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How to Build a Fire: The Genetics of Autoinflammatory Diseases

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Abstract

Systemic autoinflammatory diseases (SAIDs) are a heterogeneous group of disorders caused by excess activation of the innate immune system in an antigen-independent manner. Starting with the discovery of the causal gene for familial Mediterranean fever, more than 50 monogenic SAIDs have been described. These discoveries, paired with advances in immunology and genomics, have allowed our understanding of these diseases to improve drastically in the last decade. The genetic causes of SAIDs are complex and include both germline and somatic pathogenic variants that affect various inflammatory signaling pathways. We provide an overview of the acquired SAIDs from a genetic perspective and summarize the clinical phenotypes and mechanism(s) of inflammation, aiming to provide a comprehensive understanding of the pathogenesis of autoinflammatory diseases.

1. INTRODUCTION

The innate immune system represents an evolutionarily ancient host defense mechanism that is primarily mediated by cell surface and intracellular pattern recognition receptors and complementary systems expressed by myeloid cells, such as phagocytes and dendritic cells (107). These receptors may function directly by recognizing pathogens and/or indirectly by mediating secondary signals to induce rapid cellular responses. While innate immunity lacks the specificity of adaptive immunity, it can act fast because receptor rearrangement and clonal expansion are not required, as they are for adaptive immunity.

When innate immunity goes awry, however, it can result in autoinflammatory diseases. The term horror autoinflammaticus was introduced in 1999 [along with the description of the TNFR1-associated periodic fever syndrome (TRAPS)] to denote a group of inflammatory diseases driven by the activation of innate immune cells (105, 106). This nosology also served to distinguish patients with autoinflammatory diseases from those with classical autoimmune diseases that arise from defects of adaptive immune cells.

Systemic autoinflammatory disorders (SAIDs) are rapidly expanding and genetically heterogeneous inflammatory diseases caused by the spontaneous activation of the innate immune system (7, 99). Disease onset of SAIDs typically occurs during childhood, in contrast to the classical and more common adult-onset autoimmune diseases such as lupus and rheumatoid arthritis. SAIDs are characterized by recurrent episodes of fevers and a spectrum of inflammatory features, most commonly in the skin, joints, gut, and eyes. Severe disease manifestations include osteomyelitis, central nervous system inflammation, and neurological impairments. With a wide array of clinical phenotypes, these diseases are challenging to diagnose and classify in both clinical practice and research settings.

Based on the understanding of the molecular genetics of diseases and the affected inflammatory pathways, SAIDs can be broadly classified into several major categories based on key disease mediators, including interleukin-1 (IL-1), type I interferon (IFN-I), nuclear factor kappa B (NF-κB), and complement-mediated diseases (99, 138). This classification is mainly conceptual, as these inflammatory pathways are not mutually exclusive and are interregulated. Most SAID patients display a strong inflammatory gene expression signature in peripheral blood leucocytes/monocytes, resulting in the elevated production of proinflammatory cytokines such as interleukins (IL-1β, IL-6, IL-8, IL-17, IL-18), tumor necrosis factor (TNF), and interferons (IFN-α, IFN-β, and IFN-γ). Affected tissues are often infiltrated with myeloid cells, including macrophages, neutrophils, and monocytes. Persistent dysregulation of immune pathways can affect various cellular functions, including cell death, protein degradation, autophagy, and protein homeostasis.

Here, we review the complex genetics of SAIDs, incorporating the most recent discoveries in this field, and discuss the current understanding of molecular mechanisms leading to autoinflammation.

2. GENETICS OF MONOGENIC AUTOINFLAMMATORY DISEASES

The first genetic cause of autoinflammation was established with the identification of the Mediterranean fever (*MEFV*) gene as responsible for familial Mediterranean fever (FMF). Since this landmark discovery, germline and somatic pathogenic mutations in more than 50 genes have been linked to SAIDs (**Figure 1**). The genetics of SAIDs is complex and heterogeneous, including dominant, recessive, and X-linked germline and somatic variants, which, at the molecular level, could act as gain-of-function (GoF) or loss-of-function (LoF) pathogenic variants, depending on the mutation's effect on the protein function, and ultimately resulting in the activation of various immune and inflammatory pathways. High-impact, mostly de novo variants result in

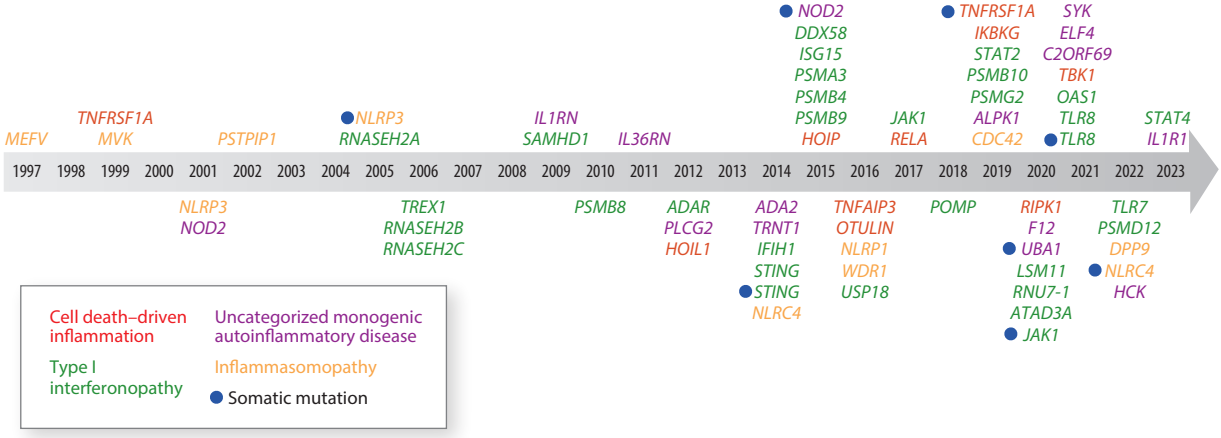


Figure 1

Timeline of gene discoveries for monogenic autoinflammatory diseases. The genetic basis of the first known autoinflammatory disease, familial Mediterranean fever, was defined in 1997. With advances in immunology and molecular genetics, more than 50 monogenic autoinflammatory diseases have been identified. Abbreviations: *ADA2*, adenosine deaminase 2; *ADAR*, adenosine deaminase RNA-specific; *ALPK1*, alpha kinase 1; *ATAD3A*, ATPase family AAA domain containing 3A; *C2ORF69*, chromosome 2 open reading frame 69; *CDC42*, cell division cycle 42; *DDX58*, DExD/H-box helicase 58; *DPP9*, dipeptidyl peptidase 9; *ELF4*, E74-like ETS transcription factor 4; *F12*, coagulation factor XII; *HCK*, HCK proto-oncogene, Src family tyrosine kinase; *HOIL1*, heme-oxidized IRP2 ubiquitin ligase-1; *HOIP*, HOIL1-interacting protein; *IFIH1*, interferon induced with helicase C domain 1; *IKBKG*, inhibitor or nuclear factor kappa B kinase regulatory subunit gamma; *IL1RN*, interleukin 1 receptor antagonist; *ISG15*, Interferon-stimulating gene 15; *JAK*, Janus kinase 1; *LSM11*, U7 small nuclear RNA associated; *MEFV*, Mediterranean fever; *MVK*, mevalonate kinase; *NLRC4*, NLR family CARD domain-containing 4; *NLRP*, NLR family pyrin domain-containing; *NOD2*, nucleotide binding oligomerization domain containing 2; *OAS1*, 2′-5′-oligoadenylate synthetase 1; *OTULIN*, OTU deubiquitinase with linear linkage specificity; *PLCG2*, phospholipase C gamma 2; *POMP*, proteasome maturation protein; *PSMA3*, proteasome 20S subunit alpha 3; *PSMB*, proteasome 20S subunit beta; *PSMG2*, proteasome assembly chaperone 2; *PSMD12*, proteasome 26S subunit non-ATPase 12; *PSTPIP1*, proline-serine-threonine phosphatase–interacting protein 1; *RIPK1*, receptor-interacting serine/threonine kinase 1; *RNASE*, ribonuclease; *RNU7-1*, RNA, U7 small nuclear 1; *SAMHD1*, SAM and HD domain–containing deoxynuclease triphosphate triphosphohydrolase 1; *STAT2*, signal transducer and activator of transcription 2; *STING*, stimulator of interferon genes; *SYK*, spleen-associated tyrosine kinase; *TBK1*, TANK-binding kinase 1; *TLR*, toll like receptor; *TNFAIP3*, TNF alpha-induced protein 3; *TNFRSF1A*, TNF receptor superfamily member 1A; *TREX1*, three prime repair exonuclease 1; *TRNT1*, tRNA nucleotidyl transferase 1; *UBA1*, ubiquitin like modifier activating enzyme 1; *USP18*, ubiquitin specific peptidase 18; *WDR1*, WD repeat domain 1.

constitutive immune activation and early-onset phenotypes, while milder disease-associated variants tend to show variable disease expressivity that is dependent on influence from other genetic and nongenetic modifying factors. Furthermore, pathogenic variants in the same gene can exhibit variable inheritance patterns; they can affect various aspects of protein function, resulting in distinct clinical phenotypes. A growing number of SAIDs can be explained by the non-Mendelian inheritance of somatic variants predominantly but not exclusively in myeloid cells. Cell-specific expression of mutated proteins further adds to the complexity of SAIDs by governing organ-specific manifestations (see **Supplemental Table 1**).

Supplemental Material >

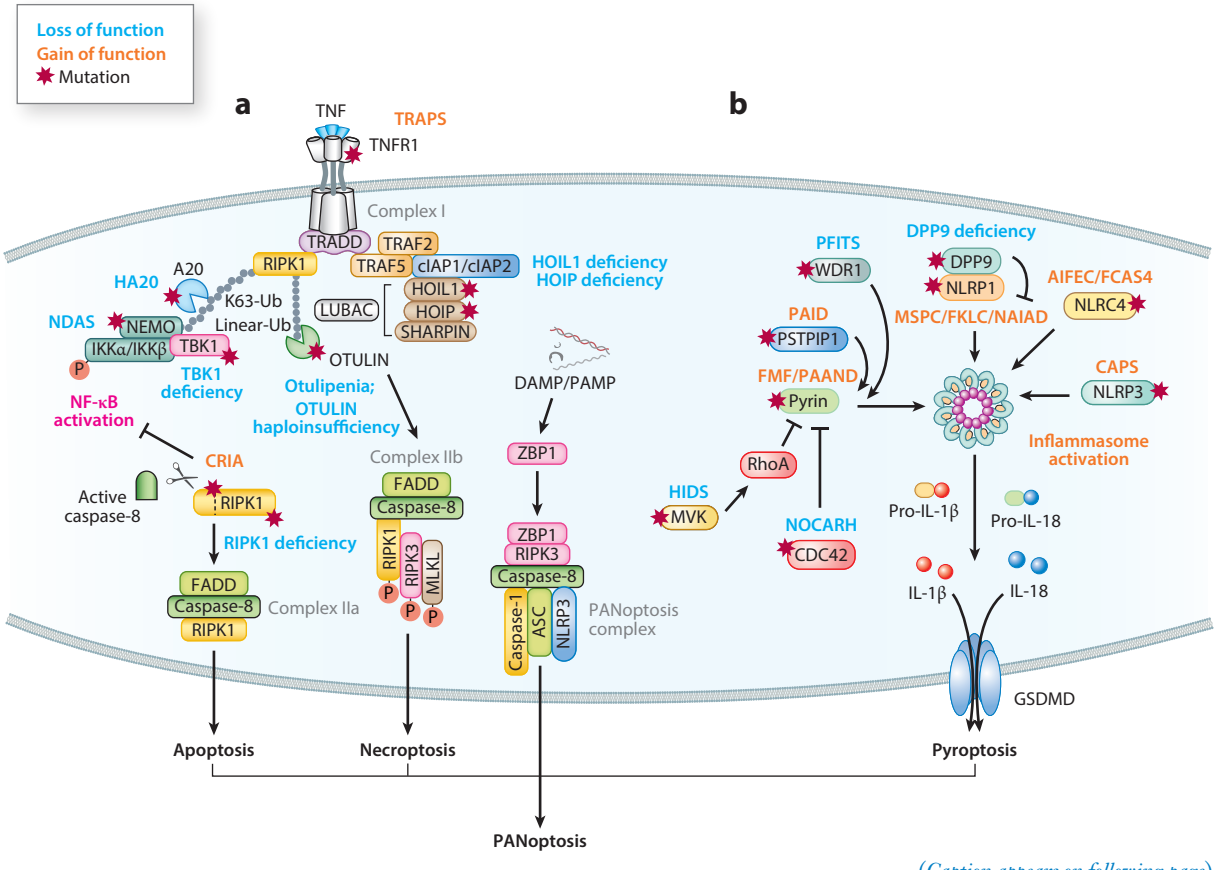
Most SAIDs are rare, except for FMF and deficiency of adenosine deaminase 2 (DADA2). As with many other inborn errors of immunity, more than half are recessively inherited and, as such, often identified in consanguineous families or founder populations. The founder effect has been noted for FMF mutations in patients from Eastern Mediterranean populations, hyper-immunoglobulinemia D syndrome (HIDS)-associated mutation in the Dutch population, and DADA2-associated mutations in the Northern European and South Asian populations.

To simplify the discussion, we organized SAIDs based on affected molecular and cellular pathways, with the understanding that these disturbances cross-activate each other to drive vicious circles of inflammation.

2.1. Cell Death–Driven Inflammation

Programmed cell death (PCD), including apoptosis and necroptosis, are cellular processes controlled predominantly by TNF and critical to maintaining homeostasis (173). Lytic forms of cell death, such as necroptosis, which leads to the release of cell contents, activate immune receptors to induce inflammation. Nonlytic forms of cell death, such as apoptosis, can be pathogenic when defective clearance of cell debris leads to the release of inflammatory mediators (**Figure 2**).

Excessive and unrestrained PCD due to genetic defects has been implicated in the pathogenesis of many SAIDs and primary immunodeficiencies (163). Several diseases, including deficiency of two elements of the linear ubiquitin chain assembly complex (LUBAC)—HOIL1-interacting protein (HOIP), and heme-oxidized IRP2 ubiquitin ligase-1 (HOIL1)—as well as receptor-interacting serine/threonine kinase 1 (RIPK1) deficiency, RIPK1 cleavage resistance, RELA haploinsufficiency, OTU deubiquitinase with linear linkage specificity (OTULIN) deficiency, and TANK-binding kinase 1 (TBK1) deficiency, are caused by dysregulation in cell death pathways.



(*Caption appears on following page*)

Figure 2 (*Figure appears on preceding page*)

Autoinflammatory diseases mediated by cell death pathways and inflammasomes. (*a*) The TNF-mediated cell death pathway is activated by stimulation of TNFR1 by TNF, followed by formation of complex I, consisting of trimerized TNFR1, TRADD, RIPK1, TRAF2, and TRAF5. This complex is regulated by K63 or linear ubiquitination, which is controlled by a set of E3 ligases and deubiquitinases, including cIAP1/cIAP2, LUBAC, A20, and OTULIN. NEMO and TBK1 are recruited to the linear ubiquitin chains on RIPK1 to take part in the conduction of NF-κB signaling. In the setting of NF-κB inhibition, RIPK1 is activated and binds with FADD and caspase-8, leading to complex IIa and complex IIb formation, where RIPK1 is cleaved by caspase-8 to execute apoptosis. If the cleavage of RIPK1 by caspase-8 is impaired, RIPK1 undergoes dimerization via the C-terminal death domain, leading to its activation and subsequent interaction with RIPK3 and MLKL to form the complex IIb (necrosome), which promotes necroptosis. (*b*) NLRP1, NLRP3, pyrin, and NLRC4 inflammasomes are regulated by various proteins, including DPP9, WDR1, PSTPIP1, MVK, and CDC42. After activation of inflammasomes, procaspase-1 is self-activated and cleaves several substrates, including the proinflammatory cytokines IL-1β and IL-18. GSDMD is another substrate of caspase-1, whose cleavage leads to the liberation of its N-terminal domain to form pores in plasma membranes and causes a type of inflammatory cell death termed pyroptosis. Abbreviations: A20, TNF alpha–induced protein 3; AIFEC, autoinflammation with infantile enterocolitis; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; CAPS, cryopyrin-associated periodic syndromes; CDC42, cell division cycle 42; cIAP, cellular inhibitor of apoptosis protein; CRIA, cleavage-resistant RIPK1–induced autoinflammatory; DAMP, damage-associated molecular pattern; DPP9, dipeptidyl peptidase 9; FADD, Fas-associated via death domain; FCAS, familial cold autoinflammatory syndrome; FKLC, familial keratosis lichenoides chronica; FMF, familial Mediterranean fever; GSDMD, gasdermin-D; HA20, haploinsufficiency of A20; HIDS, hyperimmunoglobulin D syndrome; HOIL1, heme-oxidized IRP2 ubiquitin ligase-1; HOIP, HOIL1-interacting protein; IL, interleukin; LUBAC, linear ubiquitin chain assembly complex; MLKL, mixed-lineage kinase domain-like pseudokinase; MSPC, multiple self-healing palmoplantar carcinoma; MVK, mevalonate kinase; NAIAD, *NLRP1*-associated autoinflammation with arthritis and dyskeratosis; NDAS, *NEMO* deleted exon 5 autoinflammatory syndrome; NEMO, NF-κB essential modulator; NF-κB, nuclear factor kappa B; NLRC4, NLR family CARD domain-containing 4; NLRP3, NLR family pyrin domain-containing 3; NOCARH, neonatal onset of cytopenia, autoinflammation, rash, and hemophagocytic lymphohistiocytosis; OTULIN, OTU deubiquitinase with linear linkage specificity; PAAND, pyrin-associated autoinflammation with neutrophilic dermatosis; PAID, PSTPIP1-associated inflammatory disease; PAMP, pathogen-associated molecular pattern; PFITS, periodic fever, immunodeficiency, and thrombocytopenia syndrome; PSTPIP1, proline-serine-threonine phosphatase–interacting protein 1; RIPK1, receptor-interacting serine/threonine kinase 1; RIPK3, receptor-interacting serine/threonine kinase 3; SHARPIN, SHANK-associated RH domain–interacting protein; TBK1, TANK-binding kinase 1; TNF, tumor necrosis factor; TNFR1, tumor necrosis factor receptor 1; TRADD, TNFRSF1A-associated via death domain; TRAF, tumor necrosis factor receptor-associated factor; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; Ub, ubiquitination; WDR1, WD repeat domain 1; ZBP1, Z-DNA-binding protein 1.

Proinflammatory cytokines such as TNF and IL-6 drive inflammation by stimulating inflammatory gene expression and inducing cell death, which further propagates disease progression (163).

2.1.1. RIPK1-associated autoinflammation and immunodeficiency. RIPK1 is a key modulator of inflammation and cell death pathways in response to different types of cellular stimulation (173, 176, 180). The cell death–inducing activity of RIPK1 needs to be strictly regulated to ensure cellular homeostasis (173). Pathogenic variants in *RIPK1* are associated with two distinct conditions: RIPK1 deficiency/immunodeficiency 57 with autoinflammation (38, 93) and cleavage-resistant RIPK1-induced autoinflammatory (CRIA) syndrome (83, 156). These two diseases exhibit different inheritance patterns and present with distinct immunological profiles (177). Interestingly, a shared feature of these two diseases is that TNF-stimulated peripheral blood monocytes (PBMCs) of patients are sensitized to cell death by necroptosis and apoptosis.

Patients with biallelic LoF mutations in *RIPK1* are born with severe and potentially lethal immunodeficiency. Notably, RIPK1-deficient patients also have autoinflammatory manifestations, such as inflammatory bowel disease (IBD) and arthritis. In contrast, CRIA syndrome is dominantly inherited and caused by heterozygous pathogenic missense variants that affect the specific amino acid residues 321–324, which are critical for RIPK1 cleavage by caspase-8. The reported mutations of aspartic acid 324 (Asp324) to valine (Val), histidine (His), tyrosine (Tyr), asparagine (Asn) or glycine (Gly) and leucine 321 (Leu321) to arginine (Arg) render RIPK1 noncleavable (83, 132, 156). Patients with CRIA syndrome mainly present with recurrent fevers and lymphadenopathy.

2.1.2. LUBAC deficiencies. The LUBAC consists of three elements: HOIL1, HOIP, and SHANK-associated RH domain–interacting protein (SHARPIN), which assemble linear ubiquitin (M1-linked ubiquitin) chains to substrate proteins. Linear ubiquitin chains are essential for the regulation of many immune and nonimmune signaling pathways, including the proteasome (69, 124)

2.1.2.1. HOIL1 deficiency (RBCK1). Biallelic LoF variants in *HOIL1* result in a spectrum of phenotypes, from severe immunodeficiency, autoinflammation, and polyglucosan storage myopathy (amylopectinosis) to early-onset progressive muscle weakness and cardiomyopathy without immune dysregulation (21, 115, 166). Boisson et al. (21) identified three LoF *HOIL1* mutations: (*a*) a frameshift mutation, (*b*) a large deletion that encompasses exons encoding the ubiquitin-like (Ubl) domain, and (*c*) a nonsense mutation in the novel zinc finger (NZF) domain of HOIL1 predicted to cause premature truncation. The Ubl domain is important for LUBAC formation and linear ubiquitination. Functional studies revealed that HOIL1 deficiency leads to decreased expression of the entire LUBAC. Fibroblasts from HOIL1-deficient patients displayed impaired NF-κB activation, resulting in diminished transcription of NF-κB-induced genes in response to stimulations by TNF and IL-1β. In addition, B cells from these patients displayed impaired response to CD40L, which explains the immunodeficiency and invasive pyogenic bacterial infection in this disease. The autoinflammatory component of HOIL1 deficiency might be explained by the enhanced response of PBMCs to IL-1β or by hypersensitivity to cell death–inducing stimuli.

2.1.2.2. HOIP deficiency (RNF31). HOIP is the main catalytic component of the LUBAC that possesses E3 ligase activity for linear ubiquitylation (144). A homozygous missense mutation in *HOIP* was first reported in a single patient with autoinflammation, immunodeficiency, subclinical amylopectinosis, and systemic lymphangiectasia (20). The *HOIP* variant p.Leu72Pro is located in the PNGase/UBA- or UBX-containing (PUB) domain (which interacts with various effectors) and is shown to result in decreased expression, assembly, and activity of the LUBAC. Oda et al. (118) reported a second patient with novel compound heterozygous *HOIP* mutations disrupting messenger RNA (mRNA) splicing (c.1197G>C and c.1737+3A>G). These two mutations are found in the NZF and ubiquitin-associated (UBA) domains of HOIP, respectively. Interestingly, the patient's PBMCs showed, in addition to TNF, a higher IFN gene-expression signature after stimulation with proinflammatory cytokines, which further expands the molecular mechanisms of LUBAC deficiency. Similar to the fibroblasts in HOIL1 deficiency, HOIP-deficient fibroblasts have impaired TNF- and IL-1β-driven NF-κB activation, contributing to immunodeficiency, while stimulated myeloid cells are sensitized to cell death.

2.1.3. OTULIN deficiency/ORAS/otulipenia. OTULIN-related autoinflammatory syndrome (ORAS, or otulipenia) is caused by biallelic LoF mutations in the linear deubiquitinase OTULIN, which acts as a negative regulator of the LUBAC and the NF-κB pathway (92). Thus far, only six patients with ORAS have been reported, and all but one patient are from founder populations. Most pathogenic variants are classical LoF mutations, while missense mutations are shown to affect protein stability. This rare disease is characterized by early-onset, severe, multisystem autoinflammation in the skin, joints, and gastrointestinal tract (39, 190). Stimulated PBMCs and fibroblasts from patients show hallmark features of activated canonical NF-κB pathway: increased degradation of inhibitory IκBα and increased phosphorylation of IKKα/IKKβ. OTULIN deficiency is associated with myeloid cell–specific dysregulation in TNF signaling and cell death. A recent study demonstrated that OTULIN haploinsufficiency underlies susceptibility of tissue-resident, nonhematopoietic cells in the skin and lungs to the staphylococcal virulence factor α toxin–induced infection (146).

2.1.4. NDAS (*IKBKG*). X-linked recessive hypomorphic variants in *IKBKG* (also known as *NEMO*; encodes the regulatory gamma subunit of the IκB kinase complex) have been linked to anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) (44). Recently, hemizygous mutations that affect the splicing of exon 5 in *IKBKG* were identified in four patients, both males and females with a distinct clinical phenotype from EDA-ID, which is termed NEMO deleted exon 5 autoinflammatory syndrome (NDAS) (42). Subsequently, Lee et al. (89) reported three boys with NDAS that presented with inflammatory manifestations starting in the first month of life. NDAS is characterized by systemic autoinflammation, hypogammaglobulinemia, autoimmune cytopenia, elevated inflammatory markers, and strong IFN-I and NF-κB transcriptional signatures. The preliminary functional studies demonstrated that NDAS-associated variants disrupt the interaction between NEMO and TBK1.

2.1.5. TBK1 deficiency. TBK1 is a regulator of IFN-I, NF-κB, and TNF-induced RIPK1-dependent cell death (RCD) (3). Taft et al. (152) identified four patients with biallelic LoF mutations in *TBK1* who suffered from chronic systemic autoinflammation. Functional studies demonstrated that TBK1 defects resulted in sufficient production of IFN-I via RIG-I/MDA5, which explains the lack of increased vulnerability to viral infections. Autoinflammation is driven by TNF-induced RCD, as demonstrated in patient-derived fibroblasts that showed higher rates of necroptosis in vitro and augmented apoptosis in PBMCs ex vivo.

2.1.6. RELA haploinsufficiency. The NF-κB transcription complex consists of five subunits: RELA (aka p65), RELB, c-Rel, NF-κB1 (aka p105/p50), and NF-κB2 (aka p100/p52). Activation of RELA is required for regulation of cell death, differentiation of leucocytes, and homeostasis of intestinal epithelial cells.

In 2017, Badran et al. (14) reported four patients with RELA haploinsufficiency, an autosomal-dominant autoinflammatory disease with chronic mucocutaneous ulceration and intestinal inflammation presenting in early childhood. A LoF mutation in *RELA*, which affects the donor splice site of exon 6 (c.559+1G>A), leads to a reduction of RelA expression. The patients' fibroblasts exhibited increased apoptosis in response to TNF and defective expression of NF-κB-dependent antiapoptotic genes. The patients' PBMCs showed impaired IL-6 secretion upon TNF stimulation, indicating defective NF-κB activation (14). Subsequently, 21 additional patients were described, including family cases with reduced penetrance (1, 12, 30). The phenotype of RELA haploinsufficiency is broad given the diverse function of NF-κB.

2.1.7. TRAPS (*TNFRSF1A*). Tumor necrosis factor receptor 1–associated periodic syndrome (TRAPS) is an autosomal dominant disease caused by missense mutations in *TNFRSF1A*, which encodes the 55-kD receptor for TNF. The binding of TNF to the membrane-bound receptor induces receptor trimerization and activation, which signal to regulate cell survival, apoptosis, and inflammation (81).

TNFRSF1A mutations responsible for TRAPS were first reported by McDermott et al. (106) in 1999. This disease is characterized by recurrent long-lasting fever episodes, severe abdominal pain, periorbital edema, conjunctivitis, migratory erythematous skin rash, and arthritis. Most pathogenic mutations affect highly conserved cysteine residues in the extracellular domain of the TNFR1 protein, leading to protein misfolding and retention in the cytosol. Another common pathogenic variant, p.Thr79Met, affects a highly conserved hydrogen bond required for protein folding. The misfolded mutant proteins accumulate in immune cells and are thought to trigger endoplasmic reticulum (ER) stress and activate the unfolded protein response (UPR). TRAPS-associated mutations are considered LoF, based on their impact on protein function, while they have a GoF effect in activating inflammatory pathways (149).

2.1.8. Haploinsufficiency of A20 (*TNFAIP3*). A20 protein plays a vital role in the negative regulation of inflammation and immunity. Heterozygous LoF mutations in *TNFAIP3* lead to the autoinflammatory disease haploinsufficiency of A20 (HA20).

Zhou et al. (188) first described HA20 by analyzing six families with a dominantly inherited inflammatory disease resembling polygenic Behçet's disease (BD). The disease was associated with novel heterozygous frameshift and truncated variants in the ovarian tumor (OTU) domain. The inflammatory signature in HA20 is explained by insufficient suppression of NF-κB activity as well as enhanced nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome activity. Both pathways contribute to the overproduction of proinflammatory cytokines, including IL-1β, IL-6, IL-18, IFN-γ, and TNF. To date, hundreds of HA20 patients of various ancestries have been reported with an expanding spectrum of clinical phenotypes spanning BD; systemic lupus erythematosus (SLE); periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA); IBD; and cases with primary immunodeficiency (PID). In addition to nonsense and truncating mutations, pathogenic missense variants have been reported in some patients, and they are shown to affect protein stability and phosphorylation (175). HA20-associated mutations are also identified throughout the gene; in particular, variants in the ZnF4 domain are associated with a severe phenotype.

2.2. Inflammasomopathies

Inflammasomes are intracellular multimolecular complexes consisting of sensor, adaptor, and effector proteins. They serve as central hubs for the activation of inflammatory responses via IL-1β and/or IL-18 upon stimulation by a set of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). The NLRP3 inflammasome complex was first discovered in 2002 (103), and several inflammasomes have been well characterized during the last two decades, including pyrin, NLRP1, NLRP3, and NLRC4 inflammasomes. Germline and somatic GoF mutations in proteins that nucleate inflammasomes cause caspase-1 activation, resulting in increased production of IL-1β and IL-18.

In general, high-impact mutations that affect residues in the NACHT domain critical for ATP binding and oligomerization result in constitutive inflammasome activation in a dominant fashion. Milder mutations that affect C-terminal autoinhibitory domains may need to be present on both alleles to reach the threshold for protein activation and sometimes require additional environmental factors, such as cold temperature, to assemble active inflammasomes. Dysregulation of regulators of inflammasome function, such as PSTPIP1, WDR1, DPP9 and CDC42, can also cause inflammasome activation and manifestations of SAIDs (**Figure 2**).

2.2.1. Pyrin-associated diseases (*MEFV*). FMF is a recessively inherited disorder caused by biallelic missense mutations in *MEFV*, which encodes pyrin (51, 67). The pyrin protein recognizes bacteria-induced modifications in Rho GTPase activity, which are known as pathogen virulence factors. The prevalence of FMF is very high in multiple Mediterranean populations, with an estimated carrier frequency of 1 in 10. FMF is characterized by recurrent short episodes of fever, serositis, monoarticular arthritis, and susceptibility to systemic amyloid A (SAA) amyloidosis (111). The causative FMF mutations affect the function of a C-terminal B30.2 domain that has autoinhibitory activation and a sensor for a yet-unidentified ligand. At the molecular level, FMF-associated variants are LoF, while at the functional level, they reduce the threshold for pyrin activation, which results in increased IL-1β secretion and pyroptosis (140).

Monoallelic missense mutations in the N-terminal and central B-box/coiled-coil (CC) domains are associated with more severe inflammatory phenotypes. Patients with the heterozygous variants p.Ser242Arg or p.Glu244Lys, which disrupt pyrin inhibition by phosphorylation at serine 242,

present with neutrophilic dermatosis [pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)] (160). These patients possess constitutively active pyrin inflammasomes and experience longer attacks of systemic inflammation than patients with FMF. Why these specific mutations result in severe skin inflammation is yet unclear, but interestingly this phenotype is similar to pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome (discussed below). Finally, heterozygous missense pathogenic variants in and around the central domains of pyrin are associated with another severe inflammatory phenotype and susceptibility to SAA. These mutations may facilitate pyrin oligomerization or prevent binding to putative inhibitory proteins.

2.2.2. PAID (PAMI/PAPA/PAC/PAPASH) (*PSTPIP1*). PSTPIP1-associated inflammatory diseases (PAID) (64) include PSTPIP1-associated myeloid-related inflammatory (PAMI) (181); PAPA; pyoderma gangrenosum, acne, and ulcerative colitis (PAC); and pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis (PAPASH) (104) syndromes. The main clinical manifestations of PAID include neutrophilic skin inflammation, cystic acne, and purulent aseptic arthritis.

PSTPIP1 (also known as CD2BP1) is a cytoskeletal adaptor protein expressed in myeloid cells that interacts with pyrin, PTPN12, WASP, c-Abl, and FasL. Missense mutations in the Fer/CIP4 homology-bin/amphiphysin/Rvs (F-BAR) domain of PSTPIP1 decrease binding to protein tyrosine phosphatase (PTP)-PEST, which results in increased protein phosphorylation and increased association with pyrin. As a result, the pyrin inflammasome is hyperactivated to produce IL-1β and IL-18.

2.2.3. HIDS (*MVK*). The *MVK* gene encodes mevalonate kinase, which is involved in the biosynthesis of cholesterol and isoprenoids. The production of isoprenoids is vital for the regulation of many signaling pathways. Complete deficiency of *MVK* is associated with the severe neurodevelopmental disorder mevalonic aciduria, while biallelic hypomorphic mutations cause HIDS (45, 162), an early-onset disease manifesting with recurrent fevers, arthritis, and in some cases high IgD levels. HIDS patients have a shortage of the isoprenoid geranylgeranyl pyrophosphate (GGPP), which is essential for the proper localization and activation of many proteins, including Rho GTPases. Among other proteins, Rho GTPases regulate the function of NLRP3 and pyrin inflammasomes (112). Pyrin activation likely arises from the loss of activity of the small GTPase RhoA involved in regulating pyrin phosphorylation, while the precise mechanisms linking *MVK* mutations to NLRP3 inflammasome activation are still unclear.

2.2.4. NOCARH (*CDC42*). CDC42 is a small Rho GTPase that regulates cell morphology, motility, polarity, and cell cycle progression. CDC42 is critical for remodeling the actin cytoskeleton. Heterozygous pathogenic variants in the brain-specific isoform of *CDC42* cause Takenouchi-Kosaki syndrome, characterized by impaired neurodevelopment and macrothrombocytopenia (102, 154). In 2019, Lam et al. (84) reported de novo missense mutations in the last part of the C-terminal domain of the ubiquitously expressed transcript isoform, at amino acid residues 186 and 188, in patients with neonatal-onset cytopenia with dyshematopoiesis, autoinflammation, rash, and hemophagocytic lymphohistiocytosis (NOCARH) syndrome. These mutations affect posttranslational modifications by palmitoylation and affect subcellular localization of CDC42 (31). A recent study illustrated the mistrafficking of mutant CDC42 (p.Arg186Cys) to the Golgi apparatus as a direct cause of pyrin inflammasome activation (116).

2.2.5. MSPC, FKLC, and NAIAD (*NLRP1*). The *NLRP1* gene is highly expressed in keratinocytes, and GoF disease–associated mutations activate the proinflammatory milieu in the skin

and promote the proliferation of epithelial cells. These mutations cause a range of skin phenotypes, including multiple self-healing palmoplantar carcinoma (MSPC) (182), familial keratosis lichenoides chronica (FKLC), and NLRP1-associated autoinflammation with arthritis and dyskeratosis (NAIAD) (54). MSPC and FKLC are caused by distinct monoallelic GoF mutations that disrupt either the N-terminal autoinhibitory pyrin domain (PYD) or leucine-rich repeat (LRR) domain (182), leading to constitutive NLRP1 inflammasome activation. Cultured keratinocytes from these patients spontaneously secrete high levels of IL-18. Several mutations that cause NAIAD have been discovered, including the homozygous mutation p.Arg726Trp in helical domain 2 (HD2) of NACHT; the de novo heterozygous mutation p.Pro1214Arg in the function-to-find domain (FIIND), which is critical for autoproteolytic cleavage; and the homozygous variant p.Thr775Asn in the linker domain (46, 54). The associated phenotypes are not limited to skin.

2.2.6. DPP9 deficiency. Dipeptidyl peptidase 9 (DPP9) functions as an inhibitor of NLRP1 by directly binding to the NLRP1-FIIND domain. This scaffolding function of DPP9 is necessary to maintain NLRP1 in its inactive state and to repress inflammasome assembly and activation (62, 183). Patients with deficiency of DPP9 exhibit spontaneous activation of the NLRP1 inflammasome in their cultured keratinocytes and present with growth retardation, pancytopenia, airway infections, and skin pigmentation abnormalities (59). The stop-gain mutations p.Arg111*, p.Ser214*, and p.Gln851*, which lead to deletion of the C-terminal catalytic domain of DPP9, are predicted to completely abolish its enzymatic activity. The missense mutation p.Gly167Ser occurs in a flexible loop at the periphery of the DPP9 substrate binding site. Similar to that of NLRP1-associated disease, the missense mutation carrying primary keratinocytes secretes increased levels of proinflammatory cytokines IL-1β and IL-18.

2.2.7. CAPS (FCAS/MWS/NOMD) (*NLRP3*). Cryopyrin-associated periodic syndromes (CAPS) are a group of autoinflammatory disorders caused by heterozygous GoF mutations in *NLRP3*, the gene encoding cryopyrin. CAPS-causing mutations are associated with three disease phenotypes graded by severity. The mildest form is familial cold autoinflammatory syndrome (FCAS) with cold-induced fever, skin involvement, and arthralgia. Muckle-Wells syndrome (MWS) shows characteristics of a multisystem disease, often with central nervous system involvement. FCAS and MWS were the first SAIDs discovered to be caused by pathogenic variants in *NLRP3* (61). The most severe form is neonatal-onset multisystem inflammatory disease (NOMID) with early-onset and widespread inflammation (6). The disease incidence is estimated at 1–3 per million. The clinical symptoms of NOMID/MWS include fever, nonpruritic urticaria-like rash, arthralgia, bony overgrowth, aseptic meningitis, sensorineural deafness, and eye inflammation.

CAPS is associated with heterozygous GoF missense mutations that lead to NLRP3 inflammasome activation, caspase-1 cleavage, and overproduction of IL-1β. Most of the known CAPS-associated variants reside in the NACHT domain. Typically, de novo mutations result in a more severe phenotype seen in the perinatal period, while milder mutations are dominantly inherited with variable manifestations. A rare mutation (p.Asp21His) in the N-terminal PYD is associated with an ophthalmologic condition known as keratoendotheliitis fugax hereditaria (157). Mutations in the LRR domain are associated with milder inflammation and late-onset phenotypes such as isolated hearing loss. The milder phenotype may be attributed to the inability of these variants to directly activate the NACHT domain.

A mutation in the LRR domain, p.Arg920Gln, was found in a patient with episodes of fever, sore throat, and extensive oropharyngeal ulceration. This variant enhances the interaction between NLRP3 and its endogenous activator, NimA-related protein kinase 7 (NEK7), by affecting the charge complementarity between the two proteins (27).

2.2.8. AIFEC and FCAS4 (*NLRC4*). The NLRC4 inflammasome is highly expressed in gut epithelial cells. *NLRC4* GoF mutations are associated with autoinflammation with infantile enterocolitis (AIFEC) and FCAS4. Patients present with early-onset recurrent fever and enterocolitis and are susceptible to macrophage activation syndrome (MAS). Romberg et al. (135) and Canna et al. (26) demonstrated that patient-derived monocytes and macrophages exhibit constitutive inflammasome activation and increased secretion of IL-1β and IL-18. Kitamura et al. (75) identified a heterozygous missense mutation, p.His443Pro, in the nucleotide oligomerization domain (NOD) of NLRC4 that results in FCAS4. In general, patients with GoF mutations in the NACHT domain are prone to develop MAS, while mutations outside of this domain are more likely to be associated with a milder FCAS-like phenotype.

The biallelic rare hypermorphic variant p.Ala160Thr in *NLRC4* was recently reported in a patient with episodes of systemic inflammation, gastrointestinal symptoms, rash, arthralgia, and uveitis. The mutated residue Ala160 is in the vicinity of the adenosine triphosphate (ATP) binding pocket but is not directly exposed in the structure, as is the case with other MAS-associated mutations, and results in a modest increase in IL-1β/IL-18 production. Carriers of this heterozygous variant are enriched in a cohort study of patients with ulcerative colitis (148).

2.2.9. PFITS (*WDR1*). The *WDR1* gene encodes actin-interacting protein-1 (AIP1), which regulates cofilin-mediated actin depolymerization. Homozygous or compound heterozygous LoF mutations in *WDR1* are linked to periodic fever, immunodeficiency, and thrombocytopenia syndrome (PFITS) (80, 126, 147) with severe phenotypes. WDR1 plays an important role in lymphocyte differentiation, which explains the severe immunodeficiency in affected individuals. Some patients develop autoimmune manifestations, including chronic thrombocytopenia, anemia, severe stomatitis, and perianal ulcerations. Disturbances in the actin cytoskeleton are sensed by the pyrin inflammasome, and the inflammatory phenotype is thought to be driven by IL-18.

2.3. Type I Interferonopathies

Type I interferonopathies (IFNopathies) are a group of SAIDs caused by constitutive activation of the interferon signaling pathway. Genes involved in IFN-I production and/or signaling are critical for immune responses against viral pathogens. The clinical spectrum of type I IFNopathies is broad, ranging from systemic autoinflammation to distinct organ-specific manifestations mainly in the brain and the skin (37). In contrast to IFNopathies, LoF mutations in genes that function as intracellular sensors for microbial nucleic acids are linked to heightened susceptibility to infections, including coronavirus disease 2019 (COVID-19) (178). Thus, pathogenic variants in the same gene, depending on their effects on protein function, can result in systemic inflammation or immunodeficiency [e.g., Toll-like receptor 7 (TLR7)].

The first type I IFNopathy described in the literature was Aicardi-Goutières syndrome (AGS), comprising a group of early-onset neurological debilitating diseases caused by dysregulated sensing or processing of nucleic acids (35, 36). Another representative group of interferonopathies is proteasome-associated autoinflammatory syndromes (PRAAS), which result from defects in the assembly and function of the proteasome complex. IFNopathies are also linked to a deficiency of proteins that function as negative regulators of the IFN-I signaling pathway, such as ISG15, USP18, and SOCS1. Additionally, biallelic GoF mutations in *STAT2* cause a defect in USP18 activation and thus impair the negative regulation of IFN. Recently, three variants in the SH2 domain of STAT4 were identified in four disabling pansclerotic morphea (DPM) patients. A functional analysis demonstrated that the mutations are GoF variants, and inhibition of JAK-STAT signaling with ruxolitinib resulted in decreased hyperinflammatory signals in fibroblasts in vitro, as well as attenuation of inflammatory markers and clinical symptoms in two patients (14a).

Pathogenic mutations have been identified in several other genes that function in IFN-I signaling, including *DDX58/RIGI*, *OAS1*, *TLR7*, *TLR8*, *ATAD3A*, and *JAK1* (**Figure 3**). A hallmark feature of IFNopathies is the IFN response gene signature (IRG-S) that can be measured in blood or cerebrospinal fluid (CSF). This test for IRG-S has been increasingly used in the evaluation of patients with SAIDs. Targeted treatment of IFNopathies with JAK inhibitors often ameliorates disease activity, while haematopoietic stem cell transplantation (HSCT) can be curative in patients with severe immune dysregulation. The genotype-to-phenotype correlation in IFNopathies is an intriguing area of investigation, as incomplete penetrance is common among these conditions. Lessons from IFNopathies have provided insights into molecular mechanisms that initiate and sustain inflammation in more common autoimmune diseases such as SLE.

2.3.1. PRAAS. Proteasomes are multiprotein complexes with ATP-dependent proteolytic activities that mediate the clearance of K48 ubiquitin chain–tagged proteins. The catalytic core of the proteasome complex is composed of 14 different subunits stacked in four septamer rings. Immune cells contain a specialized immunoproteasome that selectively incorporates catalytic subunits encoded by *PSMB8*, *PSMB9*, and *PSMB10*. Proteasome assembly and function are regulated by proteasome maturation protein (POMP), among other chaperone proteins.

Defects in proteasome subunits or chaperones lead to PRAAS, which are characterized by early-onset recurrent fevers, neutrophilic dermatosis, lipodystrophy, calcinosis, progressive joint contractures, and multiorgan failure. Currently, pathogenic LoF mutations that cause PRAAS have been found in *PSMA3* (encodes α7), *PSMB4* (encodes β7), *PSMB8* (encodes β5i), *PSMB9* (encodes β1i), *PSMB10* (encodes β2i), *PSMD12* (encodes Rpn5), and the chaperones essential for proteasome assembly, including *PSMG2* (encodes proteasome assembly chaperone PAC2) and *POMP* (2, 22, 41, 68, 72, 74, 82, 114, 123, 127, 137, 174). The inheritance of PRAAS-associated LoF variants is complex and includes biallelic pathogenic mutations in a single subunit and digenic variants in two different subunits, as well as monoallelic LoF variants. Most patients have biallelic LoF mutations in *PSMB8*. Biallelic LoF has also been identified in *PSMB4* and *PSMG2* (22, 41). In addition, a dominantly inherited severe form, proteasome-associated autoinflammatory syndrome with immunodeficiency (PRAAS-ID), is caused by a de novo heterozygous mutation in *PSMB9* (p.Gly156Asp) that affects the highly conserved residue essential for the maturation and activity of the immunoproteasome (72). Similarly, monoallelic de novo inherited mutations with a dominant-negative effect in POMP result in severe immune dysregulation (127). Heterozygous LoF mutations in the 19S regulatory protein PSMD12 were initially reported in patients with neurodevelopmental phenotypes, but additional studies showed an IFN-I–mediated inflammatory gene expression signature in this disease (174).

2.3.2. Aicardi-Goutières syndrome. AGS is a leukoencephalopathy presenting with basal ganglia calcifications, progressive cerebral atrophy, lymphocytosis, and elevated IFN-α in CSF (36). Patients may also develop signs of autoimmunity, including cytopenia, autoantibodies, arthritis, and peripheral vasculitis (35). AGS is a genetically heterogeneous disease caused by biallelic LoF mutations in genes involved in nucleic acid metabolism, including *TREX1* (32, 33), *RNASEH2A*, *RNASEH2B*, *RNASEH2C* (23, 32, 34), *SAMHD1* (32, 133, 134), and *ADAR* (32, 134), or by a monoallelic GoF mutation in the dsRNA sensor *IFIH1/MDA5* (25, 32). Defects in these nucleases, nucleic acid modifiers, and sensors result in inappropriate activation of the IFN-I pathways. The list of genes that cause AGS phenotypes is continuing to expand. Biallelic LoF mutations in *LSM11* and *RUN7-1* have recently been identified in AGS patients (159).

2.3.3. SAVI (*TMEM173*). Stimulator of interferon genes (STING), also known as transmembrane protein 173, is an ER membrane protein that participates in cytosolic DNA sensing. Upon

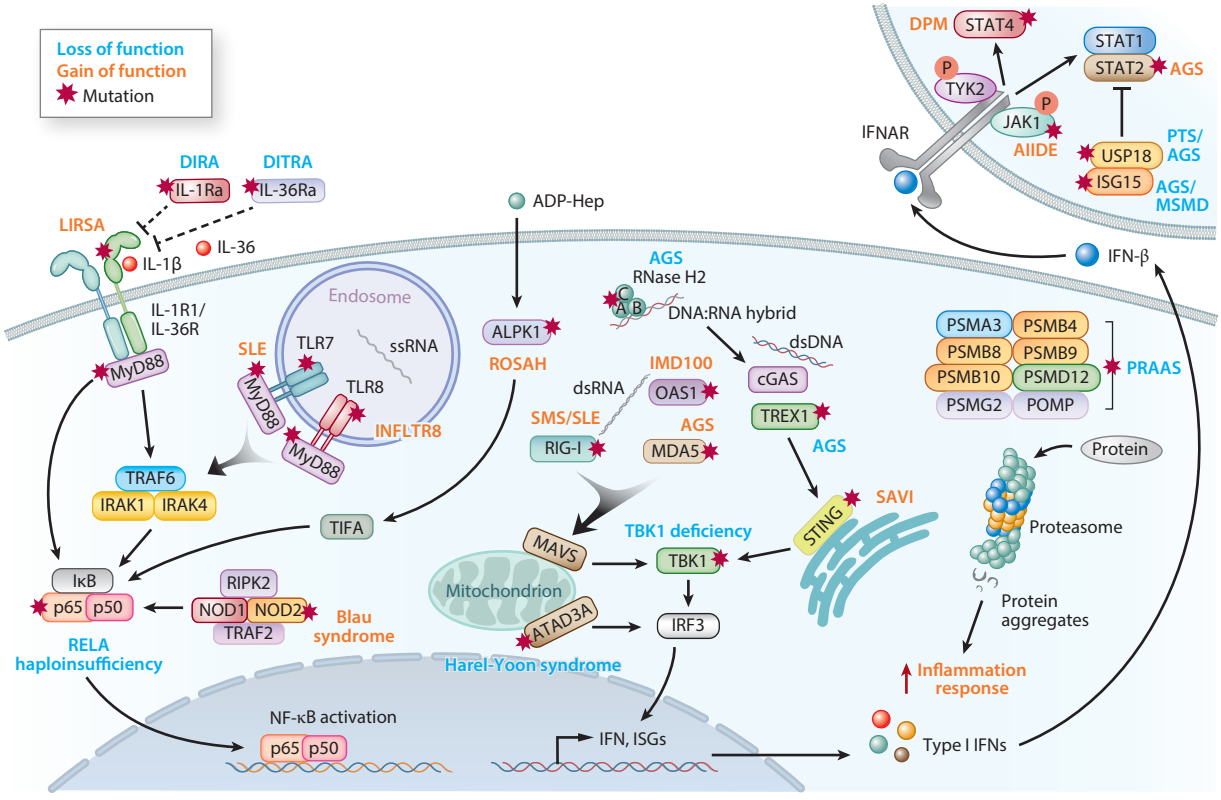


Figure 3

Type I interferonopathies and NF-κB-mediated autoinflammatory diseases. Mislocalized DNAs and RNAs in intracellular compartments are considered PAMPs or DAMPs, which can be recognized by various PRRs. RIG-I and cGAS recognize dsRNA and dsDNA, respectively. TLR7 and TLR8 are endosomal Toll-like receptors that sense ssRNA. IFN or NF-κB signaling is initiated upon activation of these PRRs. The secreted IFN-I stimulates IFN receptors of the effector cells. Proteasomes are multiprotein complexes that play a role in the clearance of K48 ubiquitin-tagged proteins. Defective proteasome activity leads to the accumulation of misfolded proteins and triggers cellular stress responses. The IL-1 signaling pathway is activated by the binding of proinflammatory cytokines such as IL-1α, IL-1β, and IL-36 to IL-1R1 or IL-36R, and inhibited by IL-1Ra and IL-36Ra. Uncontrolled activation of both IL-1 and TLR pathways can lead to heightened NF-κB signaling. MyD88 is an adaptor protein for most TLRs and IL-Rs. Recessive loss-of-function mutations are found in patients with Immunodeficiency 68. A germline gain-of-function mutation was reported in a patient with severe arthritis (142). Somatic gain-of-function mutation Leu265Pro is found in patients with B-cell lymphomas, Schnitzler's syndrome, IgM MGUS, and Waldenstrom macroglobulinemia. Abbreviations: ADP-Hep, adenosine diphosphate-heptose; AGS, Aicardi-Goutières syndrome; AIIDE, autoinflammation, immune dysregulation, and eosinophilia; ALPK1, alpha kinase 1; ATAD3A, ATPase family AAA domain containing 3A; cGAS, cyclic GMP-AMP synthase; DAMP, damage-associated molecular pattern; DIRA, deficiency of the interleukin-1 receptor antagonist; DITRA, deficiency of the interleukin-36 receptor antagonist; dsDNA, double-stranded DNA; dsRNA, double-stranded RNA; IFN, interferon; IFNAR, type I IFN receptor; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; IL-36Ra, IL-36 receptor antagonist; IMD, immunodeficiency; INFLTR8, inflammation, neutropenia, bone marrow failure, and lymphoproliferation caused by TLR8; IRAK, interleukin 1 receptor-associated kinase; IRF3, interferon regulatory factor 3; ISG15, interferon-stimulating gene 15; JAK1, janus kinase 1; LIRSA, Loss of Interleukin-1 Receptor to Interleukin-1 Receptor Antagonist; MAVS, mitochondrial antiviral signaling protein; MGUS, monoclonal gammopathy of undetermined significance; MSMD, Mendelian susceptibility to mycobacterial disease; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor kappa B; NOD, nucleotide oligomerization domain; OAS1, oligoadenylate synthetase 1; PAMP, pathogen-associated molecular pattern; PRAAS, proteasome-associated autoinflammatory syndromes; PRR, pattern recognition receptor; PTS, pseudo-TORCH syndrome; RELA/p65, RELA proto-oncogene, NF-κB subunit; ROSAH, retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and headache; SAVI, STING-associated vasculopathy; SLE, systemic lupus erythematosus; SMS, Singleton-Merten syndrome; ssRNA, single-stranded RNA; TBK1, TANK-binding kinase 1; TLR, Toll-like receptor; TREX1, three prime repair exonuclease 1; TYK2, tyrosine kinase 2; USP18, ubiquitin-specific peptidase 18.

DNA sensing by the intracellular sensor cyclic GMP-AMP (cGAMP) synthase (cGAS), 2′,3′-cGAMP is produced as a secondary messenger to activate STING, followed by TBK1-interferon regulatory factor 3 (IRF3) activation. The cGAS-STING pathway has an important role in the induction of IFN-I, and heterozygous GoF mutations in *TMEM173* are found in patients with severe small vessel vasculitis and interstitial lung disease. De novo pathogenic mutations in STING reside in the highly conserved connector helix loop domain and lead to constitutively activated STING and increased production of IFN-I. Milder mutations in *TMEM173* are associated with lupus erythematosus–like syndromes and familial chilblain lupus (71, 76, 108). Mutations that mildly affect STING activation may need to be inherited in the biallelic state to autoactivate the protein (94).

2.3.4. *DDX58*-associated diseases. DExD/H-box helicase 58 encodes RIG-I, an RNA helicase that recognizes double-stranded RNA viruses to activate IFN-I production. Pathogenic variants of *DDX58* activate the IFN pathway in the absence of exogenous RNA ligands. Mutations in *DDX58* as well as *IFIH1* (associated with AGS) have been implicated in rare cases of Singleton-Merten syndrome (SMS, also known as SGMRT), an autosomal dominant interferonopathy characterized by glaucoma, aortic calcification, psoriasis, and dental and skeletal abnormalities (129). Recently, Peng et al. (125) identified a novel heterozygous *DDX58* variant (p.Arg109Cys) in five unrelated families with lupus nephritis. This variant disrupts RIG-I autoinhibition and thereby causes constitutive IFN activation. These results expanded the clinical phenotypes of DDX58-related disease from SMS to SLE.

2.3.5. OAS1-associated diseases. Oligoadenylate synthetase 1 (OAS1) is a type I interferon–inducible protein involved in the initiation of antiviral immune responses. Cho et al. (29) identified three heterozygous missense mutations in the *OAS1* gene in five patients who presented with infantile-onset pulmonary alveolar proteinosis, respiratory insufficiency, and hypogammaglobulinemia. Subsequently, Magg et al. (97) reported four additional heterozygous *OAS1* GoF mutations that caused a polymorphic immunodeficiency. These pathogenic mutations induce transcription changes in monocytes, B cells, and T cells that influence ribonuclease L (RNase L)–dependent cellular antiviral defense, apoptosis, protein translation arrest, and cellular RNA degradation. By contrast, biallelic LoF *OAS1* mutations have been identified in patients with severe COVID-19 (16, 66), illustrating a critical function of OAS1 in the defense against SARS-CoV-2.

2.3.6. TLR7/TLR8-associated diseases. The TLR family is a group of pattern recognition receptors that recognize pathogen signatures including single- and double-stranded DNA or RNA. *TLR7* and *TLR8* reside on the X chromosome, and the protein products are positioned on the endosomal membrane. Hemizygous GoF mutations in *TLR7* and *TLR8* cause a complex immune dysregulation comprising immunodeficiency, inflammation, neutropenia, bone marrow failure, and lymphoproliferation (49, 57).

Brown et al. (24) reported five female patients with SLE from three unrelated families with heterozygous GoF mutations (p.Tyr264His, p.Arg28Gly, and p.Phe507Leu) in *TLR7*. As TLR7 can escape X chromosome inactivation (XCI) in human B cells, plasmacytoid dendritic cells (pDCs), and monocytes (145), these causal variants can lead to enhanced TLR7 expression in females. These missense variants increased the affinity for the TLR7 ligands guanosine, cGMP, and ssRNA. By contrast, several studies have identified LoF mutations in *TLR7* in patients with severe COVID-19 (50, 100, 161).

Aluri et al. (10) identified six unrelated male patients with GoF mutations in *TLR8* presenting with refractory neutropenia, lymphoproliferation, B-cell defects, and bone marrow failure. Whether TLR8 escapes XCI in human immune cells is unclear. Remarkably, five out of six patients

were found to harbor somatic variants with less than 30% mosaicism in peripheral blood samples. In addition to hematopoietic cells, these variants have also been found in fibroblasts, suggesting an early mutational event during development. The mosaic and germline variants reduced the threshold for TLR8 activation, which results in the activation of T cells, and increased production of NF-κB-induced cytokines that may cause inflammatory phenotypes in the bone marrow.

2.3.7. Harel-Yoon syndrome (*ATAD3A*). ATAD3A is a mitochondrial membrane protein that functions to stabilize mitochondrial DNA (mtDNA). Heterozygous mutations in *ATAD3A* cause Harel-Yoon syndrome, a neurodevelopmental disorder, while compound heterozygous mutations cause neonatal lethal pontocerebellar hypoplasia, hypotonia, and respiratory insufficiency syndrome (PHRINL). Lepelley et al. (90) reported seven patients with dominant-negative heterozygous mutations in *ATAD3A* associated with neurological disorders, including developmental delay, dystonia and seizures, and systemic sclerosis with enhanced IRG-S expression in blood. These variants affect the ATPase activity of ATAD3A and result in the leakage of mtDNA and IFN production via cGAS-STING.

2.3.8. AIIDE (*JAK1*). Janus kinase 1 (JAK1) is one of four JAK proteins that mediate the signaling of cytokines and growth factors by phosphorylating signal transducer and activator of transcription (STAT) proteins. JAK1 and tyrosine kinase 2 (TYK2) function directly downstream of the type I IFN receptor (IFNAR) complex to activate STAT1 and STAT2.

In 2017, Del Bel et al. (43) reported a heterozygous missense mutation, p.Ala634Asp, in the *JAK1* gene in a mother and her two sons who presented with autoinflammation, immune dysregulation, and eosinophilia (AIIDE). In vitro studies with patients' B and T cells showed enhanced STAT1 and STAT3 activation in response to stimulation, consistent with a GoF effect. The second GoF pathogenic variant, p.His596Asp, was found in the conserved pseudokinase domain, resulting in increased phosphorylation of JAK1 and STAT proteins (153).

2.3.9. Defect in negative regulation of interferon signaling. The IFN signaling pathway is initiated via ligand binding with IFNAR and subsequent multistep phosphorylation events, leading to the transcription of hundreds of ISGs. Among these inducible genes, ISG15 and USP18 form a complex that negatively regulates the IFN-I response. Excessive IFN-I signaling can be caused by biallelic LoF mutations in these negative regulators (9, 110, 179). Homozygous GoF mutations in *STAT2* can also perturb the negative regulation of IFN-I by USP18 (47, 56).

In patients with ISG15 deficiency, homozygous nonsense or frameshift mutations result in protein destabilization and increased proteolysis of USP18. These patients exhibit calcification of the basal ganglia and elevated IFN-α/β immunity (179). Interestingly, they are also more susceptible to mycobacterial infections [i.e., Mendelian susceptibility to mycobacterial diseases (MSMD)] because ISG15 has a function in the stimulation of IFN-γ production. USP18 deficiency is a more severe disease, initially described as the pseudo-TORCH syndrome (PTS), characterized by microcephaly, enlarged ventricles, and cerebral calcification at birth (110). The central role of IFN in USP18 deficiency was supported by the dramatic response to JAK inhibition (9). The identification of biallelic GoF mutations in *STAT2* revealed a surprising and important role of STAT2 in the negative regulation of IFN-I. STAT2 is considered to be a positive regulator of IFN signals via its function in the transcription factor complex. The identified homozygous mutations in *STAT2*, p.Arg148Gln and p.Arg148Trp, exhibit poor STAT2 binding to USP18, and thus perturb the normal negative regulator function of USP18 in the IFN pathway (47, 56).

Suppressor of cytokine signaling 1 (SOCS1) is another negative regulator of both type I and type II IFN signaling. Heterozygous LoF mutations in *SOCS1* lead to multisystem inflammatory syndrome in children or familial autoinflammatory syndrome with or without immunodeficiency

(58, 88). Patients presented with early-onset autoimmune manifestations, recurrent infections, fever, otitis media, and oral ulcers. The identified causal mutations are located in different protein domains: near the kinase inhibitory region domain, in the middle SRC-homology 2 (SH2) domain, and in the SOCS box. Disruption of specific domains may be responsible for the variable impairment of SOCS1 function.

2.4. Uncategorized Monogenic Autoinflammatory Diseases

The current classifications of SAIDs are based on affected molecular and cellular pathways, but there is a group of SAIDs with complex or distinct pathogenic mechanisms, which are difficult to group into the categories above.

2.4.1. DADA2 (*ADA2/CECR1*). DADA2 is an autosomal recessive disease and the first molecularly characterized monogenic form of vasculitis affecting small- and medium-size arteries (48, 189). ADA2 is an extracellular deaminase highly expressed in myeloid cells that may also contribute to immune cell differentiation. The onset of the disease is usually in early childhood, and common clinical features include fevers, skin rash, recurrent ischemic strokes, and humoral immunodeficiency. Patients with vasculitis typically harbor missense variants with partially retained enzymatic function, while the complete ADA2 deficiency (i.e., biallelic nonsense, insertion/deletion, and frameshift variants) results in severe hematological manifestations, including bone marrow failure. There are over 100 pathogenic variants identified in patients of various ancestries, while missense mutations p.Gly47Arg and p.Arg169Gln are founder mutations in South Asian/Middle Eastern and Northern European populations, respectively. The estimated frequency of ADA2 mutations is 1 in 240 people, with potentially over 30,000 patients worldwide (70). ADA2 modulates monocyte polarization, and its deficiency leads to unbalanced differentiation toward proinflammatory M1 macrophages, which causes vasculitis (87). Treatment with TNF inhibitors (TNFi) is remarkably efficacious in preventing strokes and ameliorating features of systemic inflammation, while it is less effective for patients with hematologic manifestations (120).

2.4.2. PLAID/APLAID (*PLCG2*). The *PLCG2* gene encodes phospholipase Cγ2 (PLCG2), a transmembrane enzyme that catalyzes the production of 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG), which act as second messenger molecules to activate downstream nuclear factor of activated T cells (NFAT) and mitogen-activated protein kinase (MAPK) or the NF-κB pathway, respectively. Heterozygous variants that affect protein autoinhibition are linked to two clinically distinct disorders: PLCG2-associated antibody deficiency and immune dysregulation (PLAID) and autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation (APLAID). Ombrello et al. (121) described three families with cold-induced urticaria and immune dysregulation carrying small genomic deletions in the autoinhibitory C-terminal Src-homology 2 (cSH2) domain. Zhou et al. (187) identified a missense variant, p.Ser707Tyr, in the same domain in a family with severe systemic and organ-specific inflammation and humoral deficiency, without cold-induced symptoms. In addition, several other missense mutations, p.Ala708Pro, p.Leu848Pro, p.Leu845_Leu848del, and p.Met1141Lys, have been linked to APLAID. All these pathogenic mutations result in the hyperactivation of PLCγ2, increased production of the second messenger molecules DAG and IP3, calcium release, and upregulation of the downstream extracellular signal–regulated kinase (ERK) and other immune pathways.

2.4.3. SIFD (*TRNT1*). Transfer RNA (tRNA) nucleotidyltransferase 1 (TRNT1) is a ubiquitously expressed enzyme that catalyzes the addition of the CCA tail at the 3′ end of both cytosolic and mitochondrial precursor tRNA. Biallelic LoF in *TRNT1* causes sideroblastic anemia with B-cell immunodeficiency, periodic fever, and developmental delay (SIFD) (8, 28). Complete TRNT1

deficiency is incompatible with life, while hypomorphic LoF mutations that retain residual activity cause SIFD. Genotype–phenotype correlation analysis found that pathogenic variants in the central catalytic domain cause a more severe phenotype, whereas mutations in the N- or C-terminal region cause a milder phenotype (143). Higher residual TRNT1 activity is associated with retinitis pigmentosa and erythrocytic microcytosis (RPEM).

2.4.4. Defects in the negative regulation of IL-1 signaling. The proinflammatory activity of IL-1 family cytokines is modulated by a set of receptor antagonists and anti-inflammatory cytokines. Deficiency of the interleukin-1 receptor antagonist (DIRA) is caused by biallelic LoF mutations in *IL1RN*, which is highly expressed in the epidermis. The unopposed effects of IL-1α and IL-1β signaling result in systemic inflammation manifesting as pustular skin lesions, sterile multifocal osteomyelitis, and periostitis (5, 131). Deficiency of the interleukin-36 receptor antagonist (DITRA) caused by biallelic LoF mutations in *IL36RN* is characterized by recurrent fevers with generalized pustular psoriasis (101, 122). The disease expressivity of these conditions is variable and at least partly dependent on environmental factors. Recently, a novel AID caused by a missense variant in IL-1R1 was identified and named LIRSA (Loss of Interleukin-1 Receptor to Interleukin-1 Receptor Antagonist) (168). The p.K131E variant in IL-1R1 abolishes the interaction between IL-1R1 and its antagonist IL-1Ra. The patient exhibited chronic recurrent multifocal osteomyelitis, with highly inflammatory cytokines and chemokines in the serum, and responded well to treatment with anti-IL-1β (**Figure 3**).

2.4.5. SYK-associated immune dysregulation. The *SYK* gene encodes a protein tyrosine kinase expressed in immune cells and epithelial cells of the gastrointestinal mucosa. SYK is an essential regulator of B-cell development and function, as well as a regulator of B-cell receptor (BCR)-mediated signaling.

Wang et al. (167) identified five GoF variants of *SYK* in patients with immunodeficiency, colitis, arthritis, skin inflammation, and variable B- and T-cell abnormalities. Most patients develop symptoms in infancy or early childhood, but the disease expressivity is variable. The pathogenic variants caused increased phosphorylation of SYK at Tyr525/Tyr526 and enhanced activity of downstream ERK and NF-κB pathways.

2.4.6. C2ORF69 deficiency. C2ORF69 regulates mitochondrial membrane potential and oxidative respiration in cultured neurons and controls glycogen branching enzyme 1 (GBE1). Inactivation of C2orf69 in zebrafish results in lethality by 8 months of age due to brain inflammation. Two groups independently identified 16 unrelated patients with severe autoinflammation, failure to thrive, and progressive leukoencephalopathy carrying homozygous LoF *C2ORF69* variants (86, 172). RNA sequencing of Epstein-Barr virus–transformed lymphocytes from one patient revealed upregulation of genes involved in oxidative phosphorylation (OXPHOS), suggesting that C2ORF69 may play a role in cellular metabolism inside the mitochondria.

2.4.7. HCK-driven pulmonary and cutaneous vasculitis. Hematopoietic cell kinase (HCK) is an SRC family tyrosine kinase expressed predominantly in granulocytes and monocytes. Similar to the activity of other members of the SRC-family kinases (SFKs), the activity of HCK relies on the Tyr522 residue in the C terminus. Phosphorylation of Tyr522 promotes a conformation change to autoinhibit the kinase activity. A heterozygous LoF mutation in *HCK* that causes increased kinase activity, p.Tyr515*, was identified in a patient with cutaneous vasculitis and chronic pulmonary inflammation that progressed to fibrosis (73). The mutant HCK enhanced myeloid cell priming, migration, and effector functions, resulting in the production of the inflammatory cytokines, including IL-1β, IL-6, IL-8, and TNF.

2.4.8. AIFBL2/DEX (*ELF4*). ELF4 belongs to the E-twenty-six (ETS) domain transcription factor family and is involved in a variety of biological processes, including development and function of natural killer cells, T cells, and macrophages. ELF4 also acts as a negative regulator of inflammatory responses. It is activated upon phosphorylation by TBK1 and can translocate into the nucleus to bind *IFNB1*, *CSF2*, *IL-3*, *CXCL8*, and *PRF1* promoters.

LoF mutations in *ELF4* have been reported to cause autoinflammatory syndrome, familial, X-linked, Behcet-like 2 (AIFBL2), also known as deficiency in ELF4, X-linked (DEX). Three hemizygous mutations, p.Trp251Ser, p.Ala339Profs*32, and p.Trp231Arg, were reported in four unrelated male patients with early-onset fever, mucosal autoinflammation, and IBD (151, 158). Patients lacking functional ELF4 exhibited heightened expression of IL-17, augmented T_H17 cell responses, and proinflammatory responses in macrophages.

2.4.9. FACAS (*F12*). The *F12* gene encodes coagulation factor XII, which serves important functions in coagulation, fibrinolysis, complement activation, and regulation of the kallikrein-kinin system. Previously, human factor XII (FXII) deficiency was linked to a potentially life-threatening hereditary angioedema (HAE) type III. In 2020, Scheffel et al. (139) reported a four-generation family with a history of cold-induced urticaria, autoinflammatory, fever, headache, arthralgia, and fatigue syndrome linked to a heterozygous missense mutation, p.Trp268Arg, in *F12*, termed FXII-associated cold autoinflammatory syndrome (FACAS). This missense variant causes changes in protein conformation and exposes the activation loop. The mutant protein is constitutively active and results in an overactive kallikrein-kinin system, high levels of plasma bradykinin, and increased expression of IL-1β in the skin.

2.4.10. ROSAH (*ALPK1*). Alpha-kinase 1 (ALPK1) is an atypical protein kinase that functions as a cytosolic innate immune receptor for bacterial 7-carbon sugar ADP-β-D-manno-heptose (ADP-hep). ADP-hep directly binds the N-terminal domain of ALPK1, stimulating its kinase domain to phosphorylate and activate TRAF-interacting protein with a forkhead-associated domain (TIFA) and NF-κB (185).

A heterozygous GoF mutation in the *ALPK1*, p.Thr237Met, was identified in five families with a distinct retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and migraine headache (ROSAH) syndrome (171). This mutation resides in the N-terminal domain and activates downstream targets of the NF-κB signaling pathway. Subsequently, the same pathogenic variant was identified in over 20 ROSAH patients (78, 184). In addition to the enhanced NF-κB activity, some patients display a pronounced systemic inflammatory phenotype partially mediated by IFN-I signaling.

3. DIGENIC AUTOINFLAMMATORY DISEASES: PRAAS

Our discussion so far has focused on monogenic SAIDs. Some SAIDs are inherited in a digenic manner, in which heterozygous mutations in two distinct genes show additive effects in driving the disease phenotype. PRAAS were the first autoinflammatory diseases reported to have digenic inheritance (22).

The proteasome is important cellular machinery that catalyzes most of the protein degradation, and the integrity of each subunit is of great importance to the overall function of the multimeric complex. A subset of patients is found to carry pathogenic variants at two genes (*PSMB8/PSMA3*, *PSMB8/PSMB4*, or *PSMB9/PSMB4*). The synergistic effect of these variants is functionally validated, and patients with these digenic mutations often present with a severe phenotype (22).

4. POLYGENIC OR MULTIFACTORIAL AUTOINFLAMMATORY DISEASES

Several SAIDs are considered polygenic, including Still's disease/systemic juvenile idiopathic arthritis (SJIA), BD, Crohn's disease, and PFAPA. Genome-wide association studies (GWASs) represent a powerful approach to map the polygenic architecture by identifying common susceptible alleles in large cohorts of patients. In BD, GWASs identified risk alleles in *IL-23R/IL-12RB2*, *IL-10*, *STAT4*, *CCR1–CCR3*, *KLRC4*, *ERAP1*, *TNFAIP3*, and *FUT2* genes in Turkish and Japanese populations (155). Subsequently, targeted sequencing of 14 candidate genes revealed contributions of rare missense variants of *IL-23R*, *TLR4*, *NOD2*, and *MEFV* to the pathogenesis of BD. Manthiram et al. (98) reported shared genetic variants among individuals with recurrent canker sores, PFAPA, and BD in two European-American cohorts and a Turkish cohort with PFAPA. These include susceptibility variants in *STAT4*, *IL-10*, *IL-12A*, and *CCR1–CCR3* genes.

NOD2/CARD15 is among the strongest susceptibility genes in Crohn's disease. The three most common risk alleles are p.Arg702Trp, p.Gly908Arg, and p.Leu1007fs. All are located in the LRR domain and affect the sensing activity or the putative autoinhibitory function of LRRs. Crohn's disease susceptibility alleles are considered functionally hypomorphic as they impair mucosal barrier function and bacterial clearance (7). By contrast, high-impact heterozygous missense GoF variants in the nucleotide-binding NACHT domain cause the early-onset severe granulomatous autoinflammatory disease Blau syndrome (19). Activated NOD2 upregulates the NF-κB signaling pathway; thus, this disease is mediated mainly by TNF.

5. MOSAIC AUTOINFLAMMATORY DISEASES

Somatic mutations that cause SAIDs have been identified in *NLRP3* (113, 136, 186), *NLRC4* (165), *TNFRSF1A* (77), *NOD2* (40, 109), *STING* (95), *TLR8* (10), and *UBA1* (17). These somatic mutations mostly occur in myeloid cells, and they are found in genes associated with dominantly inherited SAIDs. The ratio of somatic mosaicisms varies among different diseases; in some cases, it can be as low as 5% in peripheral blood samples, although it might be higher in bone marrow cells. Most patients with somatic mutations present with a late-onset and milder disease. Thus far, only one recessively inherited disease, disseminated superficial actinic porokeratosis, has been reported to result from one germline and one cell-specific somatic mutation in the *MVK* gene (79).

A study in patients with CAPS found that up to 20% of patients carry a somatic mutation in *NLRP3* and that 50% of these mutations are clustered in the HD2 versus 9% of germline pathogenic variants (96). Only a few *NLRP3* mutations exist in both the germinal and somatic state, as the mosaic mutations could be lethal if present in the germinal state.

Both GoF germline and somatic mutations in *NOD2* cause Blau syndrome. Gonosomal mosaicism has been reported in one family, with the mildly affected father carrying a somatic p.Arg334Gln mutation and two siblings with early-onset disease caused by the germline mutation (109). Gonosomal mutations are also reported in patients with TRAPS and CAPS (60).

UBA1 is a major E1 enzyme that initiates 99% of cellular ubiquitylation. Its somatic mutations have been identified in a severe adult-onset autoinflammatory disease termed VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic). Patients present with recurrent fevers, thrombosis, pulmonary infiltrations, and vacuoles in myeloid and erythroid precursor cells. Missense mutations at the Met41 residue affect the normal transcription of the UBA1 isoform expressed in hematopoietic cells, leading to an alternative isoform with impaired catalytic activity. Given the severity of the VEXAS phenotype, finding the Met41 substitution as a germline mutation is unlikely. Only three female patients are reported, and the disease expression is attributed to monosomy X or skewed X-inactivation.

A somatic mutation, p.Ser703Ile, in *JAK1* was reported by Gruber et al. (55) in a young patient with immunodysregulatory syndrome and asymmetric manifestations of disease. This mutation was identified in cells derived from all three germ layers, suggesting an early mutational event. The mutant transcript is preferentially expressed in PBMCs and renders cells hyperresponsive to cytokine stimulation.

Somatic mutations in *TNFAIP3*, *PLCG2*, and *SYK* are also found in patients with various types of lymphoma or can be associated with resistance to targeted therapies. With the development of new highly sensitive detection methods, somatic mutations will likely be identified in other SAID genes, both in patients with systemic inflammation and in lymphoproliferative diseases.

6. EPIGENETICS IN AUTOINFLAMMATORY DISEASES

Epigenetics is emerging as a new factor in the pathophysiology of autoinflammatory diseases. Epigenetic modifications likely account for variable disease penetrance and expressivity to some degree in all SAIDs.

Biallelic mutations in *LSM11* and *RNU7-1*, the components of the RDH pre-mRNA-processing complex, are associated with a disturbance of chromatin-bound histone stoichiometry and an altered distribution of nuclear cGAS (159). The RDH pre-mRNA misprocessing impairs tolerance to endogenous self-nucleic acids and leads to increased IFN-I signaling, and the patient's clinical phenotype is consistent with AGS.

CAPS patients with *NLRP3* mutations show strong demethylation of proinflammatory genes in monocytes and macrophages in response to IL-1β, whereas an IL-1 blockade reversed these effects (130, 170). These findings indicate that increased IL-1β production may prime DNA demethylation, which could maintain and/or amplify inflammation.

MicroRNAs (miRNAs) are implicated in the regulation of inflammatory processes over the past decade (117). Recently, several studies have identified a role of miRNAs in the pathogenesis of FMF (4, 11, 15, 65, 85, 164), expanding the genetic mechanisms of this monogenic SAID.

7. COPY NUMBER VARIANTS AS THE CAUSE OF AUTOINFLAMMATORY DISEASES

Improved resolution of genetic diagnostic modalities has enabled the detection of small-size CNVs in the exonic and intronic regions. Several CNV loci are implicated in the pathogenesis of SAIDs, for example, β-defensin genes in patients with psoriasis or Crohn's disease (18, 63). In DADA2, intronic Alu repetitive elements lead to either duplication or deletion of exon 7, both of which have been reported in patients (91, 141). Deletions of exon 19 and of exons 20–22 of *PLCG2* in the protein-autoinhibitory SH2 domain are both shown to cause PLAID (121).

Patients with trisomy 8 mosaicism and chromosome 8 duplications [trisomy 8-positive myelodysplastic syndrome (MDS)] have a propensity to develop systemic inflammatory disease with mucocutaneous lesions and recurrent fevers resembling BD or PFAPA syndrome (13, 53, 119). Patients with trisomy 21 are shown to have an IFN gene expression signature, as least partly due to the duplication of interferon-receptor genes *IFNAR1* and *IFNAR2*, which makes these patients hypersensitive to interferon stimulation. However, chronic suppression of IFN signaling by negative regulators eventually weakens the antiviral responses in Down syndrome patients (128, 150, 169). A large genomic deletion that encompasses the *TNFAIP3* gene is described in a patient with a severe inflammatory and neurodevelopmental disease (52).

8. CONCLUSIONS AND FUTURE DIRECTIONS

The current understanding of the pathogenesis of SAIDs has been dramatically expanded in the past ten years with the description of novel disease mechanisms, including digenic and polygenic

variations, CNVs, somatic mutations, and epigenetic dysregulation. The knowledge obtained from studies of SAIDs has not only helped the diagnostic evaluation and treatment of these patients but also increased our understanding of the intricate regulatory networks of innate immunity and the contribution of innate immune response to human health. However, a definitive diagnosis of monogenic SAIDs is currently in about 30% of patients, which suggests that we still have much work to do in defining the causes of systemic autoinflammation. Future investigation should be geared toward genome sequencing, the evaluation of noncoding regions, and epigenetic regulation. New technologies are being developed to facilitate the molecular diagnosis of these disorders with high accuracy and at a reduced cost. A comprehensive understanding of the molecular pathogenesis of SAIDs is the key to define novel treatment targets for these and other more common human inflammatory conditions.

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