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Pathogenic Insights from Genetic Causes of Autoinflammatory Inflammasomopathies and Interferonopathies

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Abstract

A number of systemic autoinflammatory diseases (SAIDs) arise from gain-of-function mutations in genes encoding IL-1 activating inflammasomes and cytoplasmic nucleic acid sensors including the receptor and sensor STING and result in increased IL-1 and Type-I interferon (IFN) production respectively. Blocking these pathways in human diseases has provided proof-of-concept confirming the prominent roles of these cytokines in disease pathogenesis. Recent insights into the multilayered regulation of these sensor pathways and insights into their role in amplifying the disease pathogenesis of monogenic and complex genetic diseases spurred new drug development. This review provides insights into the pathogenesis and genetic causes of these "prototypic" diseases caused by gain-of function mutations in IL-1 activating inflammasomes (inflammasomopathies) and in interferon-activating pathways (interferonopathies) including SAVI (STING-associated vasculopathy with onset in infancy), AGS (Aicardi-Goutières Syndrome) and proteasome associated autoinflammatory syndromes (PRAAS) that link activation of the viral sensors STING, "self" nucleic acid metabolism and the ubiquitin-proteasome-system to "Type-I IFN production" and human diseases. Clinical responses and biomarker changes to JAK inhibitors confirm a role of IFNs and a growing number of diseases with "interferon signatures" unveil extensive crosstalk between major inflammatory pathways. Understanding these interactions promises new tools in tackling the significant clinical challenges in treating patients with these conditions.

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Keywords

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This review summarizes the genetic causes, pathomechanisms and clinical disease manifestations of systemic autoinflammatory diseases (SAIDs) caused by inflammasome and viral sensing pathway dysregulation. The discovery of the genetic causes provided key insights into disease pathogenesis and treatment and linked intracellular germline-encoded pattern recognition receptor pathways with the activation of major proinflammatory cytokines that lead to the identification of novel treatment targets.

Inflammasomes are cytosolic multiprotein oligomers that sense microbial or danger signals and induce IL-1 and IL-18 activation and/or cell death. Gain-of-function (GOF) mutations in four inflammasome-encoding genes cause inflammasomopathies that all enhance the assembly of IL-1 activating inflammasomes[1, 2]. Most of those conditions respond to treatment with IL-1 inhibitors including specific IL-1β blocking antibodies, thus confirming their predominant pathogenic link to inflammasome mediated IL-1β activation[3, 4]. However, clinical heterogeneity points to disease or inflammasome-specific differences in organ susceptibility to inflammation and organ damage that have not been fully explored or resolved.

On the other hand, autoinflammatory Type I interferonopathies comprise an expanding group of autoinflammatory diseases caused by mutations in the Type I interferon (IFN-I) axis[5–8], that present with an enhanced interferon response gene signature (IRGS) in blood cells and a characteristic set of clinical and laboratory features[9]. The response to treatment with JAK inhibitors that can reduce interferon (IFN) signaling[10–12] has been used to "validate" a role for IFN-I in these diseases. However, the inflammatory targets of JAK inhibitors are diverse and clinical validation exclusively targeting IFN-I signaling have not been conducted. As the downstream inflammatory pathways in the diseases termed interferonopathies can be complex, a systematic evaluation of the contribution of IFN to disease pathogenesis is critical.

Although the genetic causes and targeted treatment for the two disease groups differ, all patients present with systemic inflammation (elevation of acute phase reactants and in many instances rashes) and making a clinical diagnosis particularly early in the course of the disease challenging. However, hematologic changes during disease flares differ in IL-1 mediated compared to IFN mediated diseases, with increase in leukocyte and thrombocyte counts in IL-1 mediated disease flares and with decreases in absolute lymphocyte count and a rise in the IRGS in the interferonopathies (Table 1). In fact, the overlapping and differing hematologic and clinical features can aid in making a clinical diagnosis before genetic work up is completed and may allow for swift initiation of treatment.

However, differences in clinical disease characteristics, complex dysregulation of multiple inflammatory pathways recent data on upregulation of IL-1 mediated pathways by IFN-

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I, point to extensive crosstalk in responding to intracellular stress and in coordinating inflammatory signaling pathways.

INFLAMMASOMOPATHIES AND INFLAMMASOME MEDIATED AUTOINFLAMMATORY DISEASES

Familial Mediterranean fever (FMF) was the first autoinflammatory disease genetically described. Its discovery led to the concept of innate immune dysregulation as pathogenic mechanism for “periodic fever syndromes” and resulted in the separation of autoinflammatory diseases caused by predominantly innate immune dysregulation and autoimmune diseases with predominantly adaptive immune dysregulation. In the pre-WES (whole exome sequencing) era, disease-causing mutations in the gene *MEFV,* which encodes the protein pyrin, were first identified from a 115-kb familial Mediterranean fever candidate interval on chromosome 16p by positional cloning, in 1997[13, 14]. Similarly, autosomal dominant missense mutations in *NLRP3* were identified in families with familial cold autoinflammatory syndrome (FCAS) in 2001[15]. These discoveries preceded the description of the paradigm shifting concept of the IL-1 activating NLRP1 inflammasome by Jürg Tschopp and colleagues in 2002[16]. Within 20 years using data mining of homologous proteins, a total of 6 inflammasomes were molecularly characterized. Autoactivating mutations in 4 of these inflammasomes, *NLRP1, NLRP3, NLRC4 and MEFV/*Pyrin cause monogenic human autoinflammatory diseases. A list of different pathogen-associated molecular patterns (PAMPs) and/or danger associated molecular patterns (DAMPs) that are known to activate these various inflammasomes are provided in (Fig 1). Molecular mechanisms leading to AIM2 and to CASP4/5 as well as to the non-canonical inflammasome activation have been characterized, but yet monogenic diseases caused by mutations in these genes have not been identified. [1, 2, 4]

The mechanisms of inflammasome activation and regulation are subject to ongoing research but share common principles and were refined by recent cryo-EM studies of the NLRP3 and NLRC4 inflammasomes, which have provided novel insights into inflammasome activation[17–19]. Recognition of an inflammasome activating PAMP/DAMP triggers a conformational change and oligomerization of an inflammasome receptor[1, 2, 17–19] (Fig 2). The oligomerized pyrin domains (PYDs) or caspase activation and recruitment domains (CARDs) then recruit apoptosis-associated speck-like protein containing a card (ASC), which polymerizes to form large protein aggregates termed ASC “specks”[20]. Pro-caspase-1 is recruited to the ASC specks via CARD-CARD interaction and is activated[21]. Active caspase-1 cleaves pro-IL1, pro-IL18 and gasdermin D into active moieties[22]. These studies revealed a sensitive system where small amounts of PAMP/DAMP propagate a rapidly escalating response via the formation of filaments and specks. Most inflammasomes with the exception of AIM2 (Fig 1), have regulatory autoinhibitory domains, and ligand binding relieves an autoinhibitory conformation to allow activation (for example NLRP3, NLRC4 activation shown in Fig 2A&B)[17–19]. In the case of NLRP1, the autoinhibitory domain needs to be degraded to trigger inflammasome activation, and most of the disease-causing mutations are located in the autoinhibitory domains[23, 24] (Fig 2C).

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NLRP1 inflammasome – a “booby trap” for pathogen lethal factors

NLRP1 was the first molecularly characterized inflammasome. It is the only inflammasome receptor with a FIIND (function-to-find) domain and is activated by bacterial lethal factors. Posttranslational autoproteolysis within the FIIND domain (between residue p.F1212 and p.S1213 for humans) cleaves the protein into N- and C-terminal fragments that remain noncovalently attached in an autoinhibited state (Fig 2). Degradation of the N-terminal fragment triggered by bacterial lethal factors (including cleavage by *Bacillus anthracis* lethal factor protease, or ubiquitination by *Shigella flexneri* effector IpaH7.8) frees the C-terminal fragment and allows oligomerization and activation[23, 24]. These studies revealed an elegant mechanism of host defense. While many pathogens target degradation of host defense proteins to improve their survival, degradation of the “NLRP1 N-terminal fragment” triggers NLRP1 inflammasome activation and decreases pathogen survival, which has aptly been characterized as “booby trap”[25]. Based on this model, the N-terminal fragment might interact with the C-terminal fragment to suppress the activation of the latter (Fig 2). Indeed, almost all current NLRP1 autoinflammatory mutations lie in the N-terminus before the cleavage site at p.F1212-p.S1213[26–29]. The only exception is the mutation at residue p.P1214, which is located right after the cleavage site and might in fact also be crucial for the interaction with the N-terminal fragment for autoinhibition.

Autosomal dominant GOF mutations in the PYD domain of *NLRP1,* located in chromosome 17p13.2, cause the pre-cancerous conditions, multiple self-healing palmoplantar carcinoma (MSPC)[26] and familial keratosis lichenoides chronica (FKLC)[27]; and a missense mutation, p.M77T, causes inherited corneal intraepithelial dyskeratosis *without* systemic inflammation (Mendelian Inheritance in Man number (MIM#) 615225, www.omim.org)[27, 30]. Furthermore, single nucleotide polymorphisms (SNPs) in *NLRP1* have been associated with diseases including vitiligo and have been termed vitiligo-associated multiple autoimmune disease susceptibility 1 (VAMAS1)[31]. Similarly, an autosomal recessive mutation between the NACHT and leucine-rich repeat (LRR) domain, p.T755N, causes congenital juvenile recurrent respiratory papillomatosis (JRRP, MIM# 618803), which is thought to be caused by infections with human papilloma virus HPV-6 or −11 and presents without systemic inflammation[29]. These diseases point to a potential role of *NLRP1* not only in inflammation but also in keratinocyte, melanocyte and epithelial cell differentiation[32,33] and may provide insights in how viral infections affect and modify keratinocyte and epithelial cell differentiation[34]. In contrast, recessive GOF mutations between the NACHT and the FIIND domain or an autosomal dominant mutation at the autolytic cleavage domain of FIIND, cause NLRP1-associated autoinflammation with arthritis and dyskeratosis (NAIAD/AIADK, MIM# 617388) that clinically presents with systemic inflammation that responds to IL-1 blockade[28].

NLRP3 inflammasome – the frontrunner of inflammasome biology

The NLRP3 inflammasome was the first cytoplasmic sensor discovered to be linked to IL-1 production in human disease and to establish a role for disease[15, 35–41]. Familial cold-induced inflammatory syndrome-1 (FCAS1, MIM# 120200) caused by autosomal GOF mutations in *NLRP3* was first identified in 2000/2001 and now includes the disease spectrum of Muckle-Wells syndrome (MWS; MIM# 191900), and the most severe

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phenotype of neonatal-onset multisystem inflammatory disease (NOMID), also known as Chronic infantile neurologic cutaneous and articular (CINCA) syndrome, (MIM# 607115)[15, 35–41]. Clinical features that are unique to the cryopyrinopathies include a neutrophilic urticaria presented with the systemic inflammatory attacks (induced in FCAS and chronic in MWS and NOMID) and the early development of sensorineural hearing loss and neutrophilic aseptic meningitis in the more severe disease spectrum. These pathologies provide early clues to a diagnosis. Interestingly, DFNA34, Deafness, autosomal dominant 34 is caused by a heterozygous mutation, p.R920Q, in *NLRP3* (canonical transcript NM_00107982)[42], and KEFH, Keratoendothelitis fugax hereditaria is caused by a heterozygous mutation, p.D21H, in *NLRP3*, present with organ specific, localized inflammation suggestive of local interactive factors that activate the inflammasome[43, 44].

NLRP3 has been the center of inflammasome studies, as it is activated by a surprisingly diverse set of stimuli. These include ATP, crystalline, pore-forming toxins, and various types of pathogens[45–49], which have been extensively reviewed[50–54]. These stimuli all induce “cell stress/damage” and lead to potassium efflux[55, 56], but the exact nature of the NLRP3 activator that cause increased inflammasome activation in hematopoietic and non-hematopoietic cells remain elusive. Recently, the Cryo-EM structure of the NLRP3-NEK7 complex revealed that both NEK7 binding and the NACHT conformational change are required for NLRP3 activation[19] (Fig. 2). Consistent with this model, almost all disease-causing cryopyrin-associated periodic syndrome (CAPS) mutations lie in the NACHT domain and surround the ADP-binding site. These pathogenic mutations affect the stability of the autoinhibitory domain and lead to autoactivation. Disease-causing variants were also found in the NEK7 binding site within the LRR domain at residues p.G755 and p.R918. In fact, the missense mutations, p.G755A and p.G755R increase the interaction with NEK7, which causes autoactivation[19]. Furthermore, some *NLRP3* mutations are located inside or close to sumoylation motifs and impair NLRP3 sumoylation which leads to activation of the NLRP3 inflammasome[57] and Table 2. These studies suggest mechanisms of how disease-causing mutations cause NLRP3 inflammasome autoactivation, which implies more broadly that disease-causing mutations at other post translational modification sites may similarly lower the autoinhibition of the NLRP3 inflammasome[53, 54].

Pyrin inflammasome – battlefield of host and pathogen

FMF (MIM# 249100) is a periodic fever syndrome that classically presents with 1–3-day episodes of recurrent systemic inflammation and serositis that is most prevalent in Mediterranean countries[13, 14]. Mechanisms triggering activation of the pyrin inflammasome were characterized in 2014, when Xu *et al.* showed that pyrin senses Rho GTPase inactivation by bacterial toxins[58]. Pyrin does not directly sense pathogen molecular patterns but senses a physiological change caused by the infectious agent, which resembles plant “resistant” genes[59]. Rho GTPase inactivation prevents the phosphorylation of PKN1/2 and subsequently of 2 pyrin residues, that when phosphorylated, bind a protective guard molecule, 14–3-3, which keeps the pyrin inflammasome inactive[60]. This mechanism further explains how mevalonate kinase deficiency (MKD) or HIDS (MIM# 260920), a periodic fever syndrome caused by LOF mutations in *MVK,* shares clinical similarities including periodic (typically) 3-day fever and rash flares, with FMF[61–63]. *MVK* encodes

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mevalonate kinase, deficiency of which creates a shortage of geranylgeranyl-pyrophosphate, the substrate for PTM by geranylgeranylation of the key molecular switches that control distinct signaling pathways, including GTPases, Kras and RhoA. Thus RhoA inactivation through lack of PTM prevents the protective phosphorylation of pyrin and leads to pyrin inflammasome activation and inflammation[60, 64].

Furthermore, autosomal-dominant missense mutations of the binding sites of 14–3-3 to pyrin at the serine residues, p.S208 or p.S242, cause chronic autoactivation and a clinical syndrome presenting with recurrent episodes of neutrophilic dermatosis, fever, elevated acute-phase reactants, termed pyrin-associated auto-inflammation with neutrophilic dermatosis (PAAND) also termed acute febrile neutrophilic dermatosis (AFND) (MIM# 608068)[65].

A role for pyrin in pathogen sensing was established as *Yersinia pestis*, the organism causing the plague, deactivates pyrin[66]. YopM, a *Yersinia pestis* lethal factor, binds to the autoinhibitory domain of pyrin, B30.2 domain, and connects host ribosome S6 kinases (RSKs) with pyrin that enable its phosphorylation and suppress pyrin inflammasome activation. Interestingly, FMF mutations in the B30.2 domain autoactivate pyrin but reduce binding affinity to YopM, which prevents YopM mediated pyrin inactivation[66]. This selective advantage of FMF causing pyrin mutations has been proposed to confer protection from *Yersinia pestis* infections and may have led to positive haplotype selection of some frequent FMF mutations that explain the high FMF carrier frequencies in the Mediterranean and Middle East[66].

NLRC4 inflammasome – ultra high IL18 and the risk of developing macrophage activation syndrome

The NAIP-NLRC4 inflammasome recognizes flagellin and bacterial type-3-secretion-system needle protein. Ligands that bind NAIPs trigger a conformational change of NAIP and the recruitment of 10–12 NLRC4 monomers to oligomerize (Fig 2). GOF mutations in NLRC4 cause a human autoinflammatory disease (MIM# 616050, 616115)[67–69]. Different from the other inflammasomes, these patients have constitutively highly elevated serum IL-18 levels that predisposes to disease flares and the development of macrophage activation syndrome (MAS) in the context of infections. Preliminary results and limited treatment experience with recombinant IL-18BP suggest a role for IL-18 in triggering MAS in these patients[70]. Although IL18 was also induced by other inflammasomes, the level is much lower compared to NLRC4 patients. The constitutively high serum IL18 levels may predispose to the development of MAS by also enhancing IFNγ production. IFNγ blockade in murine models was as effective as treatment of MAS with IL-18 inhibition [71, 72]. The presence of high IL-18 levels in NLRC4 GOF mutant mouse chimera who received wild type bone marrow suggests that NLRC4 inflammasome activation can lead to production of high IL-18 levels in non-hematopoietic cells and points to the need to improve insights into the respective roles of inflammasomes in regulating immune and non-immune functions in non-hematopoietic cells. Serum IL-18 has since become a clinical marker in screening for the risk for genetic predisposition of MAS and in monitoring disease progression[71, 73].

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TYPE I INTERFERONOPATHIES – DYSREGULATION OF INTERFERON INDUCTION AND SIGNALING

The autoinflammatory Type I interferonopathies present with systemic and organ specific inflammation and a chronically elevated IRGS in blood cells that correlates with disease flares. Insights into the disease pathogenesis come from discoveries that link the type I interferon induction to activation of viral sensors.

Accumulation of cytosolic nucleic acids is a signal of viral infection, which triggers IFN-I production through activation of cytosolic viral sensors including the DNA sensor cGAS (belonging to the nucleotidyltransferase family, encoded by *MB21D1*), or RNA sensors MDA5 or RIG-I (encoded by *IFIH1* or *DDX58* respectively). All viral sensors induce transcription of IFN-I when activated, which signals in an autocrine and paracrine fashion through the IFN-I receptor and leads to the induction of interferon response genes[74] (Fig 3). Recognition of cytosolic dsDNAs by cGAS trigger the synthesis of a second messenger 2'3'cGAMP[75–77], which binds to the adaptor STING[78–81] and activates the protein kinase, TBK1, that phosphorylates the transcription factor, IRF3, which then translocates into the nucleus and initiates the transcription of IFN-I. Similarly, cytosolic RNAs induce IFN-I by binding to the signaling adaptor MAVS, which leads to the activation of NF-κB and the induction of a TBK1 and IRF3-mediated type I interferon response[82–85]. The interferons stimulate through the IFN-I receptors IFNAR1 and/or IFNAR2, which leads to activation of the JAK-STAT pathway, formation of the ISRE (interferon-stimulated response element) signaling complex (STAT1, STAT2 and IFR9), and transcription of genes with ISRE binding promotor sites, namely the interferon response genes (IRG)[86]. Expanding functions of STING were discovered recently not only in pathogen recognition but in maintaining cell homeostasis and in regulating and coordinating interferon-independent pathways[87–90].

Cytosolic nucleic acids are also generated in physiologic conditions, such as during DNA replication and RNA transcription. These self-nucleic acids are tightly controlled to avoid their accumulation in the cytosol and the subsequent induction of an interferon response. In fact, loss-of-function mutations (LOF) in a number of genes that are involved in nucleic acid metabolism, which includes the DNase *DNASE2, TREX1*, the Rnases *RNASEH2A, RNASEH2B, RNASEH2C,* the DNA replication regulators *SAMHD1 and POLA191,* and the RNA editing enzyme *ADAR*[74, 92–94] (Figure 3) cause "interferonopathies". The nucleic acid sensing pathways that lead to IFN production in these diseases have been extensively reviewed[10–12, 74] and will only be summarized below.

Aicardi-Goutières Syndrome (AGS) and AGS-like diseases – dysregulation in cytosolic DNA/RNA clearance and sensing by the intracellular sensors

Genetic discoveries have linked mutations in self DNA/RNA sensing pathways to clinically relevant IFN dysregulation and provided insights into pathogenesis and novel targets of treatment. LOF mutations in the nucleic acid regulators *TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR* (MIM# 225750, 610333, 610181, 610329, 612952, 615010), and GOF mutations in the cytosolic RNA sensor MDA5 encoded by *IFIH1* (MIM# 615846) cause severe leukoencephalopathy syndromes with systemic IFN

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signatures/IRGS and vasculopathy with variable disease severity called, Aicardi-Goutières syndrome (AGS).[92–100] Recently, recessive biallelic LOF mutations in *LSM11* and *RNU7–1* (MIM# 619486, 619487) which encode components of the replication-dependent histone pre-mRNA–processing complex were identified to cause AGS[100]. Heterozygous GOF mutations in p.R822Q of *IFIH1* or another cytosolic RNA sensor, RIG-I encoded by *DDX58*, cause Singleton-Merten syndromes 1 and 2 (MIM # 182250 and 616298 respectively), which is characterized by variable expression of glaucoma, aortic calcification, and skeletal abnormalities, without dental anomalies[101].

Autosomal recessive LOF mutations in *TTC37*, *SKIV2L* affect processing of RNA and cause a syndrome of intractable diarrhea and mild neurologic symptoms (MIM# 222470 and 614602). These two genes encode the 2 components of the Ski2-Ski3-Ski8 (SKI) complex, a multi-protein complex that is involved in the 3'-end degradation of messenger RNAs. Patients also presents with liver disease leading to liver cirrhosis, immunodeficiency (69%), hair abnormalities, facial dysmorphism, and mild mental retardation called Trichohepato-enteric syndromes 1 and 2 (THES1 and THES2)[102–105].

Mitochondrial double-stranded (ds)RNA can also accumulate and leak into the cytosol and activate the MDA5 RNA sensing pathway[106]. This is prevented by the mitochondrial RNA helicase *SUV3* and the polynucleotide phosphorylases PNPase *PNPT1*[107, 108], and *RNASET2*[109], which degrade the mitochondrial dsRNA. LOF mutations in *PNPT1* lead to enhanced IRGS that resulted in an early-onset mitochondrial disorder with severe encephalomyopathy, choreoathetotic movements, hypotonia, variable deafness, and combined oxidative phosphorylation deficiency 13 (COXPD1) (MIM# 614932)[107]; and recessive LOF mutations in *RNASET2* (MIM# 612951) lead to infantile-onset cystic leukoencephalopathy and upregulation of ISGs[109].

SAVI (STING-associated vasculopathy with onset in infancy) and SAVI-like diseases – constitutive activation of STING, an intracellular sensor and adaptor molecule

GOF mutations in the cytosolic DNA sensing pathway adaptor and di-nucleic acid sensor, STING (encoded by *STING1*) cause SAVI (STING-associated vasculopathy with onset in infancy, MIM# 615934), which presents with early-onset systemic inflammation, cold-induced vasculopathy and/or interstitial lung disease. So far, SAVI-causing mutations were found in a total of 11 different residues[110–117], including 3 recently identified novel sites[118]. SAVI presents with variable and often severe and progressive interstitial lung disease and with peripheral vasculitis and patients develop a vasculopathy that can be mild or severe and lead to gangrene and progressive loss of tissue.

Recently other monogenic diseases with SAVI-like features of vasculopathy and/or interstitial lung disease demonstrated a role of STING in their disease pathogenesis. LOF mutations in *ADA2* cause the autoinflammatory disease, DADA2 (MIM# 615688) [119–125]; and COPA (COPI coat complex subunit alpha) deficiency causes the autoinflammatory disease, COPA syndrome (MIM# 616414) [126]. Some DADA2 patients present with peripheral vasculitis similar to SAVI patients that involves cold-exposed, predominantly acral areas; and some COPA patients present with lung disease reminiscent of the interstitial lung disease in SAVI. Indeed, adenosine deaminase 2 encoded by *ADA2,* was shown to

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have DNase activity[127]; ADA2 deficiency in the THP-1 human monocyte cell line leads to cytosolic DNA accumulation and subsequent enhanced interferon induction in a STING-dependent manner[127]. COPA was recently found to mediate STING transportation from Golgi to endoplasmic reticulum[128–130], and deficiency in COPA retains STING in the Golgi, which leads to constitutive activation of STING and enhanced production of IFN-I[117, 131, 132]. Furthermore, a role of the innate immune sensors on shaping adaptive immune function has been explored in COPA patients. It was proposed that the enhanced IRGS in thymic epithelia cells may impair the thymic selection of T cells and result in an increase in autoreactive T cells and a decrease in regulatory T cells thus driving autoimmunity in COPA syndrome[128, 133].

Besides COPA, the calcium sensor STIM1 also regulates STING localization by retaining STING at the endoplasmic reticulum[134]; furthermore, *STIM1* deficiency (MIM# 612783) also leads to enhanced IRGS[134–137]. However, the clinical phenotype of STIM1 deficiency differs from SAVI in that patients present with defective enamel and nail development and recurrent infections due to defective T-cell function[138], which indicates that STIM1 has additional functions other than regulating STING localization.

Spondyloenchondrodysplasia (SPENCD; MIM# 607944) is caused by LOF mutations in *ACP5* and is another disease with clinical similarities to SAVI[139, 140]. The mechanism remains unclear. Some reports indicate that ACP5 is involved in dephosphorylating Osteopontin (OPN), an important regulator in TLR7/8 mediated interferon-alpha induction and development of adaptive immune response[141, 142]. ACP5 deficiency was thought to lead to accumulation of phosphorylated OPN, which causes autoinflammation[139, 143]. However, direct evidence of ACP5 inactivating OPN has not been reported, and another report on SPENCD didn't reveal a role of OPN[140]. Moreover, patients with GOF mutations in *SPP1*, the gene encoding OPN, develop autoantibodies, and showed predominately adaptive immune dysregulation[144].

Regulation of the IFN response gene signature through other mechanisms

Novel Pseudo-TORCH syndromes with skin necrosis reveal dysregulation in interferon signaling through prevention of binding of the negative regulator USP18—Interferon signaling is also tightly regulated (Fig 3) through regulation of induction/transcription of IFN-Is and through regulation of signaling though the IFN receptor. SOCS1 can directly suppress the JAK activity, and the JAK-STAT signaling complex is degraded by the proteasome system to turn off the signaling[145–147]. It has been hypothesized that SOCS1, USP18 and ISG15 may mediate the ubiquitination and/or ubiquitin-like modifications of signaling proteins, which mark them for proteasome degradation[148]. Haploinsufficiency in SOCS1 has recently been associated with early-onset autoimmunity [149] and multisystem inflammatory syndrome in children (MIS-C) [150]. Discoveries of LOF mutations in *USP18* or *ISG15* and GOF mutations in STAT2 have confirmed the critical role of USP18 as negative regulator in IFN signaling.[151–154] Interestingly, all three conditions lead to a defined clinical phenotype presenting with intracranial bleeds and/or calcifications and necrotizing skin lesions in the context of enhanced interferon signaling responses. USP18 deficiency has been termed pseudo-

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TORCH syndrome 2 (MIM# 617397), ISG15 deficiency leads to immunodeficiency 38 with basal ganglia calcification (MIM# 616126), and *STAT2* mutations at position p.R148 cause pseudo-TORCH syndrome-3 (MIM# 618886).

The molecular mechanisms remain incompletely understood, but ISG15 seems to stabilize binding of USP18 to JAK1 which inhibits activation of STATs. STAT2 may function as a negative regulator of interferon signaling either by sequestering or degrading STAT1[155, 156]. STAT2 also functions as transcription factor in interferon signaling[8, 157], and the mutation at the p.R148 residue specifically affects the suppressor function of STAT2 while maintaining its function as transcription factor[153, 154].

CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome)/PRAAS (proteasome-associated autoinflammatory syndrome), an Interferonopathy caused by proteasome deficiencies—Besides the interferonopathies caused by defects in the viral sensor/interferon signaling axis, there is an increasing number of "immune dysregulatory diseases" that present with IFN signatures that are mediated independent of the viral sensors and may or may not be the major mediators of the inflammatory response. These conditions present with clinical features of neutrophilic or monocytic panniculitis and progressive lipodystrophy and include CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome)/PRAAS (proteasome-associated autoinflammatory syndrome, MIM# 256040, 618048, 617591) caused by LOF mutations in genes encoding for components of the proteasome system, including the proteasome subunits *PSMB8, PSMB9, PSMB4, PSMA3, PSMB10,* and proteasome assembling proteins *POMP and PSMG2*, which all lead to an elevated IRGS. [158–161] In some patients, elements of an elevated integrated stress response (ISR) have been described[162, 163]. The response to JAK inhibitors that correlates with the reduction in IRGS and clinical improvement[164, 165] suggests a prominent role of IFN signaling in CANDLE, which suggested that CANDLE is an interferonopathy with IFN driving the abnormal immune response. The immune dysregulation in CANDLE is however complex, and the pathomechanisms that link the IFN signature to proteasome defects remain incompletely understood. Deficiencies in the proteasome system affect the degradation of essential proteins in IFN signaling, and link impaired protein metabolism to the triggers of an elevated interferon response gene signature. A role for the UPR in inducing IFN is being explored[166].

MORE THAN AN "INTERFERONOPATHY"? – COMPLEX SIGNALING PATHWAYS REVEALED BY THE MONOGENIC "AUTOINFLAMMTORY INTERFERONOPATHIES" PROPOSE NOVEL TREATMENT TARGETS BEYOND INHIBITION OF IFN SIGNALING

Recently CANDLE-like diseases that present with panniculitis were identified by genetic analysis of patients with an elevated IFN signature in peripheral blood and include NEMO-NDAS (NEMO exon5 deletion associated autoinflammatory syndrome)[167]. Four patients, 3 male and one female, who presented with moderately elevated interferon response

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gene signatures harbored *de novo* splicing site variants in the X-linked gene *IKBKG* [167]. These splicing variants all lead to an in-frame deletion of exon 5 (exon 5 skipping) in IKBKG which encodes NF-kB essential modulator (NEMO). Like CANDLE, patients with NEMO-NDAS present with panniculitis, but progressive B cell lymphopenia and hypogammaglobulinemia, progressive liver disease and CNS bleeds early in life distinguish NEMO-NDAS from CANDLE. Different from previously reported patients with NEMO deficiency[168–171], infections are not a prominent feature in most NEMO-NDAS patients; some patients with NEMO-NDAS develop conical teeth. Incomplete responses to JAK inhibitors and superior clinical responses to TNF inhibition[167] suggested that increased IFN signaling may not be the critical pathomechanisms that drives the systemic inflammatory response.

An elevated IRGS during active disease is a hallmark of AGS, SAVI and CANDLE, but variable responses to treatment with JAK inhibitors suggest more complex immune dysregulation. While CANDLE patients respond well to JAK inhibitors as outlined above, responses are only partial for patients with SAVI[164, 172–174] and AGS[175]. Recent discoveries of interferon-independent functions of STING, which include activation of the NFκB signaling pathway, dysregulation of autophagy and cell death[88, 89, 176–178] support the involvement of interferon and JAK-independent functions in disease pathogenesis.

Moreover, we do not understand the variable disease manifestations and severity in patients with SAVI[110–117]. Recent data point to heterogeneous mechanisms of STING autoactivation, including the 180° rotation model for connector region mutations[131], the C-terminal tail blocking model for polymer interface mutations[132], and a reconciled model based on novel disease-causing mutations[118]. The role of these variants in differentially activating interferon-independent pathways is currently not understood but may explain some of the phenotypic heterogeneity in SAVI patients with various disease-causing mutations. Furthermore, murine models of STING point to IRF3 independent mechanisms that cause lung disease and to the heterogeneity in clinical presentation and disease severity based on allele-specific mutation and level of STING expression in various hematopoietic and non-hematopoietic cell types and provide tools for further dissecting the effect of STING signaling and the development of STING inhibitors as target for treatment[179, 180]

Current disease models fail to explain the clinical heterogeneity of disease manifestations between SAVI and AGS. STING has a well-documented role in AGS (Figure 3). In murine models of *Trex1* deficiency, the phenotype can be rescued by knocking out *Sting1*[92]. However, patients with AGS develop severe CNS disease, that can include calcifying leukoencephalopathy and microcephaly. These clinical features are not reproduced in the murine model and are not seen in patients with SAVI who have constitutive STING activation. In contrast, the severe vasculitis and interstitial lung disease that are hallmark presentations in SAVI, are absent in patients with AGS. These observations suggest that STING-independent pathomechanisms may contribute to CNS disease in patients with AGS. In fact, overexpression of IFNα in the CNS of mice mimics the human encephalopathy and suggests a role for IFN signaling in causing neuronal damage and death[181] and generation of iPS cell derived TREX1-deficient neuronal progenitor cells differentiated into neurons, and astrocytes demonstrated a significant increase in intracellular DNA species including L1

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retroelements, which correlated with neuronal toxicity. Inhibition of L1 reverse transcription IFN signaling inhibition in TREX1-deficient astrocytes improved cell death suggesting tissue specific effects of the mutations[182]. Understanding the pathogenesis of CNS disease in AGS may advance the discovery of neuroprotective strategies that may ultimately be beneficial in neurogenerative diseases beyond AGS.

Constitutive STING activation is seminal in the pathogenesis of interstitial lung disease in SAVI patients and recent data that disease-causing mutations in *COPA*, the gene encoding COPI Coat Complex Subunit Alpha, fails to constrain STING activation in the Golgi by preventing its transport from the Golgi to the ER, links STING activation to the pulmonary disease in COPA patients[128–130]. Moreover, data on a role for STING in other potentially "interferon-amplified" diseases including SLE[183] make STING an attractive molecular target for therapeutic intervention not only in SAVI and AGS which may address the control of IFN independent immune dysregulation of STING.

Cosstalk between IFN, inflammasome pathways and other pathways add additional layers of complexity to these diseases. NLRP3 inflammasome can be activated by intracellularly activated complement components, which is fundamental to human TH1 induction and regulation.[184] NLRC4 germline GOF mutation, in the NBD domain, the HD1 domain, (p.T337S p.V341A) or in the LRR domain, (p.W665C)[185] can all cause MAS and early-onset enterocolitis (NLRC4-MAS), which are IL-1 and IL-18 driven and result in the induction of IFN-γ [71]. The presence of an IFN signature in a subset of patients with high IL-18 levels and pulmonary alveolar proteinosis[167] remains poorly understood; but is reminiscent of a role of IFN-I (described in a mucosal infection model) in upregulating IL-18 as demonstrated in a murine model of mucosal infection with HSV2. Infection induces CCL2 production from mucosal cells that recruit inflammatory monocytes. IFN-I then binds IFNAR on inflammatory monocytes, signals through IRF9 to induce the release of IL-18, which then binds to IL-18R on NK cells to induce IFN-γ[186]. It was suggested that caspase-1 activation downstream of IFN-I is mediated by the absent in melanoma 2 (AIM2) inflammasome complex[187]; a mechanism that has not been explored in these patients with high IL-18 levels and pulmonary alveolar proteinosis. Moreover, heterozygous RELA mutations cause early-onset systemic lupus erythematosus by skewing the NF-κB pathway towards transcriptional activation of IFN-I genes.[188]

Lastly, crosstalk between viral sensing pathways and inflammasome and cell death pathways have been described[189, 190]. RIG-I can trigger a MAVS-independent pathway that involves the signaling adaptor ASC that in an NLRP3-independent fashion leads to the production of IL-1β by caspase-1 activation.[190] Furthermore, sensing of cytosolic DNA through activation of the cGAS-STING pathway and RNA ligands through TLR3 or RIG-I sensors lead to necroptotic cell death in primary cells, which requires synergy of the IFN-I and TNF signaling pathway; and administration of a STING agonist leads to a fatal, shock-like inflammatory disease in mice[189]. These pathways have not systematically been explored in human diseases but raise questions whether similar mechanisms may contribute to the often-sudden death in patients with interferon signatures who develop severe infections[167]. The presence of an IFN signature in patients with CANDLE-like diseases such as NEMO-NDAS and the better clinical responses to TNF inhibitors compared to JAK inhibitors further raises

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important questions regarding the impact and involvement of inflammatory cell stress and TNF mediated cell death pathways in the disease pathogenesis. In fact, necroptosis has recently been implicated in the disease pathomechanism of a patient with NEMO mediated disease presenting with immunodeficiency and inflammatory disease manifestations[191].

CONCLUDING REMARKS

Basic research and disease-based discovery of monogenic defects in inflammasome and viral sensors provide insights into the clinical impact of these sensor mechanisms on human disease. The respective key cytokine mediators, IL-1 and IFN-I significantly influence the spectrum of the systemic and organ-specific disease manifestations in patients with the various inflammasomopathies and autoinflammatory interferonopathies. The clinical improvement with the use of targeted treatments that block IL-1, and Type-I interferon signaling respectively validate the role of these potent cytokines in causing and amplifying the inflammatory disease manifestations, but partial responses to IL-1 inhibitor and JAK inhibitor therapy reveal the unresolved complexity of disease-causing pathways in some diseases. For example, the discovery of constitutively high serum IL-18 levels in patients with GOF mutations in *NLRC4* link the NLRC4 inflammasome to the development of macrophage activation syndrome and Type-II interferon mediated pathology. New pathomechanistic insights link activation of the viral adaptor and sensor STING, to the development of pulmonary fibrosis in SAVI and COPA syndrome, but in murine models lung disease is independent of IRF3, thus suggesting a complex role of STING in pulmonary disease and in regulating adaptive immune dysfunction; and point to STING as therapeutic target in a growing number of immunedysregulatory diseases. Lastly, new diseases with complex immune dysregulation including NEMO-NDAS reveal crosstalk between IFN pathways, NFκB signaling pathways and cell death pathways and pose new challenges to diagnosis and treatment, but also bear prospect that understanding these interactions may reveals novel targets for better treatments.

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ABBREVIATIONS

SAVI	STING-associated vasculopathy with onset in infancy
AGS	Aicardi-Goutières Syndrome
CANDLE	chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome
PRAAS	proteasome-associated autoinflammatory syndrome
IFN	interferon
IFN-I	Type I interferon
IRGS	interferon response gene signature

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FMF	Familial Mediterranean fever
MIM	Mendelian Inheritance in Man
ASC	apoptosis-associated speck-like protein containing a CARD
CARD	caspase activation and recruitment domain (CARD)
PYD	pyrin domain
PAMPs	pathogen-associated molecular patterns
DAMPs	danger-associated molecular patterns
GOF	gain-of-function
LOF	loss-of function

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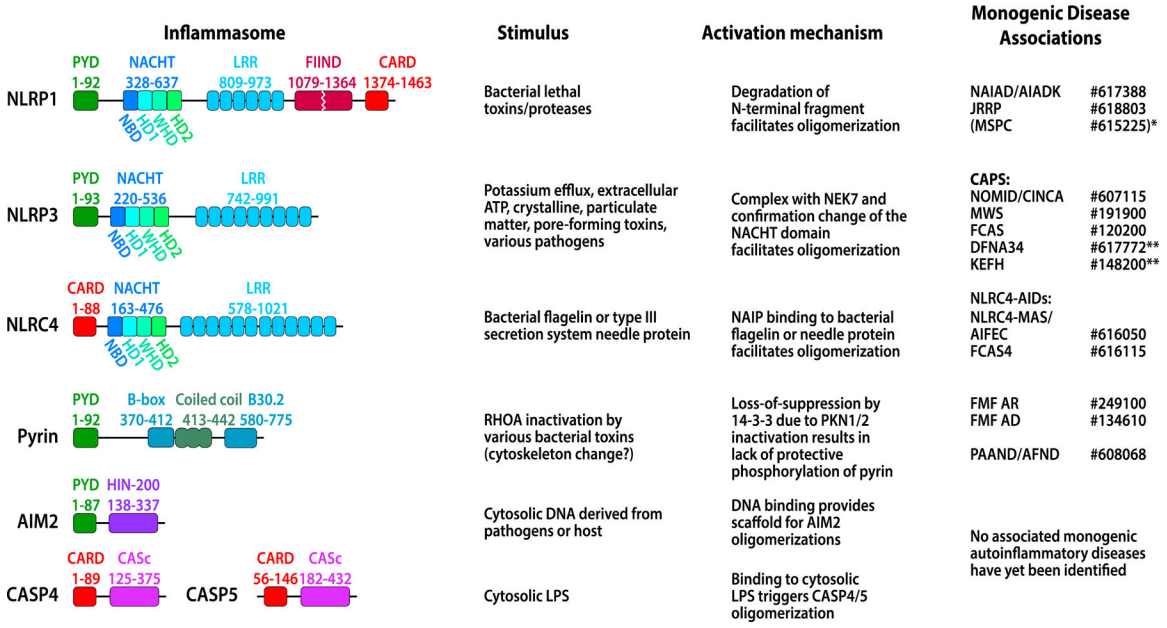

FIG 1. Characteristics of various inflammasomes.

CARD domain or PYD domain is responsible for recruiting ASC and for forming ASC specks. Other domains function as regulatory domains to prevent inflammasome autoactivation (detailed in Fig 2). Diseases related to the inflammasomes are shown in the last column with the MIM numbers (www.oimm.org). Diseases in bracket typically do not present with systemic inflammation. See text for full name of the diseases. NLRP1-associated: NAIAD or AIADK; JRRP. *MSPC is caused by mutations in the pyrin domain of *NLRP1* and leads to a precancerous skin condition without systemic inflammation. NLRP3-associated: The disease spectrum of CAPS includes the 3 severity phenotypes: NOMID, MWS, and FCAS. ** DFNA34, (Deafness, autosomal dominant 34) and **KEFH, (Keratoendothelitis fugax hereditaria) present with inflammation restricted to the inner ear and the cornea respectively with absent or minimal systemic inflammation. NLRC4-associated AIDs include NLRC4-MAS/AIFEC presenting with recurrent MAS and FCAS4 presenting with more systemic inflammation and rash. MEFV/pyrin-associated AIDs include additive gain-of function, AR (autosomal recessive) and AD (autosomal dominant) FMF, and PAAND/AFND caused by mutations in two 14–3-3-binding serine residues. Mutations in AIM2 and CASP4 have so far not been associated with human monogenic diseases.

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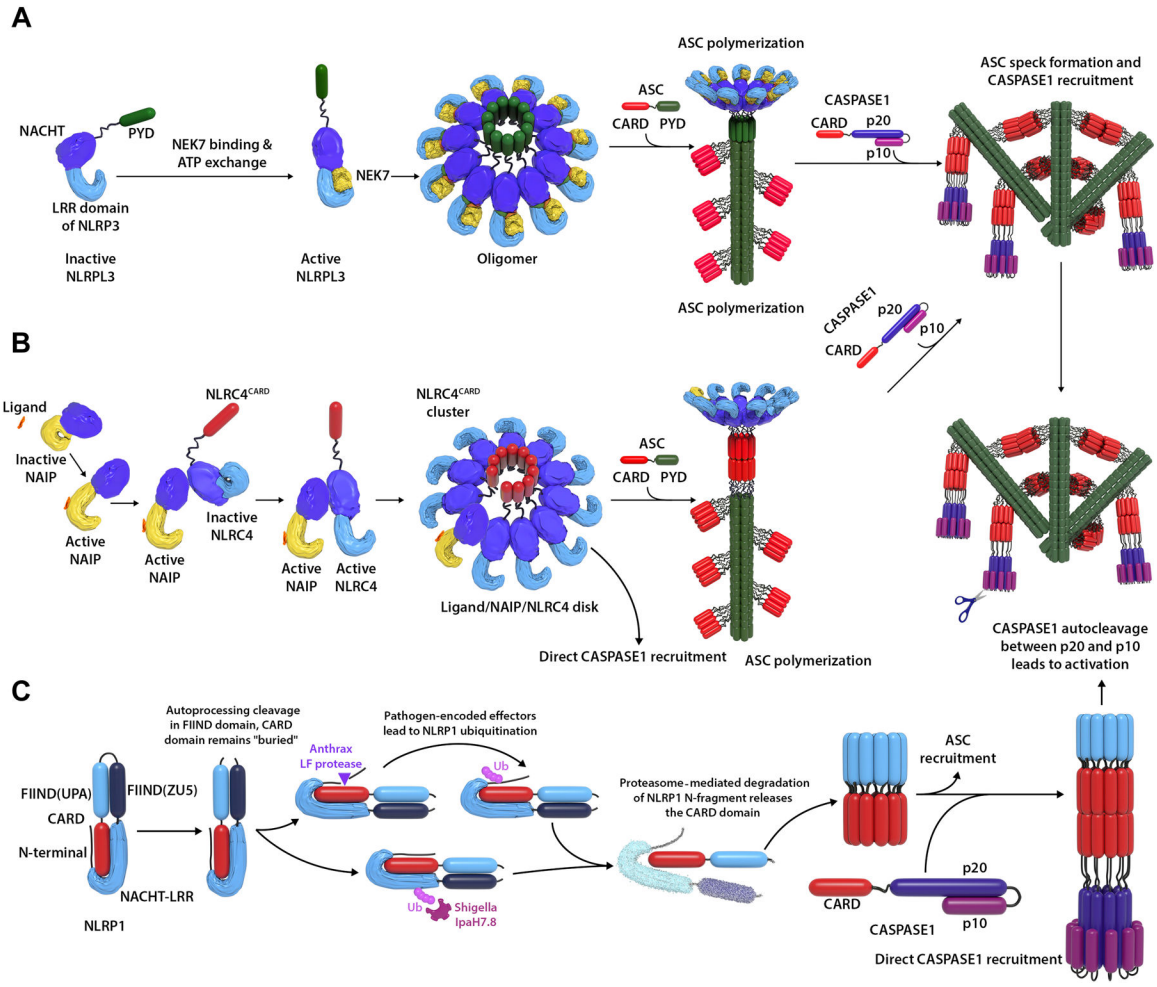

FIG 2. Mechanism of NLRP3 (A), NLRC4 (B), and NLRP1 (C) inflammasome activation.

(A) NEK7 binding and ATP exchange in NLRP3 cause a confirmation change of the NACHT domain, which allows NLRP3 oligomerization and formation of an NLRP3 disc. The PYD domains in the "disc" then recruit ASC via PYD-PYD interaction, which triggers polymer assembly of ASC. The ASC polymers can further form specks via CARD-CARD interaction between the ASC polymers. This creates a platform to recruit CASPASE1 via CARD-CARD interaction between ASC and CASPASE1. CASPASE1 is then activated by autocleavage between p20 and p10 domain, which leads to NLRP3 inflammasome activation. NLRC4 is activated in a similar way **(B)**, except initiated by ligand binding to NAIP and the ligand/NAIP/NLRC4 disc recruits ASC via CARD-CARD interaction. **(C)** NLRP1 is a "booby trap" for pathogens. In an attempt to deactivate the host immune system, some pathogen lethal factors try to degrade NLRP1. However, degradation of the NLRP1 N-terminal fragment leads to release of the CARD domain which triggers NLRP1 activation. CARD domain in NLRC4 or NLRP1 can recruit ASC to form ASC specks; they can also directly recruit CASPASE1 as shown in **(C),** right panel, direct CASPASE1 recruitment.

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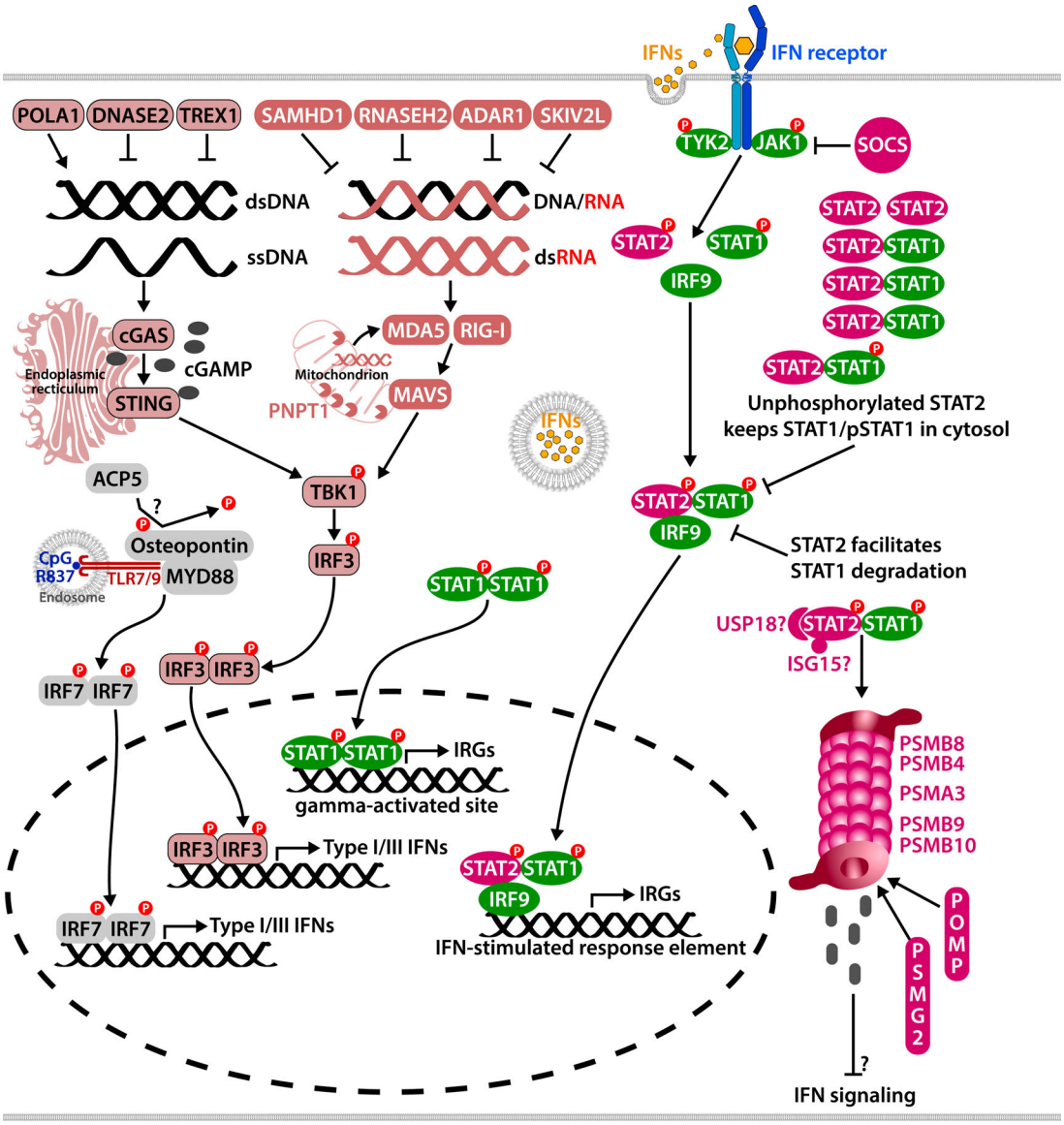

FIG 3. Interferon mediated/amplified diseases are caused by dysregulation of interferon production and signaling.

Viral replication in the cell leads to aberrant accumulation of cytosolic nucleic acids, which are sensed by the host and trigger type I/III interferon production. Cytosolic DNAs are sensed by cGAS, which produces 2’3’cGAMP, a ligand for the adaptor STING. Cytosolic RNAs are sensed by RIG-I or MDA5, which activates the adaptor MAVS. Adaptor activation leads to TBK1 phosphorylation, which phosphorylates the transcription factor IRF3 and triggers the Type I/III interferon production. Cytosolic nucleic acids are also generated in cell homeostatic processes such as DNA replication, and are degraded/reduced by various enzymes including nucleases. Mitochondrial RNAs are degraded by RNases including PNPT1. Type I and II interferons bind to their respective receptors and mediate the transcription of interferon response genes. Interferon signaling is tightly controlled by signaling suppressors including USP18, ISG15, SOCS family proteins, and STAT2, which bind to the signaling complexes for proteasome degradation. Mutations in

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proteasome components also lead to IFN production by yet unknown mechanisms. Disease-causing mutations in *ACP5* are associated with enhanced interferon signaling, possibly via Osteopontin and IRF7. Due to space limitations, two AGS associated genes, *LSM11, RNU7–1*, are not shown in the figure.

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Table 1.

Differences in flare characteristics in patients with IL-1 mediated vs. IFN-I mediated inflammatory flares

Inflammatory markers	**IL-1 mediated disease flares***	**IFN mediated disease flares**
Clinical parameters:		
CRP	Increases with disease flares	Increases with disease flares
ESR	Increases with disease flares	Increases with disease flares
Hgb	Decreases with disease flares	Decreases with disease flares
WBC	***Increases*** with disease flares due to granulocytosis	***Remains the same or decreases*** with disease flares
ALC	***Remains the same or increases*** with disease flares	***Decreases*** with disease flares
Plt count	***Increases*** with disease flares	***Decreases*** with disease flares
Research parameter/biomarker		
IFN-score	***Remains within normal range*** with disease flares	***Increases*** significantly with disease flares

CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, Hgb=hemoglobin, WBC=white blood cell, ALC=absolute lymphocyte count, Plt=platelet, N=No, Y=Yes

For clinical decisions age related normal values apply, however the table indicates that the direction of change for WBC, ALC and PLT count and IFN-score differ in IL-1 and IFN mediated changes

*The values below are derived from patients with the IL-1 mediated diseases CAPS and DIRA Disease related flares seen in patients with CANDLE/PRAAS and other interferonopathies differ from the disease flares seen in patients with IL-1 mediated diseases. Although patients in both disease groups develop fever and rashes and elevated acute phase reactants, the laboratory parameters drawn at the time of a disease flare illustrate characteristic laboratory features of the disease flares that distinguish IL-1 and IFN mediated diseases.

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Table 2.

NLRP3 mutation in close proximity with potential sumoylation sites

Sumoylation Lysin Position	Sumoylation Motif*	Position of closest human mutation	Pathogenicity prediction and clinical phenotype
K88	(A**K**RD)	D90Y	novel, VUS, (Undefined-AID)
K133	(M**K**KD) YR	R137H	MAF 0.0005, VUS, possibly pathogenic (MWS)
K204	(I**K**ME)	E206G	novel, possibly pathogenic, (Undefined-AID)
K552	(L**K**LP) SR	R556X	MAF 0.0000039, likely pathogenic (atypical FMF)
K652	(P**K**IE)	P651S	novel, likely pathogenic (MWS)
K689	(P**K**EE) EEEEK	E690K, E692K	Both novel, likely pathogenic (NOMID/CINCA)

*closest variant/mutation reported in Infevers is indicated in red in the respective (sumoylation motif) or closest to the sumoylated lysin (**K**).