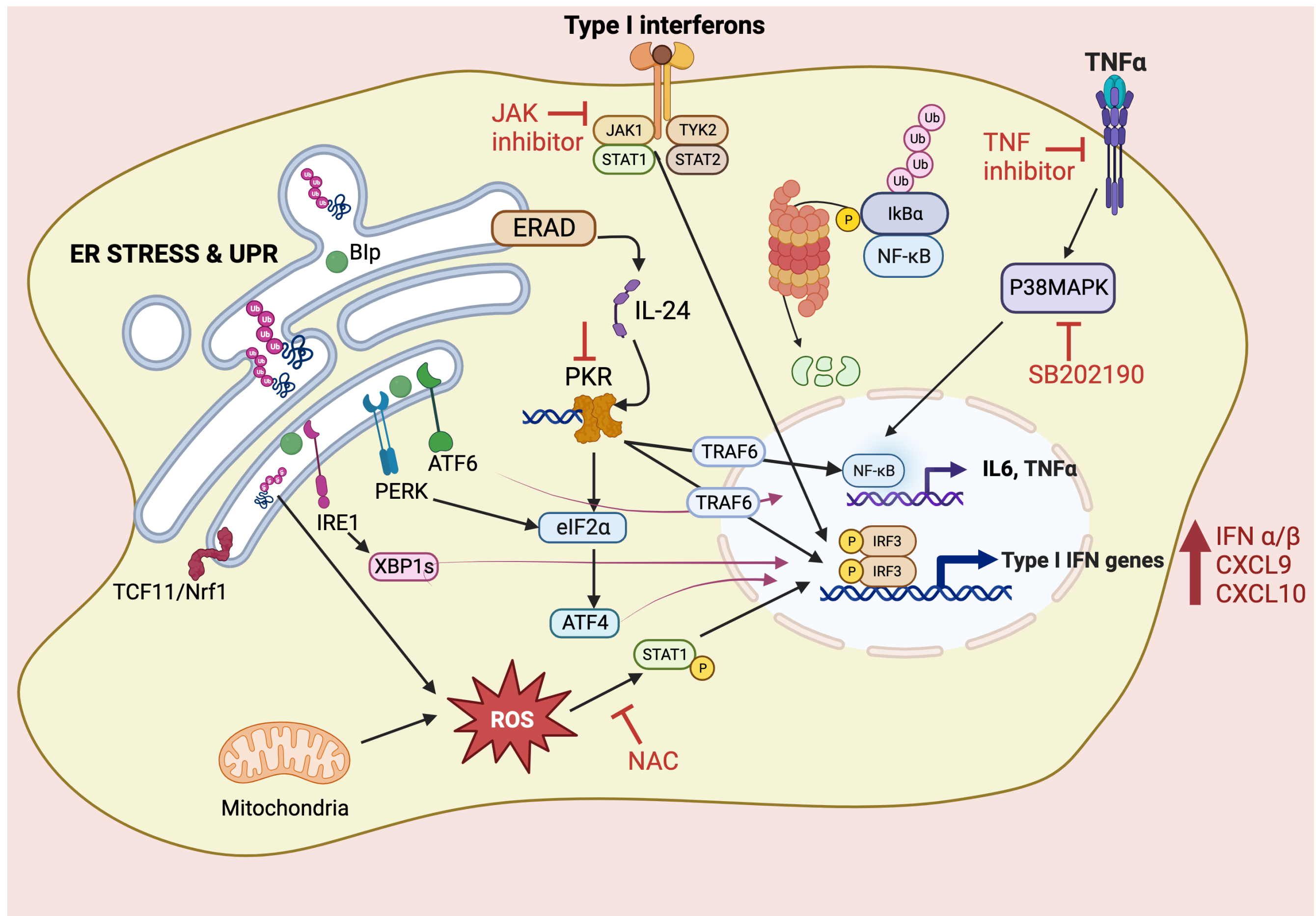

FIGURE 3 Pathways leading to inflammation. Schematic representation of an innate immune cell in which the endoplasmic reticulum (ER) stress and subsequent activation of unfolded protein response (UPR) through IRE1, PERK, and ATF6 pathways contribute to inflammation and interferon response. Protein Kinase R (PKR) is depicted as an important proteotoxic sensor by recognizing ubiquitinated IL-24 derived from ERAD. The contribution of proteasome dysfunction and TNF-α in dysregulating NF-κB and contributing to inflammation is also schematized. Possible treatments are represented in red as follows: JAK inhibitors, SB202190 inhibiting phosphorylated p38MAPK, and N-acetylcysteine (NAC). This figure is based in part on a figure previously published by Honda-Ozaki et al.[129]

to other disturbed underlying mechanisms including autophagy, dysregulated RNA and DNA binding receptors and chronic inflammation leading to the activation and/or saturation of the UPS.[109] Further investigation is needed to define these pathogenic pathways and elucidate novel drug targets.

Proteasome inhibitors have been widely studied for the treatment of multiple myeloma, a malignant B cell disorder in which there is an increased monoclonal population of plasma cells.[117] Bortezomib is a β5/β5i and β1/β1i selective immunoproteasome inhibitor that effectively targets plasma cells in multiple myeloma. Observations derived from patients with concomitant multiple myeloma and SLE, evidenced substantial improvement in SLE disease activity and decrease in autoantibody titers.[118] Specific β5i inhibition is an effective strategy to modulate these processes in inflamed tissues, in which immunoproteasomes are up regulated, while preserving the standard proteasome function for housekeeping homeostasis in other tissues. Proteasome inhibition not only targets plasma cells and inhibits autoantibody production but also reduces cytokine production by inhibiting NF-κB activation and presumably also through NF-κB independent pathways[119] and therefore reduces inflammation in general. Downregulation of cytokines such as IL-23 and IL-17 may also contribute to decrease Th17 differentiation, which is well established in the pathogenicity of autoimmune diseases. Recent research in mouse models and clinical trials has shown promising results with the use of proteasome inhibitors in SLE and other autoimmune diseases including rheumatoid arthritis, thyroiditis, and multiple sclerosis models.[120–122]

Finally, both autophagy and UPS dysfunction have been linked to neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington disease in which a decreased proteasome activity has been proposed as contributing mechanism to aberrant protein aggregation. There is currently no treatment available for these neurodegenerative diseases and further understanding of the UPS may contribute to the development of novel therapeutic strategies.[123]

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8 | TREATMENT FOR INBORN ERRORS OF IMMUNITY ASSOCIATED TO PROTEASOME DEFECTS

All forms of PRAAS are characterized by a markedly increased type I interferon response that can be modulated with JAK inhibitors to ameliorate autoinflammatory features and reducing steroid dependance.[7,124,125] JAK inhibitors differentially inhibit JAK1, JAK2, and JAK3.[126] PRAAS patients have been most often treated with Baricitinib a JAK1/2 inhibitor and this is the main recommended treatment strategy.[7,125,127,128]

The upregulation of type I interferons is an excellent biomarker for proteasome-associated IEI. However, as described above, other mechanisms upstream or in parallel to interferons may contribute to inflammation. Thus, patients may still suffer from inflammation even after type I interferon blocking. In line with these thoughts, JAK inhibition is effective to control inflammatory manifestations, but it is not completely curative in all PRAAS patients, and complementary or alternative therapies may be required.[7] Furthermore, the use of JAK inhibitors is limited in patients that present with prominent combined immune deficiency including patients with defects in POMP and PSMB9, for which hematopoietic stem cell transplant (HSCT) has shown to be curative.[71,85]

Kataoka et al. describe a patient with the *PSMB9* G156D mutation who responded to tofacitinib. He subsequently received a reduced intensity conditioning (RIC) regimen that included fludarabine, melphalan, and total body irradiation and underwent HSCT from a 7/8 unrelated cord blood. In this case, authors do not describe an increase in infections attributable to JAK inhibition and it was effective as a bridging therapy.[85] Two patients with POMP mutations received 10/10 matched unrelated donor HSCT using RIC regimen with fludarabine, melphalan, anti-thymocyte globulin, rituximab, and total lymphoid irradiation. They were described to be asymptomatic with a 100% donor chimerism after 3 years of follow-up.[71] Remarkably, HSCT was sufficient to rescue physiologic $CD8^+$ T-cell proportions in POMP patients, underscoring the role of donor dendritic cells that repopulate the thymus after HSCT in promoting $CD8^+$ T-cell differentiation. Similarly, Verhoeven et al. report on a patient with compound heterozygous mutations in *PSMB4* who received HSCT after RIC. Although he had good lymphoid lineage chimerism, he presented declining myeloid chimerism correlating with recurrence of autoinflammation and cutaneous vasculitis. He subsequently received a second HSCT with myeloablative conditioning that resulted in full donor chimerism, and recovery of most symptoms. Unlike patients with mutations in *POMP* and *PSMB9*, this patient presented with progressing lypodystrophy even after immune reconstitution.[129] This observation highlights the importance of PSMB4 in adipose tissue as previously suggested.[107]

Overall, HSCT appears as an efficient strategy to restore proteasomes, achieving protein homeostasis and control of interferon response that correlates with clinical improvement. Importantly, despite the ubiquitous expression of PSMB9 and POMP, the recovery of autoinflammatory/autoimmune phenotype after immune reconstitution in these patients strongly suggests that their clinical phenotype is mostly driven by proteasome defects in hematopoietic cells.

Cellular and animal models have recently contributed to improve our understanding of specific proteasome disorders and propose new or adjuvant therapies. Honda-Ozaki et al. developed patient-derived induced pluripotent stem cells and demonstrated that they had a reactive oxygen species (ROS)-mediated inflammatory signature at a steady state and that this signature increased significantly with stimulation. Using this model, they confirmed the upregulation of the interferon-JAK/STAT pathway in derived monocytes and identified hyperactivity of the TNF-α-p38-MAPK and increased mitochondrial oxidative stress as additional contributors to inflammation. Pan-JAK inhibitors, p38 MAPK inhibitor, and antioxidants ameliorated the inflammatory phenotype.[130,131] The establishment of this model was key to the identification of antioxidants as potential treatment and will likely contribute to identifying additional therapeutic compounds for PRAAS. Mouse models have also been instrumental in identifying therapeutic targets. Sasaki et al. used a PSMB8 knock-in model to uncover the CXCR3 pathway as novel molecular target in PRAAS. upregulation of the CXCL9/CXXL10 receptor, pathway.[132] As described above, the work of Davidson et. al. has been crucial to identify PKR driven by IL-24 as key and potentially targetable inflammatory drivers.[101] Inflammatory pathways and possible therapeutic targets are depicted in Figure 3.

9 | CONCLUSION

Inborn errors of immunity associated with pathogenic mutations of proteasome subunits are a growing area of research. Distinct phenotypes and variable responses to JAK inhibitors highlight the contribution of multiple pathways in driving inflammation. The few reported cases treated with HSCT highlight the importance of the immune system in driving inflammation. However, the role of immune-mediated inflammation disorders of the proteasome that manifest mainly as NDD is still unclear. The study of individual patients with proteasome-associated disorders have been paramount to uncover the role of specific pathways and molecules driving inflammation in these disorders, contributing to apply targeted therapeutic treatments. Although proteasome IEI can be clustered under a common umbrella, proteasome deficiency syndromes present with a heterogenous spectrum of inflammatory manifestations and advancing investigation into the tissue-specific roles of each of the proteasome subunits will likely contribute to understand clinical heterogeneity. Finally, the UPR appears as the main driver of inflammation in proteasome-associated interferonopathies and further studies to advance understanding of how UPR results in inflammation will likely contribute to uncover new therapeutic targets to improve overall outcomes in these patients.

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AUTHOR CONTRIBUTIONS

CP conceived, wrote the manuscript, and created the figures for this manuscript.

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CONFLICT OF INTEREST STATEMENT

The author has no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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