Published in final edited form as:

Annu Rev Immunol. 2015 ; 33: 823–874. doi:10.1146/annurev-immunol-032414-112227.

Molecular Mechanisms in Genetically Defined Autoinflammatory Diseases: Disorders of Amplified Danger Signaling*

Adriana Almeida de Jesus†, **Scott W. Canna**†, **Yin Liu**†, and **Raphaela Goldbach-Mansky**
Translational Autoinflammatory Diseases Section, National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH), Bethesda, Maryland 20892

Raphaela Goldbach-Mansky: goldbacr@mail.nih.gov

Abstract

Patients with autoinflammatory diseases present with noninfectious fever flares and systemic and/or disease-specific organ inflammation. Their excessive proinflammatory cytokine and chemokine responses can be life threatening and lead to organ damage over time. Studying such patients has revealed genetic defects that have helped unravel key innate immune pathways, including excessive IL-1 signaling, constitutive NF-κB activation, and, more recently, chronic type I IFN signaling. Discoveries of monogenic defects that lead to activation of proinflammatory cytokines have inspired the use of anticytokine-directed treatment approaches that have been life changing for many patients and have led to the approval of IL-1-blocking agents for a number of autoinflammatory conditions. In this review, we describe the genetically characterized autoinflammatory diseases, we summarize our understanding of the molecular pathways that drive clinical phenotypes and that continue to inspire the search for novel treatment targets, and we provide a conceptual framework for classification.

Keywords

autoinflammatory diseases; IL-1-mediated autoinflammatory diseases; IFN-mediated autoinflammatory diseases; cryopyrin-associated periodic syndromes; proteasome-associated autoinflammatory syndromes; inflammasomes in human disease; hereditary fever syndromes; macrophage activation syndrome

1. INTRODUCTION

Autoinflammatory diseases are immune dysregulatory conditions that typically present in early childhood with fever and disease-specific patterns of organ inflammation. In 1999, Daniel Kastner proposed the term and concept of “autoinflammatory diseases,” indicating that innate immune dysregulation may drive the clinical phenotype of two conditions caused by mutations in *MEFV*/pyrin and the *TNFRSF1A*/TNF receptor type 1 (TNFR1): familial

†These authors contributed equally.

DISCLOSURE STATEMENT

R.G.-M. received study support from SOBI, Novartis, Regeneron, and Lilly. The authors are not aware of any other affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

Mediterranean fever (FMF) and TNF receptor–associated periodic syndrome (TRAPS) (1). This concept has facilitated the understanding of a growing number of diseases for which genetic causes have since been identified and validated the role of innate immune dysregulation in causing autoinflammatory diseases. Over the last 15 years, disease-based gene discovery and basic research have gone hand in hand in deciphering the molecular mechanisms that lead to excessive innate immune responses and cause autoinflammatory phenotypes, and they have provided us with novel therapeutic targets that allow us to effectively treat some of these conditions. In this review, we provide an overview of the currently known genetically defined autoinflammatory syndromes, provide insights into their pathogenesis, and propose an extended pathogenesis-based classification system.

2. DISCOVERY OF AUTOINFLAMMATORY DISEASES CONTRIBUTES TO THE DISCOVERY OF INNATE IMMUNE PATHWAYS

The discovery of extracellular (mostly membrane-bound) and intracellular specialized pattern-recognition receptors (PRRs) that activate innate immune responses, validated the conceptual framework that was postulated by Charles Janeway (2) over 20 years ago and uncovered pathways that constitute innate immunity. These receptors are core components of danger sensing of conserved microbial pathogen-associated molecular patterns (PAMPs) and largely nonmicrobial danger signals referred to as damage-associated molecular patterns (DAMPs) (3). The extracellular receptors/sensors are mostly located on the cell surface and include most Toll-like receptors (TLRs) and the C-type lectin receptors (CLRs). The intracellular sensors are mainly located in the cytoplasm and subcellular organelles and vacuoles and include NOD-leucine-rich repeat proteins (NLRs); the AIM2-like receptors (ALRs); the RIG-I-like receptors/helicases (RLRs/RLHs); and human TLR3, 7, 8, and 9. These intracellular receptors form the cell-intrinsic surveillance system (reviewed in 4–6). Collectively, the extracellular and intracellular receptors coordinate cell and tissue responses to eradicate the inciting danger and restore tissue integrity and homeostasis (reviewed in 6).

Discovery of Cytoplasmic Pattern-Recognition Receptors (NLRs and RLRs) in Autoinflammatory Diseases

The early history of gene discovery in autoinflammatory diseases is marked by the identification of genetic causes in three such intracellular sensors/PRRs. In 1997, the same year the first mammalian TLR, TLR4, was discovered (7), two consortia identified mutations in the MEFV gene, which encodes the intracellular sensor pyrin/marenostrin, as the cause for FMF (8, 9). 2001 marked the discovery of mutations in the first two NLRs (10): Hal Hoffman (11) published his finding that gain-of-function mutations in *NLRP3* cause two conditions, familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS), and sporadic de novo mutations in the same gene cause neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular (CINCA) syndrome (12, 13); and gain-of-function mutations in *NOD2*/*CARD15* were shown to cause another autoinflammatory disease, Blau syndrome (14).

In 2002, John Bertin’s group (15) found that an adaptor protein, ASC (apoptosis-associated speck-like protein containing a CARD), linked NLRP3 to procaspase-1 via homotypic

interactions and that this complex was important for lipopolysaccharide (LPS)-induced caspase-1 activation and IL-1β cleavage. Jurg Tschopp (16) initially and fully characterized the components forming this complex using the NLRP3 homolog, NLRP1, and named the complex the inflammasome.

The discovery of the molecular link between NLRP3 and IL-1 led to the development of clinical studies using IL-1-blocking agents, starting in 2002. NLRP3, NLRP1, NLRC4, AIM2, and MEFV are the five currently known IL-1-activating inflammasomes. Mutations in three of the genes encoding for the inflammasome components, *NLRP3*, *NLRC4*, and *MEFV*, are the causes of monogenic autoinflammatory diseases that are ameliorated with IL-1-blocking treatments.

Activation of the inflammasomes occurs after stimulation through (mostly bacterial) PAMPs or a number of intracellular triggers/stressors, which results in caspase-1 and IL-1β and IL-18 activation. Similarly, antiviral immunity is mediated by intracellular sensors that recognize RNA and DNA nucleotides. 2004 marked the discovery of the first two cytoplasmic RNA sensors, the homologous helicases RIG-I and MDA5 (melanoma differentiation–associated gene 5). This novel PRR group was termed RIG-I-like receptors (RLRs) (5, 17, 18). Most recently, the discovery that the enzyme cGAS [cyclic guanosine monophosphate (GMP)–adenosine monophosphate (AMP) synthase] is activated by immunostimulatory DNA, catalyzes the formation of the second messenger cGAMP (cyclic GMP-AMP), and activates the adaptor molecule STING (stimulator of interferon genes) established the molecular mechanism that links DNA sensing to the production of IFN-β (19). Studies published in 2014 found that gain-of-function mutations in *IFIH1* (encoding MDA5) (20) and the adaptor molecule *TMEM173/STING* (21) lead to constitutive production of type I IFNs, expanding the array of cytokines associated with autoinflammatory diseases.

The discovery of a growing number of intracellular sensors and their molecular triggers may ultimately explain the still mysterious nature of the disease flares that in a disease-specific fashion can be triggered by infections, cold exposure, immunizations, psychological stress, or mechanical injury.

A growing number of genetic mutations affect enzymes or molecular pathways that result in the accumulation of molecular products that disturb cell homeostasis and thus generate cell stress. The exploration of pathways that couple intracellular stress and activate inflammatory mediators is a challenging area of ongoing investigation.

Disease-Causing Mutations Affect Innate Immune Components

One way of organizing the genetic defects that cause autoinflammatory diseases is by the component of the innate immune response they affect (22). Either they (*a*) affect intracellular sensor function, (*b*) lead to the accumulation of intracellular triggers that cause cell stress and activate intracellular sensors, (*c*) cause loss of a negative regulator of inflammation, or (*d*) affect signaling molecules that upregulate innate immune cell function (Figure 1, Table 1).

Increased intracellular sensor/pattern-recognition receptor function—A number of disease-causing mutations lead to intrinsic hyperactivity of a PRR. Although no single mutation in a cell-surface PRR has been found to cause an autoinflammatory phenotype so far, a number of gain-of-function mutations in cytoplasmic sensors or their adaptor molecules have been identified (Table 1). These include proteins that form IL-1-activating inflammasomes (MEFV and the NLRs NLRP3 and NLRC4) and an NLR that does not form an inflammasome (NOD2). Recently gain-of-function mutations in an IFN-pathway-activating RLR, MDA5, and the adaptor molecule STING, as well as an adaptor associated with NF-κB activation (CARD14) were found to be disease causing.

Accumulation of intracellular stressors that trigger pattern-recognition receptor activation—A growing number of mostly autosomal recessive loss-of-function mutations or mutations that cause haploinsufficiency cause autoinflammation via inducing cell stress or death. These mutations result in (*a*) defective enzymes that cause accumulation of unprocessed substrates, (*b*) accumulation of misfolded proteins, (*c*) cytoskeletal migration defects (possibly; 23), (*d*) generation of oxidative damage, or (*e*) accumulation of endogenous nucleotides; all of these can trigger an intracellular stress response. The resulting inflammatory responses may involve a number of proinflammatory cytokines or predominantly a single inflammatory mediator. The inflammatory pathways resulting from these conditions are still poorly characterized. The various defects that lead to autoinflammatory phenotypes are listed in Table 1. The best-studied triggers of cell stress are coupled to activation of IL-1 inflammasomes (24), but an increasing number of cell stressors that activate type I IFN pathways are being described (discussed in detail in Section 4).

Loss of a negative regulator resulting in inability to attenuate proinflammatory cytokine responses—The inability to attenuate and/or shut down an inflammatory cytokine response and restore homeostasis can cause autoinflammation. Mutations resulting in loss of the IL-1 receptor antagonist (IL-1Ra) or the IL-36 receptor antagonist (IL-36Ra) illustrate this mechanism. If untreated, patients with deficiency of the IL-1Ra (DIRA) can develop a potentially fatal systemic inflammatory response syndrome (SIRS). Replacement with recombinant IL-1Ra restores inflammatory remission (25, 26). Another example is the inability of the anti-inflammatory cytokine, IL-10, to signal through its receptor leading to systemic inflammation and severe early-onset inflammatory bowel disease (IBD) (27). These conditions have provided unequivocal evidence of the impact of single-cytokine dysregulation as the cause of autoinflammatory disease phenotypes. Lastly, mutations altering the ability of cytotoxic cells to induce cell death result in failure to terminate macrophage and dendritic cell activation and cause macrophage activation syndrome (MAS).

Increased signaling through receptors controlling innate immune cell function—Activating or loss-of-function mutations in signaling molecules that regulate innate immune cell receptor and cell function [e.g., phospholipase Cγ2 (PLCγ2), lyn kinase] cause another group of disorders with a broader spectrum of clinical disease manifestations. Mutations often affect immune receptor signaling of both, innate and adaptive immune cells,

and patients may present with overlapping clinical features of autoinflammation, mild immunodeficiencies, and/or autoimmunity.

Classification of Autoinflammatory Diseases

Grouping and classifying autoinflammatory diseases is a work in process that will need to be refined as more information on the pathogenesis of these diseases becomes available. However, critical insights into the role of a key inflammatory cytokine pathway have come from clinical studies using anticytokine therapies (Table 2) that allow for classification of the autoinflammatory diseases on the basis of the predominant proinflammatory cytokine or inflammatory pathway responsible for the disease (Figure 1*a*). First, the immediate, and in many patients complete, responses to IL-1-blocking therapies have clinically validated the concept that IL-1 is a major driver of some autoinflammatory diseases. Second, although data on cytokine dysregulation in non-IL-1-mediated diseases are less complete, an emerging role for IFN dysregulation combined with clinical similarities between these conditions and preliminary treatment data provides sufficient evidence for an IFN-mediated group of autoinflammatory diseases. A third group of heterogeneous conditions have genetic defects that lead to increased activation of NF-κB. A fourth group of disorders is organized around the shared finding of uncontrolled macrophage activation. Finally, a number of diseases cannot be classified on the basis of a pivotal inflammatory mediator because of insufficient data or because the genetic defect may affect multiple cytokines and/or inflammatory mediator pathways.

3. IL-1-MEDIATED AUTOINFLAMMATORY DISEASES (GROUP 1)

The conditions listed below have demonstrated significant clinical responses to IL-1-inhibiting therapies (24) that were pioneered in patients with the cryopyrin-associated periodic syndromes (CAPS) spectrum, including FCAS, MWS, and NOMID. Complete clinical responses to IL-1-blocking agents are also seen in the monogenic autoinflammatory bone diseases DIRA and Majeed syndrome. The classic autoinflammatory syndromes [FMF, TRAPS, hyper-IgD syndrome (HIDS)] have a more variable response to IL-1 inhibition. Figure 2 shows the component of the immune response that is affected by each mutation in this group of diseases.

Pathway Overview

IL-1β is the most powerful endogenous pyrogen and a potent recruiter and activator of neutrophils and macrophages. Its potential to cause systemic and organ-specific immunopathology in infections (29) and in IL-1-mediated autoinflammatory diseases has been reported (30). In contrast to its biologic homolog IL-1α, IL-1β requires proteolytic cleavage by an IL-1 inflammasome to become activated. This process is tightly regulated at multiple levels. The actions of both IL-1α and IL-1β are further regulated at the receptor level, where IL-1Ra (encoded by *IL1RN*) competes for binding (29) and downregulates IL-1α and IL-1β signaling. Patients with loss of function of IL-1Ra can develop life-threatening systemic inflammatory response syndrome (SIRS), thus demonstrating the important role of IL-1Ra in the negative regulation of IL-1 (25).

IL-1β release requires two danger signals. Signal one leads to transcription of pro-IL-1β and varies between cells and triggers. IL-1 activation is best studied in macrophages where signal 1 is delivered through exogenous triggers, including whole pathogens (such as *Staphylococcus aureus*, *Listeria monocytogenes*, and *Candida albicans*), PAMPs (such as LPS, nucleic acids, and muramyl dipeptide), bacterial toxins, and phagocytic events. Signal 2 results in the assembly the NLRP3 inflammasome. Inflammasome formation begins with the activation of an intracellular sensor. Several NLRs as well as the DNA sensor AIM2 can induce inflammasome assembly. The NLRP3 inflammasome is by far the best studied, and its stimuli include a variety of danger signals, including K^+ efflux, mitochondrial stress/reactive oxygen species production, and uric acid crystals, among many others (31, 32). Upon stimulation, NLRP3 overcomes autoinhibition and oligomerizes. The pyrin domains (PYDs) of the NLRP3 oligomer interact with the PYDs of the adaptor protein ASC. This process triggers a prion-like cascade of ASC polymerization that assembles ASC into large fibers. Through CARD-CARD interactions, ASC polymers recruit multiple caspase-1 molecules and drive autocatalytic activation of caspase-1 in large numbers and with great speed. This allows for cleavage of inactive pro-IL-1β (and pro-IL-18 at variable levels, highest in NLRC4 inflammasome activation) into its active form (16, 31). Caspase-1 activation in response to bacterial infections also induces rapid proinflammatory cell death, termed pyroptosis (33), to kill infected cells. These and observations of the recruitment of multiple NLR molecules into one inflammasome complex suggest plasticity in inflammasome formation (23, 34).

The major canonical sources of IL-1β are blood monocytes, tissue macrophages, and dendritic cells (29), but leukocytes producing IL-1β are found in immunologically privileged organs, such as the kidney, the heart, skeletal muscle, and the brain, and epithelial cells, which all have IL-1β-activating inflammasomes (35, 36). IL-1α is expressed at high levels in lung and intestinal epithelia as well as in spleen and liver. It can be released in response to cell damage but is also subject to noncanonical regulation through the proteolytic function of the inflammasome (37). Release of IL-1α may aid in priming by driving transcription of pro-IL-1β (29).

The effects of IL-1 signaling vary considerably based on cell type, but they include induction of TNF-α, inducible nitric oxide synthase, COX-2, prostaglandin E2, nitric oxide, type 2 phospholipase A, and pro-IL-1β, which can then perpetuate an autocrine amplification circuit. Understanding the cell- and organ-specific sources and effects of IL-1, particularly in human cells, will be critical to understanding the organ-specific disease manifestations in patients with autoinflammatory syndromes. The following sections group IL-1-mediated diseases based on the component of the immune response affected by the mutation: increased intracellular innate immune sensor function, generation of intracellular cell stress, or absence of a negative regulator.

Increased Intracellular Sensor/PRR Function

Cryopyrin-associated periodic syndromes (CAPS)—The three historically distinctly reported conditions—FCAS, MWS, and NOMID/CINCA—that constitute the disease spectrum of CAPS are all caused by gain-of-function mutations in *NLRP3*/*CIAS1*.

These conditions are rare, with an estimated prevalence of 1–2 per 1 million. Both germline and somatic mutations can cause all forms of CAPS. FCAS and MWS mutations are frequently autosomal dominant (39), and the most severe phenotype, NOMID/CINCA, is usually caused by sporadic mutations (Table 1) (12, 13). Of the more than 130 disease-causing mutations identified in *NLRP3*/*CIAS1*, 90% are located in the regulatory NACHT domain (38, 39). Of the patients without germline mutations, about 70% have somatic NLRP3 mosaicism (40).

In general, all patients with CAPS present with episodes of fever, neutrophilic urticaria, conjunctivitis, arthralgia, and elevated acute-phase reactants (41) (Table 3). Whereas FCAS symptoms are limited to the mentioned disease manifestations, MWS and NOMID patients can develop permanent hearing loss, and NOMID patients also develop joint and central nervous system damage early in life (30). Chronic cochlear inflammation induces atrophy of Corti cells, resulting in permanent hearing loss. Chronic aseptic meningitis can cause increased intracranial pressure, hydrocephalus, and papilledema, leading to brain atrophy, cognitive impairment, optic nerve atrophy, and vision loss (30). One half of NOMID patients develop a deforming arthropathy that results in abnormal epiphyseal calcification, cartilage overgrowth, and joint deformities. Premature patellar ossification and patellar overgrowth are typical findings in NOMID (42).

Despite clinical heterogeneity, all patients with FCAS, MWS, or NOMID respond dramatically and invariably to IL-1 blockade, although higher dosages are needed to treat patients with NOMID compared to those with FCAS (24).

Peripheral-blood-derived monocytes from patients with CAPS spontaneously secreted active IL-1β, whereas those from controls did not (43). Cyclic AMP (cAMP) can bind directly to the NLRP3 NACHT domain, maintaining the autoinhibited state (44). Disease-causing *NLRP3* mutations cause reduced binding of cAMP and can thereby enable spontaneous oligomerization and NLRP3 inflammasome activation (45). Consistent with this molecular mechanism, patients with CAPS do not require signal 2, and inflammasome activation with LPS alone results in rapid maximal release of IL-1β (46). Released IL-1β may result in an autocrine self-amplification loop by continuing to prime its own transcription (29).

A recent discovery may shed light on the enigma that low-grade somatic mosaicism, with as few as 5% of hematopoietic cells carrying the *NLRP3* mutation, results in a severe NOMID phenotype (40). In stimulated macrophages or in macrophages carrying a NOMID-associated *NLRP3* mutation, inflammasome particles can be released into the serum, retain enzymatic activity in the extracellular environment, and, upon being phagocytosed by neighboring macrophages, transfer inflammasome activity to unstimulated/wild-type cells (47). Oligomeric ASC particles, possibly inflammasomes, were in fact found in sera of patients with active CAPS but not patients with other inherited autoinflammatory diseases, thus providing a potential disease-amplifying mechanism that could explain the severe clinical disease manifestations caused by low-level somatic mosaicism.

Familial Mediterranean fever (FMF)—FMF is the most prevalent monogenic autoinflammatory disease, affecting more than 100,000 individuals worldwide (48). FMF

primarily affects eastern Mediterranean populations, including Sephardic Jews, Armenians, and Arabs of Turkish descent.

FMF is caused by autosomal recessive mutations in the *MEFV* gene (7, 8), although an autosomal dominant form has been postulated (49). More than 80 distinct missense mutations have been identified, the majority in exon 10, which encodes the B30.2 domain of the molecule. The most common and severe mutations are M680I, M694V, M694I, and V726A (8, 39). Most patients have their first attack in childhood, with flares typically lasting one to three days and recurring variably (from weekly to once every few years), and with symptom-free intervals between flares (50, 51). Flares include fever, generalized peritonitis, and, less frequently, nonerosive oligoarthritis. Pleuritis, pericarditis, scrotal pain, and, rarely, aseptic meningitis can occur (52). Skin rashes including erysipelas-like erythema are rare (50, 51). With ongoing chronic inflammation, FMF patients often develop systemic amyloidosis that can lead to renal failure.

Colchicine has been used since the 1970s to treat and prevent flares and to prevent the development of amyloidosis, although its precise mechanism of efficacy remains unknown (53). IL-1 blockade is efficacious for FMF but is reserved for colchicine-refractory patients (54).

Despite the early-recognized association between FMF and autoinflammatory disease, the mechanisms linking pyrin mutations to FMF remain largely unknown. *MEFV* encodes pyrin (also called TRIM 20), part of a 41-member subgroup of the tripartite motif (TRIM) superfamily that contains a TRIM (RING domain, B-box zinc fingers, and a coiled-coil domain) and a B30.2/SPRY domain. Pyrin is the only family member with an N-terminal PYD instead of a RING domain. Most of the FMF-causing mutations affect surface amino acids on protein-interacting modules of the B.20.2/SPRY domain (55). The functions of wild-type and mutated pyrin may vary between different cells. TRIM members might play a key role in restricting retroviral progression, and also in regulating PRR-mediated innate immune responses (56, 57).

Pyrin is the only group member that can bind to ASC (58). In macrophages, wild-type pyrin-ASC conjugates may act as a negative regulator on NLRP3 inflammasome assembly (58). Disease-associated mutations are thought to produce less effective negative regulators, leading to a net increase in NLRP3 inflammasome activity (59). Consistent with this hypothesis, pyrin-deficient mice have increased caspase-1 activation, increased IL-1β maturation, and defective macrophage apoptosis (60).

New data on the role of pyrin suggest that it can sense dynamic signals, such as membrane disruptions leading to inflammasome activation. In a search for the physiologic trigger for the pyrin/ASC inflammasome, it was found that pyrin can be activated through sensing the glucosylating effects of *Clostridium difficile* exotoxins A and B on small GTPases of the Rho family. Rho GTPases are a group of proteins that modulate and regulate the timing of cell division and the formation of lamellipodia and filopodia in migrating cells, like neutrophils and macrophages. Posttranslational glycosylation, as induced by *C. difficile* toxin and other mechanisms, leads to GTPase inactivation and the inability to initiate actin

cytoskeleton polymerization (61). These data suggest that pyrin may be a specific immune sensor for bacterial modifications of Rho GTPases by glucosylation, adenylylation, ADP-ribosylation, and deamidation that alter their ability to initiate cytoskeletal rearrangements (62). Interestingly, recombinant pyrin binds microtubules in vitro and colocalizes with actin filaments, suggesting the hypothesis that pyrin regulates inflammation by sensing cytoskeletal changes in granulocytes and monocytes (63, 64). These studies may ultimately shed light on the surprising efficacy of colchicine in FMF, which interferes with leukocyte migration and leukocyte adhesion by altering the number and distribution of selectins on endothelial cells and neutrophils (65, 66).

NLRC4-related macrophage-activation syndrome (NLRC4-MAS)—Activating heterozygous mutations in the inflammasome component NLRC4 were recently reported to cause recurrent fevers and severe systemic inflammation reminiscent of MAS (67, 68). The MAS phenotype includes hepatitis, splenomegaly, cytopenias, and coagulopathy and is discussed in detail in Section 6. Two mutations in four patients have thus far been identified, with both mutations arising de novo in the NLRC4 NACHT domain. Three of these patients presented with enterocolitis, and recurrent MAS flares developed in two patients soon after infancy and in one patient later in life (67, 68). Disease manifestations were conserved between patients, but there was significant variability in disease severity, which ranged from intermittent, mild flares to mortality in early infancy. Although these patients were somewhat responsive to corticosteroid immunosuppression, IL-1 inhibition may provide substantial benefit (67).

Like *NLRP3* (the gene mutated in CAPS), *NLRC4* encodes an intracellular innate immune sensor that, upon activation, oligomerizes and nucleates a caspase-1 inflammasome, resulting in maturation of IL-1β and IL-18; release of DAMPs, such as IL-1α and HMGB1; and initiation of pyroptosis (4). Like CAPS mutations, the mutations resulting in NLRC4-MAS occur in the NACHT domain and result in spontaneous inflammasome formation, possibly by impairing ADP-binding and thus destabilizing the autoinhibited state (67, 68). A number of factors, however, may explain differences in the clinical phenotype between NLRC4-MAS and CAPS. First, NLRC4 utilizes an adaptor molecule, NAIP, to recognize intracellular flagellin and components of bacterial secretion systems, whereas the various activators of NLRP3 are activated by cellular damage or stress in the absence of an adaptor molecule (69). Second, there are important differences in the cellular expression of *NLRC4* versus *NLRP3*. *NLRP3* is highly expressed in conventional dendritic cells, monocytes, and, to a lesser extent, macrophages and neutrophils, and *NLRC4* is expressed in monocytes and macrophages and also in intestinal epithelia. Third, whereas hyperactivity of either NLRP3 or NLRC4 results in excessive IL-1β secretion and pyroptosis, only NLRC4 mutations cause constitutive IL-18 hypersecretion (67, 68). Accordingly, NLRC4-MAS patients do not develop the neutrophilic urticaria seen in CAPS, but they can develop enterocolitis and MAS, and they have extremely high circulating levels of IL-18 that persist even during clinical quiescence. A recent report described a family with a mild FCAS-like phenotype associated with a dominant *NLRC4* NACHT domain mutation, suggesting overlap between NLRP3- and NLRC4-mediated phenotypes in certain genetic or environmental backgrounds (70). NLRC4-MAS appears to respond to IL-1 inhibition, similar to the many other IL-1-

mediated autoinflammatory conditions. The interplay role of chronic IL-18 exposure, IL-1, and MAS is discussed in more detail in Section 6.

Generation of Intracellular Stress

Hyper-IgD syndrome (HIDS)/mevalonate kinase deficiency (MKD)—HIDS is caused by autosomal recessive mutations in the *MVK* gene (mevalonate kinase) (71, 72). About 30 disease-causing variants have been identified, but most patients with HIDS carry at least one allele with the V377I (73) or I268T substitution (73). Most patients experience their first HIDS attack before one year of age. Episodes last three to seven days and occur every four to six weeks. Other symptoms include polyarthralgia or nonerosive arthritis of large joints; cervical lymphadenopathy; abdominal pain; vomiting; diarrhea; and variable skin lesions, including maculopapular, urticarial, nodular, and purpuric rashes. Childhood vaccinations can precipitate attacks. Treatment includes NSAIDs and chronic or intermittent use of IL-1-blocking agents, including anakinra (74, 75) and canakinumab (75). TNF inhibition with etanercept (76) may also ameliorate the disease in some patients.

The HIDS-causing mutations impair the enzymatic activity of mevalonate kinase (71, 72, 77), a key enzyme in the cholesterol synthesis pathway. Mutations in *MVK* cause depletion and shortage of farnesyl pyrophosphate and geranylgeranyl pyrophosphate: intermediates for isoprenoid synthesis and substrates used for protein prenylation (78). Flares are thought to be caused by uncontrolled release of IL-1β as a consequence of insufficient geranylgeranyl pyrophosphate generation (79). Exogenous addition of geranylgeranyl pyrophosphate to patient cells or cell cultures restores the normal regulation of IL-1β secretion. In a surprising link with the recent pyrin biology, reduced prenylation due to isoprenoid shortage leads to a decrease in Rho GTPase activity and a RhoA-dependent increase in small Rac1 GTPase activity and IL-1β hypersecretion. Inhibition of Rac1 in THP-1 monocyte cultures prevented IL-1β overproduction driven by impaired cholesterol biosynthesis (80). In the HIDS models, RhoA inactivity increased IL-1β gene transcription (signal 1) and thus provided a mechanism for NLRP3 or other inflammasome activation that is triggered by inactivity of Rho GTPases (81).

TNF receptor–associated periodic syndrome (TRAPS)—TRAPS is caused by autosomal dominant mutations in the *TNFRSF1A* gene, which encodes TNFR1. More than 100 mutations have been found to cause TRAPS, nearly all in the extracellular domain of the TNF receptor (39). Clinical manifestations usually present in childhood and adolescence but present in adulthood in about 20% of patients. Flares are prolonged, with a mean length of 14 days but sometimes lasting up to 4 weeks.

Presenting features include recurrent fever, abdominal pain, pleuritis, myalgias, arthralgias, periorbital edema, and conjunctivitis. Myalgias caused by a monocytic fasciitis can also be present (82). Neurological manifestations include headaches and, rarely, aseptic meningitis, optic neuritis, and behavioral alterations. In some centers IL-1 blockade has become the treatment of choice (83, 84), but TNF inhibition is effective in some cases (85), suggesting that more than one cytokine/inflammatory mediator may be involved in causing the disease.

TNFR1 is ubiquitously expressed on most cell types and has a cytoplasmic death domain that signals through two pathways, one leading to NF-κB activation and inflammation (86), and the other leading to caspase activation and apoptosis. Mutations in cysteines contained in the first two cysteine-rich extracellular domains result in the most severe phenotypes and affect protein structure and folding (87). Mutated TNFR1 molecules fail to bind to TNF and are not cleaved into a soluble form that can sequester free TNF-α; instead, they accumulate in the endoplasmic reticulum (ER). Meanwhile, cell surface TNFR1 levels of both wild-type and mutant protein are greatly reduced (88, 89). TRAPS patient cells are hyperinflammatory, as they spontaneously activate JNK and p38 MAP kinases (MAPKs) (89) and show exaggerated, TNF-independent mitochondrial reactive oxygen species production that may activate the IL-1 pathway (90, 91). This proinflammatory state may be further potentiated by autocrine TNF signaling through the remaining wild-type TNF receptor that is expressed on the cell surface (Figure 1). Interestingly, although the mutant TNFR1 in TRAPS induces inflammatory responses within the cell, it requires cooperation with the wild-type receptor to produce the clinical manifestations of TRAPS (89). These results may explain the partial efficacy of TNF blockade in this syndrome, which would only affect signaling through intact TNFR1s. Accordingly, a unique TRAPS mutation near the metalloproteinase cleavage site, p.V173D, results in an atypical form of disease that is strikingly responsive to TNF blockade. This mutation results in reduced shedding of the receptor and may contribute to prolonged TNF signaling (92).

Majeed syndrome—Majeed syndrome is an exceedingly rare autosomal recessive disorder caused by mutations in *LPIN2* (93). Majeed syndrome is characterized by early-onset recurrent noninfectious osteomyelitis, congenital dyserythropoietic anemia, and neutrophilic dermatosis. Sterile osteomyelitis develops in the first two years of life; it can present unifocally but becomes multifocal over time (94). Periodic fevers coincide with bone flares. Somewhat unexpectedly, IL-1-blocking therapy resulted in complete response in two patients (95).

The protein lipin-2 associates with the nuclear/ER membrane and has phosphatidate phosphatase (PAP) enzyme activity. Lipin-2 catalyzes the conversion of phosphatidate to diacylglycerol, a precursor to the phospholipids found in cell membranes that are essential for the absorption, transport, and storage of lipids and serve as a reservoir for signaling molecules. One Majeed mutation, p.S734L, alters a highly conserved serine residue in the C-LIP domain and leads to loss of lipin-2 PAP activity (96, 97). Cells lacking PAP have inflammatory responses to exogenous fatty acids, including palmitoleic acid > oleic acid > palmitic acid (97). This was confirmed in human and murine monocytic cells, where downregulation of lipin-2 in cells led to JNK-1/c-Jun-mediated hyperproduction of proinflammatory mediators (TNF-α, IL-6, and CCL-2), when the cells were exposed to excessive quantities of the saturated fatty acid palmitic acid. Overexpression of lipin-2 blunted this inflammatory response (98). Lipin-1 and -3 are highly expressed in liver and fat, whereas lipin-2 is the predominant and nonredundant PAP in monocytes. Thus, it is intriguing to speculate that lipin-2-deficient monocytes might drive the inflammatory response in Majeed syndrome whereas the redundant PAP function in other cells

compensates for the reduced or absent lipin-2 function. It is unknown how this mechanism might lead to inflammasome activation.

Loss of a Negative Regulator

Deficiency of IL-1 receptor antagonist (DIRA)—DIRA is very rare autosomal recessive disease that exists in communities with founder mutations in *IL1RN* (99). These mutations result in loss of function of IL-1 receptor antagonist. DIRA presents in the first weeks of life with systemic inflammation, pustular skin rashes, and a pathognomonic pattern of osteomyelitis involving long bones, ribs, clavicles, vertebral bodies, and hips. If untreated, a third of patients will succumb to the effects of uncontrolled IL-1 signaling. However, prompt treatment with the recombinant IL-1 receptor antagonist (anakinra) results in excellent long-term outcomes.

DIRA results from mutations causing absent or inactive IL-1Ra. In the absence of IL-1Ra, unopposed signaling through IL-1R leads to hyperresponsiveness of cells to IL-1α and IL-1β, with overproduction of a host of proinflammatory cytokines, chemokines, and other mediators (25, 26, 99).

4. IFN-MEDIATED AUTOINFLAMMATORY DISEASES (GROUP 2)

Pathway Overview

Besides their antivirus and antitumor effects, INFs have broad immune-modulating functions, including enhancing the antigen-presentation function of dendritic cells, promoting T lymphocyte response and B lymphocyte antibody production, and restraining proinflammatory cytokine production. The critical roles of type I INFs in the pathogenesis of inflammatory diseases have been increasingly recognized in recent years (100–102). Type I IFNs signal by binding with type I IFN receptors, which are ubiquitously expressed. The binding triggers activation of the kinases JAK1 and TYK2, which phosphorylate the receptors and then in turn recruit and phosphorylate STAT1 and STAT2. The phosphorylated STAT1 and STAT2, together with IRF9, form the ISGF3 transcriptional complex, which enters the nucleus and promotes expression of IFN response genes. A prominent feature of IFN responses is their feed-forward amplification. Many signaling molecules and transcription factors involved in IFN responses are products of IFN response genes themselves. Thus, blocking IFN signaling could be an effective treatment strategy for patients with upregulated IFN signaling (103).

Viral immunity evolved around sensing the presence of DNA or RNA nucleotides, which is achieved by TLR3, 7, 8, and 9 in the endosomal department and by cytosolic DNA and RNA sensors. The detection of DNA or RNA by cytosolic sensors results in activation of a common pathway and recruitment and activation of TBK1, leading to phosphorylation/activation of IRF3 and transcription of IFN-β. Two known RNA sensors, MDA5 and RIG-I, both members of the RLR family, signal through the adaptor protein MAVS (mitochondrial antiviral-signaling protein) (104), a transmembrane protein localized in mitochondria. MDA5, RIG-I, and MAVS all have a CARD that allows for homotypic protein-protein interactions. An increasing number of recognized DNA sensors, including the enzyme cGAS, signal through the ER-residing protein STING, a critical adaptor molecule that

activates a shared end pathway to INF signaling. Figure 3 shows the IFN-signaling pathway with the position of the mutated genes that affect the sensor function or result in the generation of cell stress that activates the IFN response pathways.

Similar to the regulation of the proinflammatory cytokine IL-1, the production and signaling of IFNs are tightly regulated (105). Dysregulation of either IFN signaling or its production has been linked to inflammatory diseases, including Aicardi-Goutières syndrome (AGS), autoimmune diseases such as systemic lupus erythematosus, and a growing number of conditions that clinically present as autoinflammatory diseases. Below, the proposed IFN-mediated diseases are grouped based on the component of the immune response that is affected by the mutation: increased intracellular innate immune sensor function or generation of intracellular cell stress.

Increased Intracellular Sensor/Adaptor Function

STING-associated vasculopathy with onset in infancy (SAVI)—SAVI is an extremely rare autoinflammatory disease caused by de novo gain-of-function mutations in *TMEM173*, which encodes STING (21), an adaptor protein in the cytosolic DNA–sensing pathway. Three different missense mutations in eight patients have been detected. Patients present with severe vasculitis/vasculopathy since birth that affects small dermal vessels, most severely in distal extremities, leading to vasoocclusion and gangrene and often requiring amputation. Some of the patients also develop progressive interstitial lung disease, which can be lethal.

The recent identification of the function of the enzyme cGAS as a DNA sensor and its enzymatic product cGAMP as a STING ligand greatly advanced our understanding of a cytosolic DNA–sensing pathway (106, 107). Upon binding of dsDNA, cGAS is activated and cGAMP is generated and then binds and activates STING. STING is an ER transmembrane protein that exists as a dimer independent of ligand; the binding pocket for cGAMP is located in a cleft between the two monomers (108, 109). The binding of cGAMP to STING leads to recruitment and activation of TBK1 and subsequently phosphorylation/activation of IRF3, which promotes IFN-β transcription.

The STING mutations identified in SAVI patients are closely clustered at or near an area critical for STING dimerization. Six of the eight SAVI cases we have analyzed to date have the same N154S mutation, and the other two have either a V155M or a V147L mutation. The mutant proteins form stable dimers. In mutant-STING-transfected HEK293T cells or in patients' peripheral blood mononuclear cells (PBMCs), the mutant proteins cause constitutive IFN-β transcription. As a consequence of the constitutive and/or enhanced IFN-β transcription, a strong IFN response gene signature is detected in the whole-blood RNA of all SAVI patients. Serum levels of a downstream mediator of IFN, CXCL10, were highly elevated and STAT1 protein was maximally phosphorylated in SAVI patients. Patient cells treated in vitro with JAK inhibitor showed suppression of STAT1 phosphorylation.

A unique feature of SAVI is pronounced vasculitis/vasculopathy, which is most prominent in the distal extremities. The localized severe endothelial inflammation suggests a direct effect of mutant STING in dermal vasculature. Consistent with that, we found that STING

was expressed at higher levels in dermal vascular endothelial cells than in umbilical vein endothelial cells or coronary artery endothelial cells. Furthermore, STING stimulation by cGAMP activated vascular endothelial cells and caused cell death. STING coordinates signals from multiple upstream DNA sensors and may be a target for therapeutic interventions not only for SAVI, but also for a wider variety of IFN-mediated diseases.

Aicardi-Goutières syndrome 7 (AGS7)—Gain-of-function mutations in *IFIH1* encoding MDA5, a sensor molecule in the RNA-sensing pathway, lead to both spontaneous and enhanced ligand-induced IFN-β transcription (20). As the clinical presentation is similar to the other forms of AGS, the disease is further described at the end of the following section.

Generation of Intracellular Stress

Aicardi-Goutières syndrome 1–6 (AGS1–6)—AGS is a rare disease caused by autosomal recessive mutations in the exonuclease TREX1 (three prime repair exonuclease 1); the ribonucleases RNASEH2A, RNASEH2B, and RNASEH2C; an enzyme with phosphohydrolase and nuclease activity, SAMHD1; and the dsRNA-specific adenosine deaminase ADAR1. More recently, autosomal dominant mutations in *IFIH1*, encoding MDA5, have been observed to cause an AGS-like syndrome (110). Patients with AGS present with subacute encephalomyelitis mimicking a viral infection in very early infancy that causes demyelination and neurological decline during a mostly monophasic disease flare. High levels of IFN-α in the cerebrospinal fluid at the time of flares have been used as a marker to diagnose these diseases. After the acute phase, most patients follow a nonprogressive, chronic course, without further neurological decompensation. Patients have basal ganglion calcifications and severe white matter disease on MRI, and up to 40% continue to have mostly mild rashes, often including chilblain lesions on hands and feet. Many patients have low-titer autoantibodies (111), but the contribution of the autoantibodies to the human disease remains uncertain. The disease may present a true overlap with clinical features of autoimmunity and autoinflammation (112, 113). There is currently no effective treatment (Table 1).

The pathogenesis of AGS has recently been extensively reviewed (112, 113). In brief, the pathogenesis of AGS is best studied for mutations in *TREX1*. TREX1 is a 3′→5′ DNA exonuclease, and loss-of-function mutations result in accumulation of ssDNA derived from endogenous retroelements that are proposed to activate intracellular nucleic acid sensors and lead to type I IFN production (114). Among *trex1* knockout mice, which develop myocarditis but not the central nervous system manifestations seen in patients with AGS, the disease can be abrogated in IFN type I receptor knockout animals, thus confirming a critical role of type I IFN. Loss of STING or cGAS expression also rescued the disease phenotype in the *trex1* knockout mice or abrogated the upregulated expression of IFN response genes in *trex1*-deficient murine cells, suggesting a critical role of cGAS/STING in the signaling pathway (115, 116).

The mechanism by which the other genetic mutations cause AGS is not entirely clear. *RNASEH2B*, *RNASEH2C*, and *RNASEH2A* are three subunits of the ribonuclease RNASEH2

complex, which might remove ribonucleotides from RNA/DNA hybrid molecules during the reverse transcription process of retroelements. SAMHD1 is a dNTP triphosphohydrolase that might regulate reverse transcription of retroelements by controlling the pool of dNTP. ADAR1 is an RNA-editing enzyme that catalyzes the hydrolytic deamination of adenosine to inosine in dsRNA, which is thought to prevent accumulation of RNA and triggering of the RNA sensors (117). The accumulating endogenous nucleic acids are hypothesized to trigger nucleotide sensors and type I IFN production. Transcription of retroelements is hypothesized to be a major source of the nucleic acids (118); activating nucleotides also accumulate in the process of defective DNA repair and replication (119, 120).

IFIH1 mutations encoding MDA5 result in enhanced dsRNA binding and constitutive activation of the RNA-sensing pathway with increased baseline or ligand-induced IFN signaling (20); similarly, gain-of-function mutations in STING activate the DNA-sensing pathway.

PRAAS/CANDLE syndrome—PRAAS/CANDLE (proteasome-associated autoinflammatory syndromes/chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) is a rare disease caused by an autosomal recessive mutation in *PSMB8* and mutations in additional proteasome components. Increased prevalence of PRAAS/CANDLE in several populations is due to founder mutations: G201V (disease referred to as Nakajo-Nishimura syndrome) in the Japanese population (121, 122); T75M in the Spanish, Portuguese, and Latin American populations; and A92T in the Mexican population. Patients present with systemic inflammation, atypical neutrophilic dermatosis and lipodystrophy, joint contractures, muscle atrophy, and microcytic anemia (123, 124). Mortality is high in untreated patients. Because this syndrome is associated with strong expression of IFN-regulated genes and few treatment alternatives exist, the inhibition of IFN signaling is investigated as a treatment strategy.

The ubiquitin-proteasome system is the major pathway of protein degradation outside of lysosomes in cells. Proteasomes are cylindrical structures that consist of four ring-like protein complexes, each ring containing seven different α-subunits or seven different β-subunits. Three of the β-subunits, β1, β2, and β5, are catalytically active and differ in substrate specificity. The β5-subunit has chymotrypsin-like activity, the β2-subunit trypsin-like activity, and the β1-subunit caspase-like activity (125). In hematopoietic cells, the three catalytically active β-subunits are replaced with β1i (PSMB9), β2i (PSMB10), and β5i (PSMB8) to form immunoproteasomes with increased proteolytic capacities. Although PSMB8 expression is constitutive in hematopoietic cells, it can be readily induced in nonhematopoietic cells by IFN; therefore, the effect of the mutation is not necessarily limited to hematopoietic cells. The finding that mutations in *PSMB8* lead to a severe inflammatory phenotype in humans was unexpected given that *psmb8*/*lmp7* knockout mice lack spontaneous development of systemic or muscle inflammation or lipodystrophy (126).

Proteasomes maintain proteostasis as they recognize and dispose of ubiquitinated proteins, which are often damaged and destined for degradation. All mutations found in patients with CANDLE reduce proteasome function; in some cases ubiquitinated proteins aggregate in cells, indicating an imbalance of the proteostasis process in the cells. Impaired proteostasis

and the resulting stress can lead to cytotoxicity but could also trigger an inflammatory response. In fact, ATF3 is a transcription factor induced by a variety of stress signals (127). The unfolded protein response (UPR) is a mechanism that cells employ to cope with ER stress, and recent evidence shows that it promotes production of proinflammatory cytokines, including type I IFN. Whether induction of the UPR plays a role in CANDLE and drives IFN production remains to be investigated (128). Patients with CANDLE present with high elevation of CXCL10, an IFN-inducible chemokine. STAT1 hyperphosphorylation in response to IFN stimulation and transcription profiling indicates increased expression of many IFN-regulated genes in blood from CANDLE patients. Blood and tissue from CANDLE patients had higher levels of IL-6 than those from healthy controls, and this was attributed to hyperphosphorylation of p38 (122). However, anti-IL-6 blockade is only partially effective in CANDLE patients and the IFN signature persists during the treatment, suggesting that IL-6 is not the primary cause of the disease.

Whereas healthy control cells stimulated with IFN would increase proteasome activity, CANDLE patients with the genetic defect cannot sufficiently upregulate immunoproteasome activity, resulting in cell stress that leads to IFN production and amplification of a vicious cycle of IFN stimulation.

Spondyloenchondrodysplasia with immune dysregulation (SPENCDI)—A syndrome of bone dysplasia; central nervous system involvement, including cerebral calcifications; and immune dysregulation was recently associated with loss-of-function mutations in tartrate-resistant phosphatase (TRAP; encoded by *ACP5*) (129, 130). These patients may develop early-onset fevers and a variety of autoimmune features, and the disease has been associated with a peripheral type I IFN signature (130). The in vitro abnormalities associated with TRAP implicate innate immune activation, further highlighting the intersections between autoinflammation and autoimmunity in IFN-mediated diseases.

5. AUTOINFLAMMATORY DISEASES CAUSED BY INCREASED NF-κB SIGNALING (GROUP 3)

Pathway Overview

The NF-κB pathway integrates a variety of inflammatory, metabolic, proliferative, and developmental signals into gene transcription, with effects on cytokine production, cellular differentiation, metabolism, and various forms of cell death (131). It is involved in cellular responses to stimuli such as stress, cytokines, free radicals, UV irradiation, oxidized low-density lipoproteins, and bacterial and viral antigens. NF-κB is found in almost all animal cell types, and the outcomes of NF-κB activation vary by cell type and the type and strength of stimulus. In certain contexts, NF-κB can promote inflammation not only by inducing inflammatory cytokine production, but also by promoting inflammatory cell death (necroptosis). Although NF-κB activation occurs in many autoinflammatory diseases, the conditions included in this section result from mutations that directly activate the NF-κB pathway and do not appear to converge on a single inflammatory cytokine or soluble mediator.

NF-κB-Mediated Diseases Caused by Increased Intracellular Sensor/Adaptor Function

Blau syndrome/early-onset sarcoidosis (pediatric granulomatous arthritis)— Autosomal dominant gain-of-function mutations in the NACHT domain of *NOD2*/*CARD15* cause pediatric granulomatous arthritis (PGA) (14, 132) Familial cases are traditionally called Blau syndrome, whereas sporadic cases are often referred to as early-onset sarcoidosis (133). PGA symptoms typically occur before the age of four years and present with the classic triad of granulomatous uveitis, large-joint polyarthritis, and dermatitis (134). The uveitis is usually bilateral and affects the anterior and posterior uveal compartments (134, 135); if left untreated, it leads to irreversible blindness in up to 40% of patients (135). Optimal therapy for PGA has not been established. NSAIDs can be used for mild disease, whereas severe symptoms are treated with systemic corticosteroids (136) and biologics targeting TNF and IL-1-blocking agents (135, 137). A definitive diagnosis requires genetic evidence of *NOD2* mutations (135).

Like *NLRP3* and *NLRC4*, *NOD2* is a member of the NLR family and plays an important role in innate immune defenses through detection and clearance of intracellular PAMPs (137). The NOD2 protein has the typical NLR three-domain structure, with two CARDs, a NACHT domain, and a C-terminal LRR domain (138). It is canonically activated by a component of bacterial cell walls called muramyl dipeptide, which leads to NACHT-dependent oligomerization and exposure of the CARD (139). The exposed CARD forms homotypic interactions with the serine-threonine kinase RIPK2, enabling ubiquitylation of RIPK2 by CIAP or X-linked inhibitor of apoptosis (XIAP) proteins. RIPK2 is activated to catalyze the canonical NF-κB and, to a lesser extent, AP-1 pathways, resulting in inflammatory gene transcription. Oligomerized NOD2 may also signal through MAVS to activate IRF3 (Figure 4) (140, 141). Mutations in the NACHT domain may decrease the threshold for spontaneous oligomerization, leading to constitutive activation of NF-κB and the inflammatory manifestations observed in PGA (142).

Evaluation of the role of constitutive NOD2 activity in organs affected in PGA—the eyes, synovium, and skin—may shed light on the predilection for these organs in Blau syndrome and identify new targets for therapy. Relatedly, loss-of-function *NOD2* mutations are strongly associated with Crohn disease, suggesting an important role for NOD2 in maintaining an effective gut barrier or in recruiting anti-inflammatory mediators.

CARD14-mediated psoriasis (CAMPS)—Autosomal dominant or sporadic gain-of-function mutations in the *CARD14* gene cause plaque psoriasis (143), familial pityriasis rubra pilaris (PRP), and even pustular psoriasis, suggesting a disease severity spectrum (144). These disease-causing mutations were NF-κB activating (143, 145). The skin disease in patients with *CARD14* mutations can be limited or generalized. Fever and other systemic manifestations are generally not present but can occur with superinfections of the skin (143, 145). Familial PRP is usually refractory to standard therapies (144, 146). The similarities in gene expression studies between CAMPS and nonallelic psoriasis suggest that newer drugs with efficacy in psoriasis, like those targeting IL-12/23 or IL-17 (Table 2), may be of benefit.

The expression of CARD14/CARMA3 is restricted to keratinocytes, endothelial cells, and the placenta. It is not expressed in hematopoietic cells. CARD14 is phosphorylated by protein kinase C (PKCβ or PKCΘ), allowing MALT1/BCL10 to bind and form an NF-κB-activating complex (Figure 4). Transfection of mutant *CARD14* into a keratinocyte cell line leads to increased NF-κB activation and a gene expression profile showing induction of chemokines similar to those found in psoriasis biopsies. Overall, these conditions suggest that keratinocyte dysregulation may drive the recruitment of hematopoietic cells into the skin and a pustular/psoriasis-like phenotype (143, 144).

6. AUTOINFLAMMATORY DISEASES CAUSED BY PERSISTENT MACROPHAGE ACTIVATION (GROUP 4)

Pathway Overview

Systemic macrophage activation is characterized by the accumulation of activated macrophages (also known as histiocytes) that secrete large quantities of inflammatory mediators, including cytokines, chemokines, DAMPs, lipids, etc. (147, 148). They can become hemophagocytes and engulf other hematopoietic cells. Once considered the diagnostic hallmark of MAS and hemophagocytic lymphohistiocytosis (HLH), they can be abundant in organs of the reticuloendothelial system during systemic inflammation (149). The inflammatory macrophages fail to be cleared, and the inflammatory mediators released cause fever, cytopenias, coagulopathy, hepatitis, splenomegaly, and central nervous system inflammation that can progress to sepsis-like pathophysiology, with shock and death. The progression of macrophage activation in the context of rheumatic diseases is historically called MAS, and in the context of the familial monogenic defects resulting in impaired NK or $CD8^+$ T cell cytotoxicity, it is called HLH.

Biomarkers of persistent macrophage activation in either MAS or HLH include high levels of ferritin, neopterin, soluble CD163 (150, 151), and soluble IL-2 receptor (150, 152), and serum ferritin levels in MAS and HLH predict disease severity and correlate with treatment responses (153). The excess serum ferritin is not glycosylated, suggesting abnormal secretion or release during cell death (154). Disease-based genetic discovery in patients with systemic macrophage activation has led to the emergence of two mechanistic paradigms. One involves cytotoxic lymphocyte dysfunction with exuberant lymphocyte activation and secondary macrophage activation, and a more recent paradigm of primary macrophage activation was inspired by the discovery of NLRC4-MAS (67, 68). Systemic macrophage activation, as in NLRC4-MAS, is associated with chronic overproduction of IL-18, which may also impair cytotoxicity. Thus, impaired killing of activated macrophages may be a common factor driving macrophage activation in both paradigms. The serum levels of IL-18 associated with XIAP deficiency and NLRC4-MAS are usually in the nanogram-per-milliliter range (the normal range is generally less than 200 pg/mL) and rise during flares (67, 155). Extraordinarily high IL-18 elevation is also seen in some patients with systemic juvenile idiopathic arthritis (sJIA) (156) and Still disease (157) who have had MAS. Although the importance of NK cell function in MAS remains uncertain, it is often reduced during disease flares but can normalize in between (158).

Although IL-18 is not thought to act directly on myeloid cells, it potentiates lymphocyte activation, enhances cytotoxicity, and promotes activation-induced cell death in combination with other cytokines, such as IL-2, IL-12p70, and IL-15. Chronic IL-18 exposure may cause impairments in cytotoxicity (159) or NK cell death (160) and thus might promote macrophage activation by priming lymphocyte inflammatory responses or by disabling/depleting NK cells. IL-18-induced NK cell dysfunction resulting in impaired killing of inflammatory macrophages may represent a defect shared between MAS and cytotoxicity-related HLH (Figure 5) (161). NLRC4-MAS, sJIA, and Still disease have demonstrated a response to IL-1 inhibition (157, 162, 163), underscoring the importance of IL-1 for inflammatory macrophage effector function.

Macrophage Activation Due to Increased Intracellular Sensor Function

NLRC4-MAS—NLRC4-MAS is the most compelling example of a mutation causing primary macrophage dysfunction and MAS. Because NLRC4-MAS is also an IL-1-responsive inflammasomopathy, it is discussed in more detail in Section 3. These patients' constitutive NLRC4 inflammasome activation provides the first direct link to the extraordinary levels of IL-18 seen in NLRC4-MAS and a number of similar monogenic and complex autoinflammatory disorders.

Deficiency of X-linked inhibitor of apoptosis (XIAP)—It is unclear what components of the immune response result in macrophage activation in XIAP deficiency. XIAP deficiency was first described in 2006 as an X-linked lymphoproliferative disorder of Epstein-Barr virus (EBV)-associated HLH in affected males (164). In patients with XIAP deficiency, HLH remains the most common disease presentation (165), but the spectrum of phenotypes associated with XIAP defects includes innate immune dysregulation such as IBD, uveitis, and recurrent fevers (166, 167). No correlation between genotype, residual XIAP function, and phenotype has been observed, highlighting the importance of genetic and environmental background to XIAP-related disease presentations (167).

XIAP canonically functions to limit apoptotic caspase activity. Although a variety of stimuli provoke higher rates of apoptosis in cells from patients with XIAP deficiency in vitro, the in vivo consequences of this are unknown (164, 167). However, XIAP deficiency also impairs NOD2 signaling, owing to XIAP's function in recruiting ubiquitin ligases to the complex (166; Figure 4). Some cases of IBD in XIAP deficiency may share a common pathway with cases of Crohn disease in patients carrying *NOD2* mutations, as XIAP deficiency has been identified in patients of both sexes with Crohn disease (166). Similarly to patients with NLRC4-MAS and those with other MAS-prone disorders, patients with XIAP deficiency who have had MAS have extraordinarily high serum IL-18 levels (155). However, the molecular mechanisms linking XIAP deficiency to IL-18 overproduction and MAS remain unknown.

Macrophage Activation Due to Loss of the Negative Regulatory Effects of Cytotoxic Killing

Primary defects in cytotoxicity—Lymphocyte cytotoxicity requires the transport of specialized perforin/granzyme-containing granules to the lytic synapse, where they are released and their contents induce target cell apoptosis. Familial HLH (FHL) is a group of

monogenic diseases caused by recessive mutations that impair cytotoxic function. Systemic macrophage activation in FHL is triggered by infections (usually viral) and rapidly progresses to fulminant disease. Mutations in FHL directly affect cytotoxic granule content (perforin itself; 168) or the number of proteins important for granule formation (*LYST*, *AP3B1*), tethering (*RAB27A*), docking/priming (*UNC13D*), and membrane fusion (*STX11*, *STXBP2*) (169, 170). In Chediak-Higashi (*LYST*), Griscelli (*RAB27A*), and Hermansky-Pudlak II (*AP3B1*) syndromes, genetic defects also impair melanin and neutrophil granule formation, leading to albinism and neutropenia. The frequency and severity of HLH correlate with the degree of cytotoxic impairment (169, 170). Potent immunosuppression is used to treat FHL, often as a bridge to allogenic bone marrow transplant, and mortality related to disease or immunosuppression remains high (171). Infections, most notably EBV (172), and hematologic malignancies (173) can trigger HLH in patients with normal cytotoxicity.

The mutations causing FHL illustrate the importance of NK cells as negative regulators of inflammation, namely in eliminating activated macrophages and infected dendritic cells. When infected, antigen-presenting cells stimulate cytotoxic cells to terminate the immune response by killing the infected antigen-presenting cells. Work in murine models of perforin deficiency implicated the persistence of dendritic cells in disease pathogenesis (174, 175) and highlighted perforin from NK cells as a critical regulator of macrophage and CD8 activation (176). FHL lymphocytes expand and produce mostly IFN-γ, which drives systemic macrophage activation and the HLH phenotype (177, 178), a process perpetuated by the persistence of activated macrophages (Figure 5) (161). Interestingly, higher frequencies of variations in *PRF1* and *UNC13D* have been noted in sJIA patients with a higher risk for MAS, linking FHL with MAS in sJIA (179, 180).

In most murine models of FHL and MAS, IFN-γ blockade completely abrogated the disease (181–183). Clinical trials with an IFN-γ-neutralizing antibody are underway, although evidence for IFN-γ driving human FHL and MAS is less strong (184, 185) and additional cytokines (particularly IL-18 but also IL-1α, IL-1β, and IL-6) and TLRs, as well as impaired IL-10 responses (183, 186, 187), have been implicated in human disease.

7. AUTOINFLAMMATORY DISEASES WITH YET UNCHARACTERIZED PIVOTAL PROINFLAMMATORY MEDIATORS (GROUP 5)

Syndromes Caused by Accumulation of Metabolites/Triggers That Cause Intracellular Stress or Cell Death

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA)—PAPA is a rare disorder caused by dominant mutations in *PSTPIP1*, the gene encoding CD2-binding protein 1 (CD2BP1). It presents with early-onset episodes of painful sterile and deforming arthritis, cutaneous ulcers (pyoderma gangrenosum), and pathergy: cystic lesions or skin abscesses at needle injection sites (188). Severe cystic acne and hidradenitis suppurativa of the axillae and groin develop around puberty. Fever is rarely observed. Symptoms usually persist into adulthood with significant joint destruction and impaired quality of life related to pain and physical disability (189).

IL-1 inhibition is effective for joint disease (189), but acne and pyoderma lesions persist despite immunosuppression and fastidious wound care. High-dose corticosteroids, thalidomide, cyclosporine, dapsone, tacrolimus, and IVIG have been used, with variable responses (189); anti-TNF therapy (infliximab and adalimumab) combined with IL-1-blocking agents is used in severe disease.

The pathogenesis of PAPA is still elusive. CD2BP1 is a cytoskeletal adaptor with an F-BAR domain: a highly conserved dimerization domain present in proteins involved in membrane binding/dynamics. PSTPIP1 interacts with PEST-type protein tyrosine phosphatases (PEST-PTPs) or PTPN12, Wiskott-Aldrich syndrome protein (WASP), and the pyrin inflammasome (190, 191). Disease-causing *PSTPIP1* mutations are thought to diminish the interactions with PEST-type proteins or WASP and increase interaction with pyrin (191, 192). Mouse studies suggest that *PSTPIP1* mutants may increase pyrin-associated IL-1β activation (193), but not IL-1β production from the NLRP3, AIM2, or NLRC4 inflammasomes (194). Additional studies are clearly needed, as IL-1-inhibiting approaches are only partially effective.

Recent data demonstrate that a novel PSTPIP1 mutation (p.R405C) in the SRC homology 3 (SH3) domain leads to impaired WASP binding and abnormal macrophage podosome formation (192). During the inflammatory phase of wound healing, macrophages must navigate the granulation tissue to clear apoptotic neutrophils. *PSTPIP1* defects, by impairing WASP-mediated macrophage migration, may impede wound healing and result in the exuberant granulation seen in pyoderma gangrenosum and cystic acne. Furthermore, PAPA mutations may also impair keratinocyte podosome formation, which is necessary for covering wounds of the skin but not mucosa.

Deficiency of adenosine deaminase 2 (DADA2)—Recently, autosomal recessive mutations in *CECR1*, the gene encoding the enzyme adenosine deaminase 2 (ADA2), were reported as the cause of an early-onset vasculopathy resembling polyarteritis nodosa. The patients described so far have presented with early-onset stroke, livedo reticularis, recurrent fever, hepatosplenomegaly, arterial hypertension, ophthalmologic manifestations, and myalgia. Other cutaneous manifestations have included leg ulcers, Raynaud phenomenon, subcutaneous nodules, purpura, and digital necrosis. Fourteen pathogenic mutations have been described, and suggested therapeutic interventions are anti-TNF agents, fresh-frozen plasma, recombinant ADA2, and hematopoietic stem cell transplantation (HSCT) (195, 196).

ADA2 converts adenosine to inosine and 2′-deoxyadenosine to 2′-deoxyinosine, but the affinity of ADA2 for adenosine is lower than that of ADA1 by a factor of approximately 100. Whereas ADA1 is monomeric and largely intracellular, ADA2 is dimeric and secreted.

Sideroblastic anemia, immunodeficiency, fevers, and developmental delay (SIFD)—The recently described syndrome of congenital sideroblastic anemia, B cell immunodeficiency, periodic fevers, and developmental delay is caused by autosomal recessive mutations in *TRNT1* (197). Most patients presented in infancy with transfusion-dependent anemia characterized by erythroid precursors containing perinuclear

mitochondrial iron deposits (sideroblasts). Most patients also developed recurrent noninfectious fever episodes and B lymphopenia with variable immunodeficiency and showed developmental delay including occult multiorgan failure and/or cardiomyopathy. Early allogenic bone marrow transplant was curative in one patient. Loss-of-function mutations in *TRNT1*, which encodes an enzyme critical for transfer RNA maturation, were recently associated with SIFD (198). Although impairment in transfer RNA synthesis leads to cellular stress and proposed activation of inflammatory mediators, how this stress causes the described clinical phenotype remains to be resolved.

Syndromes Caused by Loss of Negative Regulation

Deficiency of IL-36 receptor antagonist (DITRA)—Homozygous loss-of-function mutations in the *IL36RN* gene, L27P, cause pustular psoriasis and systemic inflammation. The mutations leading to this disease are largely founder mutations in Tunisians (199), but sporadic disease has been seen in unrelated English patients (200). Patients usually present with generalized pustular psoriasis and fever flares during childhood (7 days to 11 years of age) (199). Skin flares are characterized by generalized erythematous and pustular skin rashes, associated with high fevers, asthenia, increased C-reactive protein, and leukocytosis (199, 200). Secondary skin infections and sepsis may also occur (199). Disease flares may be triggered by viral or bacterial infections, withdrawal of retinoid therapy, menstruation, and pregnancy (199, 200).

IL36RN encodes IL-36Ra, which binds to the IL-36 receptor, completely blocks binding by IL-36α, -β, and -γ, and prevents NF-κB activation further downstream in response to TLR agonist stimulation (199, 200). The mutated protein is highly expressed in keratinocytes. The absence of IL-36Ra in DITRA patients leads to constitutively enhanced IL-36 receptor signaling in keratinocytes and hematopoietic cells. Similar to CAMPS, primary dysregulation of keratinocyte activation in DITRA can initiate the recruitment of hematopoietic cells into the tissue and initiate inflammatory amplification loops that lead to pustular dermatoses, in this case with systemic inflammation as well.

Definitive treatment has not been established, but acitretin has been used with variable success (199, 200). Other therapeutic regimens have included oral steroids, methotrexate, cyclosporine, and adalimumab in two patients. IL-1-blocking therapy has been reported in one patient, with only transient improvement (I. Kone-Paut, R. Goldbach-Mansky, personal communication). These data are consistent with the mouse model, which suggested that IL-36 mediates keratinocyte activation but does not induce IL-1 signaling (201).

Early-onset inflammatory bowel disease (IBD)—Autosomal recessive loss-of-function mutations resulting in defects in IL-10 (*IL10*) or either subunit of the IL-10 receptor (*IL10RA* or *IL10RB*) cause severe IBD with onset in the first year of life (30). IL-10-related mutations account for up to 25% of early-onset IBD cases (202, 203). Similarly, *IL10* promoter polymorphisms have been repeatedly associated with general IBD risk (204).

Early-onset IBD patients present with severe debilitating enterocolitis characterized by hematochezia, colonic abscesses, perianal fistulas, oral ulcers, and failure to thrive that is refractory to aggressive immunosuppression (203, 205). Nongastrointestinal involvement

includes recurrent folliculitis and, rarely, recurrent fever and chronic large-joint arthritis (203). Patients with IL-10-related early-onset IBD who underwent allogenic HSCT benefitted substantially, most achieving clinical remission (202, 203).

IL-10, an anti-inflammatory cytokine, is produced by and has effects on nearly every immune cell type and many nonimmune cells. IL-10R1 is unique to IL-10 signaling, and IL-10R2 is shared by IL-22, IL-26, and λ-IFNs IL-28A/B and IL-29 (27). IL-10 stimulation induces Jak1/Tyk2 phosphorylation, STAT3 activation, and transcriptional changes with anti-inflammatory effects (204). The severe enterocolitis observed in IL-10-deficient mice requires commensal bacteria (206) but not adaptive immune cells.

Stimulation through mutant IL-10 receptors led to impaired STAT3 phosphorylation in PBMCs (205). IL-22 signaling was normal in patients with *IL10R1* mutations but impaired in patients with mutations in *IL10R2* (207). The clinical phenotype, including folliculitis, is conserved across all three genetic defects (202, 203, 208), suggesting that loss of IL-22, IL-26, and λ-IFN signaling contributes little to pathogenesis.

The exact mechanisms leading to early-onset IBD are not well understood. $FoxP3^+$ regulatory T cells are a major source of IL-10 in the gut (209); patients with IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome lack FoxP3. IL-10 must act on gut macrophages, to prevent colitis (210). The severe and organ-specific phenotype attributable to IL-10 defects demonstrates the primacy of this cytokine in regulating immune responses to gut bacteria. The efficacy of HSCT demonstrates that the important sources of IL-10 are hematopoietic (203) and that the main nonredundant role of IL-10 is to limit the immunostimulatory effects of bacterial colonization on innate immune cells.

Syndromes Caused by Increased Immune Cell Receptor Signaling

PLAID and APLAID—Autosomal dominant mutations in *PLCγ2* cause two related syndromes: PLCγ2-associated antibody deficiency and immune dysregulation (PLAID) and autoinflammation and PLAID (APLAID). Whereas PLAID leads to cold-induced urticaria, autoimmune manifestations, and susceptibility to infections, APLAID leads to early-onset recurrent erythematous plaques and vesicopustular skin lesions associated with arthralgia, corneal erosions, and interstitial pneumonia (211). The two patients with APLAID identified thus far developed recurrent sinopulmonary infections, presumed to be due to a lack of class-switched memory B cells (211). Both patients were partially responsive to anakinra and high-dose corticosteroids (211).

***LYN*-associated autoinflammatory disease (LAID)—**We recently identified a nonsense de novo mutation in *LYN*, encoding Lyn kinase, in a patient presenting with autoinflammatory disease, including fevers and neutrophilic vasculitis, and with significant B cell dysregulation. Lyn is a widely expressed Src-family tyrosine kinase with both activating and inhibiting effects on signaling pathways. $Lyn^{up/up}$ mice have a gain-of-function mutation generated at the tyrosine position 508 (Y508F) and have severe anemia, autoimmune glomerulonephritis, and elevated ANA antibodies (212).

Cherubism—Cherubism is an autosomal dominant syndrome of childhood-onset facial swelling caused by heterozygous *SH3BP2* mutations (213). Patients develop symmetrical cysts in their maxillae and mandibles filled by expansive osteoclast-laden tissue. This tissue applies pressure on the bony cortex, with characteristic swelling (for which the disease is named) that spontaneously regresses with puberty.

SH3BP2 is a ubiquitously expressed scaffold protein that can interact with membrane lipids and a number of signaling molecules, including Syk and PLCγ1. Excessive SH3BP2 activity may exaggerate NFATc1 signals and drive osteoclast differentiation (214). *SH3BP2* mutations in mice cause TNF-α-dependent diffuse cherubism-like lesions. Macrophages and osteoclasts from these mice show enhanced Erk and Syk activation and are hyperinflammatory (215). These data, and the fact that *SH3BP2* haploinsufficiency does not cause bone lesions, support a gain-of-function mechanism.

Why jawbones are the sole sites of inflammation in cherubism remains elusive, but this may relate to specific signals derived from tooth development and/or oral flora. TNF-α inhibition does not appear to be effective in treating human cherubism (216), but inhibitors of NFAT activation, such as tacrolimus, may be beneficial (217).

8. UNCLASSIFIABLE DISEASES

Recently, heterozygous mutations in the *AP1S3* gene, which encodes a subunit of the cytosolic transport complex AP1, were described in 15 unrelated patients with pustular psoriasis. The patients presented with either generalized pustular psoriasis or palmar plantar pustulosis and tested negative for mutations in *IL36RN* and *CARD14* (218). These mutations await functional characterization.

Another autoinflammatory syndrome is caused by autosomal recessive loss-of-function mutations in the *ADAM17* gene, encoding the TNF-α converting enzyme TACE, which is necessary for the cleavage and secretion of TNF-α, epidermal growth factor, TGF-α, and some desmogleins. Two consanguineous siblings with substantial deletions in this gene and no functional protein (219) had neonatal-onset of pustular psoriasis, hair abnormalities, and diarrhea and cardiomyopathy. Although it is unclear which manifestations are related to autoinflammation versus defects in barrier surfaces, patient PBMCs oversecreted IL-1β and IL-6 in response to stimulation.

Monoallelic mutations in *NLRP12* have been associated with an autosomal dominant periodic fever syndrome known as NLRP12AD (220). The disease-causing mutations found in *NLRP12* have been associated either with a loss of the inhibitory function of NLRP12 on NF-κB signaling or with increased caspase-1 activation, but the disease-associated pathways remain unclear (221, 222).

Recurrent and long attacks of fever and abdominal pain have been described in three patients with heterozygous mutations in *TNFRSF11A*, the gene encoding RANK (receptor activator of NF-κB). Owing to the clinical similarities with the classical periodic fever syndrome TRAPS, this autoinflammatory disease has been designated TRAPS11 (223).

Autosomal recessive mutations in *SLC29A3* have been associated with H-syndrome (hyperpigmentation, hypertrichosis, hepatosplenomegaly, heart abnormalities, and hypogonadism). More recently, it was reported that 5% of a cohort of 79 patients with H-syndrome presented with recurrent fever (224). An association between a homozygous *SLC29A3* mutation and autoinflammatory manifestations has also been reported (225).

9. AUTOINFLAMMATION, AUTOIMMUNITY, IMMUNODEFICIENCY, LYMPHOPROLIFERATION, AND ANIMAL MODELS

Defining the Boundaries of Autoinflammatory Diseases

In many conditions the boundaries between autoinflammation (increased innate immunity), autoimmunity (increased adaptive immunity), and immunodeficiency (decreased innate or adaptive immunity) are fluid, and many of the diseases discussed in this review present with clinical features that cross these boundaries. The clinical phenotypes are driven by the cell type most affected by a particular mutation: Excessive activation of neutrophils, monocytes/macrophages, and dendritic cells leads to autoinflammatory symptoms; T cell and B cell dysfunction leads to autoimmunity. Failure of innate and/or adaptive immune cells to appropriately activate and recognize and clear infectious agents causes immunodeficiency and vulnerability to infections.

Clinical overlap of autoinflammation and immunodeficiency—Depending on the nature of the defect, dysregulation of the very same innate immune pathway can present with autoinflammatory phenotypes or cause immunodeficiencies. Whereas genetic defects in innate immune pathways that mediate pathogen recognition and affect the ability to eliminate infected cells lead to infections, increased or constitutive activation of innate immune pathways by infectious or noninfectious triggers leads to autoinflammation.

A number of the disorders discussed in this review have features of immunodeficiency and autoinflammation. We discussed in detail those disorders where autoinflammation is predominant and patients require immunomodulation or immunosuppression. Another group of disorders, including HOIL-1 deficiency, NF-κB essential modulator (NEMO/IKKγ) deficiency, and dominant negative mutations in IkBα, have immunodeficiency dominating over autoinflammatory features and are beyond the scope of this review. These three examples demonstrate the complexity of the NF-κB signaling pathway in immune responses (226, 227). Study of the differential action of specific immune defects in innate and adaptive immune cells may provide an understanding of the clinical features associated with autoinflammation and immunodeficiency in the same patient.

Clinical overlap of autoinflammation and autoimmunity—The innate leukocytes include NK cells; mast cells; eosinophils; basophils; and phagocytic cells, including macrophages, neutrophils, and dendritic cells. Adaptive immune cells (T and B cells) acquire or refine their receptors with antigen contact. Whereas in IL-1-mediated diseases immune activation primarily affects innate immune cells, activation of IFN in known IFN-mediated diseases leads to activation and dysregulation of T and B cells. Antinuclear antibodies, evidence of B cell activation, and other signs of adaptive cell stimulation are

often seen in the latter diseases, but the disease manifestations often occur in patients whether autoantibodies are present or not. In other instances, such as the manifestations in AGS, some pathology may be caused by specific autoantibodies.

Clinical overlap of autoinflammation and lymphoproliferation— Autoinflammatory phenotypes frequently occur in patients with excessive proliferation of immune cells. Massive expansion of immune cells in the lymph nodes, spleen, liver, or bone marrow is described as lymphoproliferation and is not malignant. These disorders are diagnosed histologically, but the genetic causes of lymphoproliferation include defects in Fas-mediated killing (*FAS*, *FASL*), defects in induction of apoptosis (*CASP8*, *CASP10*), and excessive proliferation (somatic *NRAS*, *KRAS*). EBV triggers lymphoproliferation in patients harboring mutations that affect T cell activation (*SH2D1A/SAP*, *ITK*, *CD27*). Overall, the mutations associated with lymphoproliferation largely affect adaptive immune cells and increase risk of autoimmunity and malignancy (110).

Divergence of Inflammatory Phenotypes in Animal Models of Human Disease

Mechanistic insights from immunologic studies in mice have largely framed our understanding of immune responses. However, caution is needed when extrapolating from pathomechanistic studies in murine disease models. Differences between mouse models of autoinflammatory diseases and human phenotypes are summarized in Table 4 and may be a reflection of differences found in innate immune components between mice and humans. Whereas humans have 10 TLRs and 22 NLRs, mice have 12 TLRs and 34 NLRs (228). Furthermore, immune responses to trauma, burns, and endotoxemia are very similar in humans, but these responses were not reproduced in different mouse models used in a recently reported study (229), pointing to the fact that human and mouse PRRs/effector pathways are different. We also have major gaps in our understanding of the remarkable organ specificity of autoinflammatory disease in humans (Table 3). Clinicians and researchers should be wary of extrapolation from experiments in murine models that do not capture the organ specificity seen in humans. Table 4 summarizes murine models of autoinflammatory diseases and compares phenotypes to the human disease manifestations.

10. SYNOPSIS

The disease-based discovery of the molecular mechanisms that cause autoinflammatory phenotypes (summarized in Table 3 and Figure 6) and basic research discoveries accelerated our understanding of innate immune pathways and their dysregulation over the last 15 years. These mostly monogenic defects that cause autoinflammatory disease phenotypes allow us to get glimpses into the impact of innate immune dysregulation on human disease manifestations. The insights gained from comparative research in children with various autoinflammatory disorders allowed us to build on the discovery of the IL-1-activating inflammasomes and the development of IL-1-blocking agents that have since been approved by the US Food and Drug Administration and to identify dysregulation of other key proinflammatory pathways. Examples include the exploration of pathways that link intracellular stress with IFN production and other inflammatory mediators and the study of clinical phenotypes that are caused by dysregulation in other proinflammatory pathways that

continue to point us toward novel targets for better therapeutic interventions. The organ-specific manifestations of autoinflammatory diseases signal the importance of studying innate immune regulation and dysregulation at the level of organ-specific tissues and cells.

Acknowledgments

We thank Savitha Viswanathan and Leslie Parker for their generous help in synchronizing the tables, figures, and text of this review. We thank Dr. Karyl Barron and Dr. Dan Kastner for images on HIDS, TRAPS, and FMF and Dr. Adeline Vanderver for an image of AGS. Our work was funded by the NIAMS Intramural Research Program (IRP), NIH, the Clinical Center, and NIAMS.

LITERATURE CITED

1. McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell. 1999; 97:133–44. [PubMed: 10199409]
2. Janeway CA Jr. Approaching the asymptote? Evolution and revolution in immunology. Cold Spring Harb Symp Quant Biol. 1989; 54(Part 1):1–13. [PubMed: 2700931]
3. Matzinger P. Tolerance, danger, and the extended family. Annu Rev Immunol. 1994; 12:991–1045. [PubMed: 8011301]
4. Wen H, Miao EA, Ting JP. Mechanisms of NOD-like receptor-associated inflammasome activation. Immunity. 2013; 39:432–41. [PubMed: 24054327]
5. Wu J, Chen ZJ. Innate immune sensing and signaling of cytosolic nucleic acids. Annu Rev Immunol. 2014; 32:461–88. [PubMed: 24655297]
6. Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity. 2011; 34:637–50. [PubMed: 21616434]
7. Medzhitov R, Preston-Hurlburt P, Janeway CA Jr. A human homologue of the *Drosophila* Toll protein signals activation of adaptive immunity. Nature. 1997; 388:394–97. [PubMed: 9237759]
8. International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell. 1997; 90:797–807. [PubMed: 9288758]
9. French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet. 1997; 17:25–31. [PubMed: 9288094]
10. Ting JP, Kastner DL, Hoffman HM. CATERPILLERs, pyrin and hereditary immunological disorders. Nat Rev Immunol. 2006; 6:183–95. [PubMed: 16498449]
11. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat Genet. 2001; 29:301–5. [PubMed: 11687797]
12. Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, et al. De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. Arthritis Rheumatol. 2002; 46:3340–48.
13. Feldmann J, Prieur AM, Quartier P, Berquin P, Certain S, et al. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in *CIAS1*, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am J Hum Genet. 2002; 71:198–203. [PubMed: 12032915]
14. Miceli-Richard C, Lesage S, Rybojad M, Prieur AM, Manouvrier-Hanu S, et al. CARD15 mutations in Blau syndrome. Nat Genet. 2001; 29:19–20. [PubMed: 11528384]
15. Wang L, Manji GA, Grenier JM, Al-Garawi A, Merriam S, et al. PYPAF7, a novel PYRIN-containing Apaf1-like protein that regulates activation of NF-κB and caspase-1-dependent cytokine processing. J Biol Chem. 2002; 277:29874–80. [PubMed: 12019269]
16. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell. 2002; 10:417–26. [PubMed: 12191486]

17. Yoneyama M, Kikuchi M, Natsukawa T, Shinobu N, Imaizumi T, et al. The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nat Immunol. 2004; 5:730–37. [PubMed: 15208624]
18. Yoneyama M, Kikuchi M, Matsumoto K, Imaizumi T, Miyagishi M, et al. Shared and unique functions of the DExD/H-box helicases RIG-I, MDA5, and LGP2 in antiviral innate immunity. J Immunol. 2005; 175:2851–58. [PubMed: 16116171]
19. Atianand MK, Fitzgerald KA. Molecular basis of DNA recognition in the immune system. J Immunol. 2013; 190:1911–18. [PubMed: 23417527]
20. Rice GI, del Toro Duany Y, Jenkinson EM, Forte GM, Anderson BH, et al. Gain-of-function mutations in *IFIH1* cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling. Nat Genet. 2014; 46:503–9. [PubMed: 24686847]
21. Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med. 2014; 371:507–18. [PubMed: 25029335]
22. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008; 454:428–35. [PubMed: 18650913]
23. Lamkanfi M, Dixit VM. Mechanisms and functions of inflammasomes. Cell. 2014; 157:1013–22. [PubMed: 24855941]
24. Jesus AA, Goldbach-Mansky R. IL-1 blockade in autoinflammatory syndromes. Annu Rev Med. 2014; 65:223–44. [PubMed: 24422572]
25. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med. 2009; 360:2426–37. [PubMed: 19494218]
26. Reddy S, Jia S, Geoffrey R, Lorier R, Suchi M, et al. An autoinflammatory disease due to homozygous deletion of the *IL1RN* locus. N Engl J Med. 2009; 360:2438–44. [PubMed: 19494219]
27. Glocker EO, Kotlarz D, Klein C, Shah N, Grimbacher B. IL-10 and IL-10 receptor defects in humans. Ann NY Acad Sci. 2011; 1246:102–7. [PubMed: 22236434]
28. Eitel J, Suttorp N, Opitz. Innate immune recognition and inflammasome activation in *Listeria monocytogenes* infection. Front Microbiol. 2011; 1:149. [PubMed: 21607087]
29. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. Annu Rev Immunol. 2009; 27:519–50. [PubMed: 19302047]
30. Sibley CH, Plass N, Snow J, Wiggs EA, Brewer CC, et al. Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra: a cohort study to determine three- and five-year outcomes. Arthritis Rheumatol. 2012; 64:2375–86.
31. Mariathasan S, Newton K, Monack DM, Vucic D, French DM, et al. Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. Nature. 2004; 430:213–18. [PubMed: 15190255]
32. Robbins GR, Wen H, Ting JP. Inflammasomes and metabolic disorders: old genes in modern diseases. Mol Cell. 2014; 54:297–308. [PubMed: 24766894]
33. Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: host cell death and inflammation. Nat Rev Microbiol. 2009; 7:99–109. [PubMed: 19148178]
34. Miao EA, Leaf IA, Treuting PM, Mao DP, Dors M, et al. Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria. Nat Immunol. 2010; 11:1136–42. [PubMed: 21057511]
35. Hacham M, Argov S, White RM, Segal S, Apte RN. Distinct patterns of IL-1 alpha and IL-1 beta organ distribution—a possible basis for organ mechanisms of innate immunity. Adv Exp Med Biol. 2000; 479:185–202. [PubMed: 10897420]
36. Pothlichet J, Meunier I, Davis BK, Ting JP, Skamene E, et al. Type I IFN triggers RIG-I/TLR3/NLRP3-dependent inflammasome activation in influenza A virus infected cells. PLOS Pathog. 2013; 9:e1003256. [PubMed: 23592984]
37. Gross O, Yazdi AS, Thomas CJ, Masin M, Heinz LX, et al. Inflammasome activators induce interleukin-1α secretion via distinct pathways with differential requirement for the protease function of caspase-1. Immunity. 2012; 36:388–400. [PubMed: 22444631]

38. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat Genet. 2001; 29:301–5. [PubMed: 11687797]
39. [accessed Jan 20 2015] Int Soc Syst Autoinflamm Dis. 2014. Infevers Online Database for Autoinflammatory Mutations, Montpellier, Fr., updated Oct 29http://fmf.igh.cnrs.fr/ISSAID/infevers/
40. Tanaka N, Izawa K, Saito MK, Sakuma M, Oshima K, et al. High incidence of *NLRP3* somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome: results of an international multicenter collaborative study. Arthritis Rheumatol. 2011; 63:3625–32.
41. Arostegui JI, Aldea A, Modesto C, Rua MJ, Arguelles F, et al. Clinical and genetic heterogeneity among Spanish patients with recurrent autoinflammatory syndromes associated with the *CIAS1*/*PYPAF1*/*NALP3* gene. Arthritis Rheumatol. 2004; 50:4045–50.
42. Hill SC, Namde M, Dwyer A, Poznanski A, Canna S, Goldbach-Mansky R. Arthropathy of neonatal onset multisystem inflammatory disease (NOMID/CINCA). Pediatr Radiol. 2007; 37:145–52. [PubMed: 17136361]
43. Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J. NALP3 forms an IL-1β-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. Immunity. 2004; 20:319–25. [PubMed: 15030775]
44. Haneklaus M, O'Neill LA, Coll RC. Modulatory mechanisms controlling the NLRP3 inflammasome in inflammation: recent developments. Curr Opin Immunol. 2013; 25:40–45. [PubMed: 23305783]
45. Lee GS, Subramanian N, Kim AI, Aksentijevich I, Goldbach-Mansky R, et al. The calcium-sensing receptor regulates the NLRP3 inflammasome through $Ca2^{+}$ and cAMP. Nature. 2012; 492:123–27. [PubMed: 23143333]
46. Gattorno M, Tassi S, Carta S, Delfino L, Ferlito F, et al. Pattern of interleukin-1β secretion in response to lipopolysaccharide and ATP before and after interleukin-1 blockade in patients with CIAS1 mutations. Arthritis Rheumatol. 2007; 56:3138–48.
47. Baroja-Mazo A, Martin-Sanchez F, Gomez AI, Martinez CM, Amores-Iniesta J, et al. The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response. Nat Immunol. 2014; 15:738–48. [PubMed: 24952504]
48. Heller H, Sohar E, Pras M. Ethnic distribution and amyloidosis in familial Mediterranean fever (FMF). Pathol Microbiol. 1961; 24:718–23. [PubMed: 13906231]
49. Stoffels M, Szperl A, Simon A, Netea MG, Plantinga TS, et al. *MEFV* mutations affecting pyrin amino acid 577 cause autosomal dominant autoinflammatory disease. Ann Rheum Dis. 2013; 73:455–61. [PubMed: 23505238]
50. Ben-Chetrit E, Levy M. Familial Mediterranean fever. Lancet. 1998; 351:659–64. [PubMed: 9500348]
51. Chae JJ, Aksentijevich I, Kastner DL. Advances in the understanding of familial Mediterranean fever and possibilities for targeted therapy. Br J Haematol. 2009; 146:467–78. [PubMed: 19466978]
52. Gedalia A, Zamir S. Neurologic manifestations in familial Mediterranean fever. Pediatr Neurol. 1993; 9:301–2. [PubMed: 8216544]
53. Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. N Engl J Med. 1986; 314:1001–5. [PubMed: 3515182]
54. Hashkes PJ, Spalding SJ, Giannini EH, Huang B, Johnson A, et al. Rilonacept for colchicine-resistant or -intolerant familial Mediterranean fever: a randomized trial. Ann Intern Med. 2012; 157:533–41. [PubMed: 23070486]
55. Woo JS, Imm JH, Min CK, Kim KJ, Cha SS, Oh BH. Structural and functional insights into the B30.2/SPRY domain. EMBO J. 2006; 25:1353–63. [PubMed: 16498413]
56. Uchil PD, Quinlan BD, Chan WT, Luna JM, Mothes W. TRIM E3 ligases interfere with early and late stages of the retroviral life cycle. PLOS Pathog. 2008; 4:e16. [PubMed: 18248090]

57. Tsuchida T, Zou J, Saitoh T, Kumar H, Abe T, et al. The ubiquitin ligase TRIM56 regulates innate immune responses to intracellular double-stranded DNA. Immunity. 2010; 33:765–76. [PubMed: 21074459]
58. Richards N, Schaner P, Diaz A, Stuckey J, Shelden E, et al. Interaction between pyrin and the apoptotic speck protein (ASC) modulates ASC-induced apoptosis. J Biol Chem. 2001; 276:39320–29. [PubMed: 11498534]
59. Omenetti A, Carta S, Delfino L, Martini A, Gattorno M, Rubartelli A. Increased NLRP3-dependent interleukin 1β secretion in patients with familial Mediterranean fever: correlation with *MEFV* genotype. Ann Rheum Dis. 2014; 73:462–69. [PubMed: 23505242]
60. Chae JJ, Komarow HD, Cheng J, Wood G, Raben N, et al. Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis. Mol Cell. 2003; 11:591–604. [PubMed: 12667444]
61. Jank T, Giesemann T, Aktories K. Rho-glucosylating *Clostridium difficile* toxins A and B: new insights into structure and function. Glycobiology. 2007; 17:15R–22R.
62. Xu H, Yang J, Gao W, Li L, Li P, et al. Innate immune sensing of bacterial modifications of Rho GTPases by the pyrin inflammasome. Nature. 2014; 513:237–41. [PubMed: 24919149]
63. Mansfield E, Chae JJ, Komarow HD, Brotz TM, Frucht DM, et al. The familial Mediterranean fever protein, pyrin, associates with microtubules and colocalizes with actin filaments. Blood. 2001; 98:851–59. [PubMed: 11468188]
64. Waite AL, Schaner P, Hu C, Richards N, Balci-Peynircioglu B, et al. Pyrin and ASC co-localize to cellular sites that are rich in polymerizing actin. Exp Biol Med. 2009; 234:40–52.
65. Cronstein BN, Molad Y, Reibman J, Balakhane E, Levin RI, Weissmann G. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. J Clin Investig. 1995; 96:994–1002. [PubMed: 7543498]
66. Liao G, Nagasaki T, Gundersen GG. Low concentrations of nocodazole interfere with fibroblast locomotion without significantly affecting microtubule level: implications for the role of dynamic microtubules in cell locomotion. J Cell Sci. 1995; 108(Part 11):3473–83. [PubMed: 8586659]
67. Canna SW, de Jesus AA, Gouni S, Brooks SR, Marrero B, et al. An activating *NLRC4* inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. Nat Genet. 2014; 46:1140–46. [PubMed: 25217959]
68. Romberg N, Al Moussawi K, Nelson-Williams C, Stiegler AL, Loring E, et al. Mutation of *NLRC4* causes a syndrome of enterocolitis and autoinflammation. Nat Genet. 2014; 46:1135–49. [PubMed: 25217960]
69. Strowig T, Henao-Mejia J, Elinav E, Flavell R. Inflammasomes in health and disease. Nature. 2012; 481:278–86. [PubMed: 22258606]
70. Kitamura A, Sasaki Y, Abe T, Kano H, Yasutomo K. An inherited mutation in NLRC4 causes autoinflammation in human and mice. J Exp Med. 2014; 211:2385–96. [PubMed: 25385754]
71. Houten SM, Kuis W, Duran M, de Koning TJ, van Royen-Kerkhof A, et al. Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinaemia D and periodic fever syndrome. Nat Genet. 1999; 22:175–77. [PubMed: 10369261]
72. Frenkel J, Houten SM, Waterham HR, Wanders RJ, Rijkers GT, et al. Mevalonate kinase deficiency and Dutch type periodic fever. Clin Exp Rheumatol. 2000; 18:525–32. [PubMed: 10949735]
73. Cuisset L, Drenth JP, Simon A, Vincent MF, van der Velde Visser S, et al. Molecular analysis of MVK mutations and enzymatic activity in hyper-IgD and periodic fever syndrome. Eur J Hum Genet. 2001; 9:260–66. [PubMed: 11313769]
74. Rigante D, Ansuini V, Bertoni B, Pugliese AL, Avallone L, et al. Treatment with anakinra in the hyperimmunoglobulinemia D/periodic fever syndrome. Rheumatol Int. 2006; 27:97–100. [PubMed: 16871408]
75. Galeotti C, Meinzer U, Quartier P, Rossi-Semerano L, Bader-Meunier B, et al. Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency. Rheumatology. 2012; 51:1855–59. [PubMed: 22740624]

76. Takada K, Aksentijevich I, Mahadevan V, Dean JA, Kelley RI, Kastner DL. Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome. Arthritis Rheumatol. 2003; 48:2645–51.
77. Drenth JP, Cuisset L, Grateau G, Vasseur C, van de Velde-Visser SD, et al. Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. Nat Genet. 1999; 22:178–81. [PubMed: 10369262]
78. Lutz RJ, McLain TM, Sinensky M. Feedback inhibition of polyisoprenyl pyrophosphate synthesis from mevalonate in vitro: implications for protein prenylation. J Biol Chem. 1992; 267:7983–86. [PubMed: 1569056]
79. Mandey SH, Kuijk LM, Frenkel J, Waterham HR. A role for geranylgeranylation in interleukin-1β secretion. Arthritis Rheumatol. 2006; 54:3690–95.
80. Kuijk LM, Beekman JM, Koster J, Waterham HR, Frenkel J, Coffer PJ. HMG-CoA reductase inhibition induces IL-1β release through Rac1/PI3K/PKB-dependent caspase-1 activation. Blood. 2008; 112:3563–73. [PubMed: 18684863]
81. van der Burgh R, Pervolaraki K, Turkenburg M, Waterham HR, Frenkel J, Boes M. Unprenylated RhoA contributes to IL-1β hypersecretion in mevalonate kinase deficiency model through stimulation of Rac1 activity. J Biol Chem. 2014; 289:27757–65. [PubMed: 25107911]
82. Hull KM, Drewe E, Aksentijevich I, Singh HK, Wong K, et al. The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. Medicine. 2002; 81:349–68. [PubMed: 12352631]
83. Gattorno M, Pelagatti MA, Meini A, Obici L, Barcellona R, et al. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheumatol. 2008; 58:1516–20.
84. Sacre K, Brihaye B, Lidove O, Papo T, Pocidalo MA, et al. Dramatic improvement following interleukin 1β blockade in tumor necrosis factor receptor-1-associated syndrome (TRAPS) resistant to anti-TNF-α therapy. J Rheumatol. 2008; 35:357–58. [PubMed: 18260167]
85. Bulua AC, Mogul DB, Aksentijevich I, Singh H, He DY, et al. Efficacy of etanercept in the tumor necrosis factor receptor-associated periodic syndrome: a prospective, open-label, dose-escalation study. Arthritis Rheumatol. 2012; 64:908–13.
86. Nedjai B, Hitman GA, Yousaf N, Chernajovsky Y, Stjernberg-Salmela S, et al. Abnormal tumor necrosis factor receptor I cell surface expression and NF-κB activation in tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheumatol. 2008; 58:273–83.
87. Banner DW, D'Arcy A, Janes W, Gentz R, Schoenfeld HJ, et al. Crystal structure of the soluble human 55 kd TNF receptor-human TNFβ complex: implications for TNF receptor activation. Cell. 1993; 73:431–45. [PubMed: 8387891]
88. Lobito AA, Kimberley FC, Muppidi JR, Komarow H, Jackson AJ, et al. Abnormal disulfide-linked oligomerization results in ER retention and altered signaling by TNFR1 mutants in TNFR1-associated periodic fever syndrome (TRAPS). Blood. 2006; 108:1320–27. [PubMed: 16684962]
89. Simon A, Park H, Maddipati R, Lobito AA, Bulua AC, et al. Concerted action of wild-type and mutant TNF receptors enhances inflammation in TNF receptor 1-associated periodic fever syndrome. PNAS. 2010; 107:9801–6. [PubMed: 20457915]
90. Bulua AC, Simon A, Maddipati R, Pelletier M, Park H, et al. Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS). J Exp Med. 2011; 208:519–33. [PubMed: 21282379]
91. Rebelo SL, Bainbridge SE, Amel-Kashipaz MR, Radford PM, Powell RJ, et al. Modeling of tumor necrosis factor receptor superfamily 1A mutants associated with tumor necrosis factor receptor-associated periodic syndrome indicates misfolding consistent with abnormal function. Arthritis Rheumatol. 2006; 54:2674–87.
92. Stojanov S, Dejaco C, Lohse P, Huss K, Duftner C, et al. Clinical and functional characterisation of a novel TNFRSF1A c. 605T>A/V173D cleavage site mutation associated with tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS), cardiovascular complications and excellent response to etanercept treatment. Ann Rheum Dis. 2008; 67:1292–98. [PubMed: 18180277]

93. Ferguson PJ, Chen S, Tayeh MK, Ochoa L, Leal SM, et al. Homozygous mutations in *LPIN2* are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). J Med Genet. 2005; 42:551–57. [PubMed: 15994876]

94. Majeed HA, Kalaawi M, Mohanty D, Teebi AS, Tunjekar MF, et al. Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet syndrome in two siblings. J Pediatr. 1989; 115:730–34. [PubMed: 2809904]

95. Herlin T, Fiirgaard B, Bjerre M, Kerndrup G, Hasle H, et al. Efficacy of anti-IL-1 treatment in Majeed syndrome. Ann Rheum Dis. 2012; 72:410–13. [PubMed: 23087183]

96. Donkor J, Zhang P, Wong S, O'Loughlin L, Dewald J, et al. A conserved serine residue is required for the phosphatidate phosphatase activity but not the transcriptional coactivator functions of lipin-1 and lipin-2. J Biol Chem. 2009; 284:29968–78. [PubMed: 19717560]

97. Fakas S, Qiu Y, Dixon JL, Han GS, Ruggles KV, et al. Phosphatidate phosphatase activity plays key role in protection against fatty acid-induced toxicity in yeast. J Biol Chem. 2011; 286:29074–85. [PubMed: 21708942]

98. Valdearcos M, Esquinas E, Meana C, Pena L, Gil-de-Gomez L, et al. Lipin-2 reduces proinflammatory signaling induced by saturated fatty acids in macrophages. J Biol Chem. 2012; 287:10894–904. [PubMed: 22334674]

99. Jesus AA, Osman M, Silva CA, Kim PW, Pham TH, et al. A novel mutation of IL1RN in the deficiency of interleukin-1 receptor antagonist syndrome: description of two unrelated cases from Brazil. Arthritis Rheumatol. 2011; 63:4007–17.

100. Crow YJ. Type I interferonopathies: a novel set of inborn errors of immunity. Ann NY Acad Sci. 2011; 1238:91–98. [PubMed: 22129056]

101. Bennett L, Palucka AK, Arce E, Cantrell V, Borvak J, et al. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. J Exp Med. 2003; 197:711–23. [PubMed: 12642603]

102. Hall JC, Rosen A. Type I interferons: crucial participants in disease amplification in autoimmunity. Nat Rev Rheumatol. 2010; 6:40–49. [PubMed: 20046205]

103. Lilly, Eli. Study record NCT01724580. US Natl. Inst. Health; Bethesda, MD: 2014. Compassionate use protocol for the treatment of autoinflammatory syndromes. updated July. https://clinicaltrials.gov/ct2/show/NCT01724580

104. Seth RB, Sun L, Ea CK, Chen ZJ. Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-κB and IRF 3. Cell. 2005; 122:669–82. [PubMed: 16125763]

105. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. Nat Rev Immunol. 2014; 14:36–49. [PubMed: 24362405]

106. Sun L, Wu J, Du F, Chen X, Chen ZJ. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science. 2013; 339:786–91. [PubMed: 23258413]

107. Wu J, Sun L, Chen X, Du F, Shi H, et al. Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. Science. 2013; 339:826–30. [PubMed: 23258412]

108. Ouyang S, Song X, Wang Y, Ru H, Shaw N, et al. Structural analysis of the STING adaptor protein reveals a hydrophobic dimer interface and mode of cyclic di-GMP binding. Immunity. 2012; 36:1073–86. [PubMed: 22579474]

109. Zhang X, Shi H, Wu J, Zhang X, Sun L, et al. Cyclic GMP-AMP containing mixed phosphodiester linkages is an endogenous high-affinity ligand for STING. Mol Cell. 2013; 51:226–35. [PubMed: 23747010]

110. Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency. Front Immunol. 2014; 5:162. [PubMed: 24795713]

111. Ramantani G, Kohlhase J, Hertzberg C, Innes AM, Engel K, et al. Expanding the phenotypic spectrum of lupus erythematosus in Aicardi-Goutieres syndrome. Arthritis Rheumatol. 2010; 62:1469–77.

112. Crow YJ, Vanderver A, Orcesi S, Kuijpers TW, Rice GI. Therapies in Aicardi-Goutieres syndrome. Clin Exp Immunol. 2014; 175:1–8. [PubMed: 23607857]
113. Crow YJ. Aicardi-Goutieres syndrome. Handb Clin Neurol. 2013; 113:1629–35. [PubMed: 23622384]
114. Stetson DB, Ko JS, Heidmann T, Medzhitov R. Trex1 prevents cell-intrinsic initiation of autoimmunity. Cell. 2008; 134:587–98. [PubMed: 18724932]
115. Gall A, Treuting P, Elkon KB, Loo YM, Gale M Jr, et al. Autoimmunity initiates in nonhematopoietic cells and progresses via lymphocytes in an interferon-dependent autoimmune disease. Immunity. 2012; 36:120–31. [PubMed: 22284419]
116. Ablasser A, Hemmerling I, Schmid-Burgk JL, Behrendt R, Roers A, Hornung V. TREX1 deficiency triggers cell-autonomous immunity in a cGAS-dependent manner. J Immunol. 2014; 192:5993–97. [PubMed: 24813208]
117. Agranat L, Raitskin O, Sperling J, Sperling R. The editing enzyme ADAR1 and the mRNA surveillance protein hUpf1 interact in the cell nucleus. PNAS. 2008; 105:5028–33. [PubMed: 18362360]
118. Volkman HE, Stetson DB. The enemy within: endogenous retroelements and autoimmune disease. Nat Immunol. 2014; 15:415–22. [PubMed: 24747712]
119. Yang YG, Lindahl T, Barnes DE. Trex1 exonuclease degrades ssDNA to prevent chronic checkpoint activation and autoimmune disease. Cell. 2007; 131:873–86. [PubMed: 18045533]
120. Kind B, Muster B, Staroske W, Herce HD4, Sachse R, et al. Altered spatiotemporal dynamics of RNase H2 complex assembly at replication and repair sites in Aicardi-Goutières syndrome. Hum Mol Genet. 2014; 23:5950–60. [PubMed: 24986920]
121. Kitamura A, Maekawa Y, Uehara H, Izumi K, Kawachi I, et al. A mutation in the immunoproteasome subunit *PSMB8* causes autoinflammation and lipodystrophy in humans. J Clin Investig. 2011; 121:4150–60. [PubMed: 21881205]
122. Arima K, Kinoshita A, Mishima H, Kanazawa N, Kaneko T, et al. Proteasome assembly defect due to a proteasome subunit beta type 8 (PSMB8) mutation causes the autoinflammatory disorder, Nakajo-Nishimura syndrome. PNAS. 2011; 108:14914–19. [PubMed: 21852578]
123. Liu Y, Ramot Y, Torrelo A, Paller A, Si N, et al. Mutations in proteasome subunit β type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. Arthritis Rheumatol. 2012; 64:895–907.
124. Agarwal A, Xing C, DeMartino G, Mizrachi D, Hernandez MD, et al. *PSMB8* encoding the β5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. Am J Hum Genet. 2010; 87:866–72. [PubMed: 21129723]
125. Baumeister W, Walz J, Zühl F, Seemüller E. The proteasome: paradigm of a self-compartmentalizing protease. Cell. 1998; 92:367–80. [PubMed: 9476896]
126. Stohwasser R, Kuckelkorn U, Kraft R, Kostka S, Kloetzel PM. 20S proteasome from LMP7 knock out mice reveals altered proteolytic activities and cleavage site preferences. FEBS Lett. 1996; 383:109–13. [PubMed: 8612775]
127. Chen BP, Wolfgang CD, Hai T. Analysis of ATF3, a transcription factor induced by physiological stresses and modulated by gadd153/Chop10. Mol Cell Biol. 1996; 16:1157–68. [PubMed: 8622660]
128. Eckard SC, Rice GI, Fabre A, Badens C, Gray EE, et al. The SKIV2L RNA exosome limits activation of the RIG-I-like receptors. Nat Immunol. 2014; 15:839–45. [PubMed: 25064072]
129. Lausch E, Janecke A, Bros M, Trojandt S, Alanay Y, et al. Genetic deficiency of tartrate-resistant acid phosphatase associated with skeletal dysplasia, cerebral calcifications and autoimmunity. Nat Genet. 2011; 43:132–37. [PubMed: 21217752]
130. Briggs TA, Rice GI, Daly S, Urquhart J, Gornall H, Bader-Meunier B, et al. Tartrate-resistant acid phosphatase deficiency causes a bone dysplasia with autoimmunity and a type I interferon expression signature. Nat Genet. 2011; 43:127–31. [PubMed: 21217755]
131. Jiang C, Lin X. Regulation of NF-κB by the CARD proteins. Immunol Rev. 2012; 246:141–53. [PubMed: 22435552]

132. Kanazawa N, Okafuji I, Kambe N, Nishikomori R, Nakata-Hizume M, et al. Early-onset sarcoidosis and *CARD15* mutations with constitutive nuclear factor-κB activation: common genetic etiology with Blau syndrome. Blood. 2005; 105:1195–97. [PubMed: 15459013]
133. Rose CD, Arostegui JI, Martin TM, Espada G, Scalzi L, et al. NOD2-associated pediatric granulomatous arthritis, an expanding phenotype: study of an international registry and a national cohort in Spain. Arthritis Rheumatol. 2009; 60:1797–803.
134. Rose CD, Wouters CH, Meiorin S, Doyle TM, Davey MP, et al. Pediatric granulomatous arthritis: an international registry. Arthritis Rheumatol. 2006; 54:3337–44.
135. Arostegui JI, Arnal C, Merino R, Modesto C, Antonia Carballo M, et al. NOD2 gene-associated pediatric granulomatous arthritis: clinical diversity, novel and recurrent mutations, and evidence of clinical improvement with interleukin-1 blockade in a Spanish cohort. Arthritis Rheumatol. 2007; 56:3805–13.
136. Becker ML, Rose CD. Blau syndrome and related genetic disorders causing childhood arthritis. Curr Rheumatol Rep. 2005; 7:427–33. [PubMed: 16303101]
137. Rose CD, Martin TM, Wouters CH. Blau syndrome revisited. Curr Opin Rheumatol. 2011; 23:411–18. [PubMed: 21788900]
138. Chen G, Shaw MH, Kim YG, Nunez G. NOD-like receptors: role in innate immunity and inflammatory disease. Annu Rev Pathol. 2009; 4:365–98. [PubMed: 18928408]
139. Zurek B, Proell M, Wagner RN, Schwarzenbacher R, Kufer TA. Mutational analysis of human NOD1 and NOD2 NACHT domains reveals different modes of activation. Innate Immun. 2012; 18:100–11. [PubMed: 21310790]
140. Kobayashi K, Inohara N, Hernandez LD, Galan JE, Nunez G, et al. RICK/Rip2/CARDIAK mediates signalling for receptors of the innate and adaptive immune systems. Nature. 2002; 416:194–99. [PubMed: 11894098]
141. Magalhaes JG, Lee J, Geddes K, Rubino S, Philpott DJ, Girardin SE. Essential role of Rip2 in the modulation of innate and adaptive immunity triggered by Nod1 and Nod2 ligands. Eur J Immunol. 2011; 41:1445–55. [PubMed: 21469090]
142. Ogura Y, Inohara N, Benito A, Chen FF, Yamaoka S, Nunez G. Nod2, a Nod1/Apaf-1 family member that is restricted to monocytes and activates NF-κaB. J Biol Chem. 2001; 276:4812–18. [PubMed: 11087742]
143. Jordan CT, Cao L, Roberson ED, Pierson KC, Yang CF, et al. PSORS2 is due to mutations in CARD14. Am J Hum Genet. 2012; 90:784–95. [PubMed: 22521418]
144. Fuchs-Telem D, Sarig O, van Steensel MA, Isakov O, Israeli S, et al. Familial pityriasis rubra pilaris is caused by mutations in *CARD14*. Am J Hum Genet. 2012; 91:163–70. [PubMed: 22703878]
145. Jordan CT, Cao L, Roberson ED, Duan S, Helms CA, et al. Rare and common variants in CARD14, encoding an epidermal regulator of NF-κB, in psoriasis. Am J Hum Genet. 2012; 90:796–808. [PubMed: 22521419]
146. Vasher M, Smithberger E, Lien MH, Fenske NA. Familial pityriasis rubra pilaris: report of a family and therapeutic response to etanercept. J Drugs Dermatol. 2010; 9:844–50. [PubMed: 20677542]
147. Ohyagi H, Onai N, Sato T, Yotsumoto S, Liu J, et al. Monocyte-derived dendritic cells perform hemophagocytosis to fine-tune excessive immune responses. Immunity. 2013; 39:584–98. [PubMed: 24035363]
148. Canna SW, Costa-Reis P, Bernal WE, Chu N, Sullivan KE, et al. Brief report: alternative activation of laser-captured murine hemophagocytes. Arthritis Rheumatol. 2014; 66:1666–71. [PubMed: 24470386]
149. Castillo L, Carcillo J. Secondary hemophagocytic lymphohistiocytosis and severe sepsis/systemic inflammatory response syndrome/multiorgan dysfunction syndrome/macrophage activation syndrome share common intermediate phenotypes on a spectrum of inflammation. Pediatr Crit Care Med. 2009; 10:387–92. [PubMed: 19325510]
150. Bleesing J, Prada A, Siegel DM, Villanueva J, Olson J, et al. The diagnostic significance of soluble CD163 and soluble interleukin-2 receptor alpha-chain in macrophage activation

syndrome and untreated new-onset systemic juvenile idiopathic arthritis. Arthritis Rheumatol. 2007; 56:965–71.

151. Van Gorp H, Delputte PL, Nauwynck HJ. Scavenger receptor CD163, a Jack-of-all-trades and potential target for cell-directed therapy. Mol Immunol. 2010; 47:1650–60. [PubMed: 20299103]
152. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007; 48:124–31. [PubMed: 16937360]
153. Lin TF, Ferlic-Stark LL, Allen CE, Kozinetz CA, McClain KL. Rate of decline of ferritin in patients with hemophagocytic lymphohistiocytosis as a prognostic variable for mortality. Pediatr Blood Cancer. 2011; 56:154–55. [PubMed: 20842751]
154. Fardet L, Coppo P, Kettaneh A, Dehoux M, Cabane J, Lambotte O. Low glycosylated ferritin, a good marker for the diagnosis of hemophagocytic syndrome. Arthritis Rheumatol. 2008; 58:1521–27.
155. Wada T, Kanegane H, Ohta K, Katoh F, Imamura T, et al. Sustained elevation of serum interleukin-18 and its association with hemophagocytic lymphohistiocytosis in XIAP deficiency. Cytokine. 2014; 65:74–78. [PubMed: 24084330]
156. Shimizu M, Nakagishi Y, Yachie A. Distinct subsets of patients with systemic juvenile idiopathic arthritis based on their cytokine profiles. Cytokine. 2013; 61:345–48. [PubMed: 23276493]
157. Ichida H, Kawaguchi Y, Sugiura T, Takagi K, Katsumata Y, et al. Clinical manifestations of adult-onset Still's disease presenting with erosive arthritis: association with low levels of ferritin and IL-18. Arthritis Care Res. 2014; 66:642–46.
158. Villanueva J, Lee S, Giannini EH, Graham TB, Passo MH, et al. Natural killer cell dysfunction is a distinguishing feature of systemic onset juvenile rheumatoid arthritis and macrophage activation syndrome. Arthritis Res Ther. 2005; 7:R30–37. [PubMed: 15642140]
159. de Jager W, Vastert SJ, Beekman JM, Wulffraat NM, Kuis W, et al. Defective phosphorylation of interleukin-18 receptor β causes impaired natural killer cell function in systemic-onset juvenile idiopathic arthritis. Arthritis Rheumatol. 2009; 60:2782–93.
160. Iannello A, Samarani S, Debbeche O, Ahmad R, Boulassel MR, et al. Potential role of interleukin-18 in the immunopathogenesis of AIDS: involvement in fratricidal killing of NK cells. J Virol. 2009; 83:5999–6010. [PubMed: 19339355]
161. Nedvetzki S, Sowinski S, Eagle RA, Harris J, Vely F, et al. Reciprocal regulation of human natural killer cells and macrophages associated with distinct immune synapses. Blood. 2007; 109:3776–85. [PubMed: 17218381]
162. Gattorno M, Piccini A, Lasiglie D, Tassi S, Brisca G, et al. The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheumatol. 2008; 58:1505–15.
163. Bruck N, Suttorp M, Kabus M, Heubner G, Gahr M, Pessler F. Rapid and sustained remission of systemic juvenile idiopathic arthritis-associated macrophage activation syndrome through treatment with anakinra and corticosteroids. J Clin Rheumatol. 2011; 17:23–27. [PubMed: 21169853]
164. Rigaud S, Fondaneche MC, Lambert N, Pasquier B, Mateo V, et al. XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. Nature. 2006; 444:110–14. [PubMed: 17080092]
165. Marsh RA, Madden L, Kitchen BJ, Mody R, McClimon B, et al. XIAP deficiency: a unique primary immunodeficiency best classified as X-linked familial hemophagocytic lymphohistiocytosis and not as X-linked lymphoproliferative disease. Blood. 2010; 116:1079–82. [PubMed: 20489057]
166. Aguilar C, Lenoir C, Lambert N, Begue B, Brousse N, et al. Characterization of Crohn disease in X-linked inhibitor of apoptosis-deficient male patients and female symptomatic carriers. J Allergy Clin Immunol. 2014; 134:1131–41. e9. [PubMed: 24942515]
167. Speckmann C, Lehmberg K, Albert MH, Damgaard RB, Fritsch M, et al. X-linked inhibitor of apoptosis (XIAP) deficiency: the spectrum of presenting manifestations beyond hemophagocytic lymphohistiocytosis. Clin Immunol. 2013; 149:133–41. [PubMed: 23973892]

168. Stepp SE, Dufourcq-Lagelouse R, Le Deist F, Bhawan S, Certain S, et al. Perforin gene defects in familial hemophagocytic lymphohistiocytosis. Science. 1999; 286:1957–59. [PubMed: 10583959]

169. Pachlopnik Schmid J, Cote M, Menager MM, Burgess A, Nehme N, et al. Inherited defects in lymphocyte cytotoxic activity. Immunol Rev. 2010; 235:10–23. [PubMed: 20536552]

170. Jessen B, Kogl T, Sepulveda FE, de Saint Basile G, Aichele P, Ehl S. Graded defects in cytotoxicity determine severity of hemophagocytic lymphohistiocytosis in humans and mice. Front Immunol. 2013; 4:448. [PubMed: 24379813]

171. Horne A, Trottestam H, Arico M, Egeler RM, Filipovich AH, et al. Frequency and spectrum of central nervous system involvement in 193 children with haemophagocytic lymphohistiocytosis. Br J Haematol. 2008; 140:327–35. [PubMed: 18076710]

172. Imashuku S. Clinical features and treatment strategies of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Crit Rev Oncol Hematol. 2002; 44:259–72. [PubMed: 12467966]

173. Demirkol D, Yildizdas D, Bayrakci B, Karapinar B, Kendirli T, et al. Hyperferritinemia in the critically ill child with secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction syndrome/macrophage activation syndrome: What is the treatment? Crit Care. 2012; 16:R52. [PubMed: 22715953]

174. Terrell CE, Jordan MB. Perforin deficiency impairs a critical immunoregulatory loop involving murine $CD8^+$ T cells and dendritic cells. Blood. 2013; 121:5184–91. [PubMed: 23660960]

175. Krebs P, Crozat K, Popkin D, Oldstone MB, Beutler B. Disruption of MyD88 signaling suppresses hemophagocytic lymphohistiocytosis in mice. Blood. 2011; 117:6582–88. [PubMed: 21551232]

176. Sepulveda FE, Maschalidi S, Vosshenrich CA, Garrigue A, Kurowska M, et al. A novel immunoregulatory role for NK cell cytotoxicity in protection from HLH-like immunopathology in mice. Blood. 2014 In press.

177. Zoller EE, Lykens JE, Terrell CE, Aliberti J, Filipovich AH, et al. Hemophagocytosis causes a consumptive anemia of inflammation. J Exp Med. 2011; 208:1203–14. [PubMed: 21624938]

178. Osugi Y, Hara J, Tagawa S, Takai K, Hosoi G, et al. Cytokine production regulating Th1 and Th2 cytokines in hemophagocytic lymphohistiocytosis. Blood. 1997; 89:4100–3. [PubMed: 9166851]

179. Vastert SJ, van Wijk R, D'Urbano LE, de Vooght KM, de Jager W, et al. Mutations in the perforin gene can be linked to macrophage activation syndrome in patients with systemic onset juvenile idiopathic arthritis. Rheumatology. 2010; 49:441–49. [PubMed: 20019066]

180. Zhang K, Biroschak J, Glass DN, Thompson SD, Finkel T, et al. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis is associated with MUNC13-4 polymorphisms. Arthritis Rheumatol. 2008; 58:2892–96.

181. Jordan MB, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): $CD8^+$ T cells and interferon gamma are essential for the disorder. Blood. 2004; 104:735–43. [PubMed: 15069016]

182. Pachlopnik Schmid J, Ho CH, Chretien F, Lefebvre JM, Pivert G, et al. Neutralization of IFNγ defeats haemophagocytosis in LCMV-infected perforin- and Rab27a-deficient mice. EMBO Mol Med. 2009; 1:112–24. [PubMed: 20049711]

183. Behrens EM, Canna SW, Slade K, Rao S, Kreiger PA, et al. Repeated TLR9 stimulation results in macrophage activation syndrome-like disease in mice. J Clin Investig. 2011; 121:2264–77. [PubMed: 21576823]

184. Sumegi J, Barnes MG, Nestheide SV, Molleran-Lee S, Villanueva J, et al. Gene expression profiling of peripheral blood mononuclear cells from children with active hemophagocytic lymphohistiocytosis. Blood. 2011; 117:e151–60. [PubMed: 21325597]

185. Sikora KA, Fall N, Thornton S, Grom AA. The limited role of interferon-gamma in systemic juvenile idiopathic arthritis cannot be explained by cellular hyporesponsiveness. Arthritis Rheumatol. 2012; 64:3799–808.

186. Fall N, Barnes M, Thornton S, Luyrink L, Olson J, et al. Gene expression profiling of peripheral blood from patients with untreated new-onset systemic juvenile idiopathic arthritis reveals

molecular heterogeneity that may predict macrophage activation syndrome. Arthritis Rheumatol. 2007; 56:3793–804.

187. Strippoli R, Carvello F, Scianaro R, De Pasquale L, Vivarelli M, et al. Amplification of the response to Toll-like receptor ligands by prolonged exposure to interleukin-6 in mice: implication for the pathogenesis of macrophage activation syndrome. Arthritis Rheumatol. 2012; 64:1680–88.
188. Wise CA, Gillum JD, Seidman CE, Lindor NM, Veile R, et al. Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. Hum Mol Genet. 2002; 11:961–69. [PubMed: 11971877]
189. Demidowich AP, Freeman AF, Kuhns DB, Aksentijevich I, Gallin JI, et al. Brief report: genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). Arthritis Rheumatol. 2012; 64:2022–27.
190. Wu Y, Spencer SD, Lasky LA. Tyrosine phosphorylation regulates the SH3-mediated binding of the Wiskott-Aldrich syndrome protein to PSTPIP, a cytoskeletal-associated protein. J Biol Chem. 1998; 273:5765–70. [PubMed: 9488710]
191. Shoham NG, Centola M, Mansfield E, Hull KM, Wood G, et al. Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. PNAS. 2003; 100:13501–6. [PubMed: 14595024]
192. Starnes TW, Bennin DA, Bing X, Eickhoff JC, Grahf DC, et al. The F-BAR protein PSTPIP1 controls extracellular matrix degradation and filopodia formation in macrophages. Blood. 2014; 123:2703–14. [PubMed: 24421327]
193. Yu JW, Fernandes-Alnemri T, Datta P, Wu J, Juliana C, et al. Pyrin activates the ASC pyroptosome in response to engagement by autoinflammatory PSTPIP1 mutants. Mol Cell. 2007; 28:214–27. [PubMed: 17964261]
194. Wang D, Hoing S, Patterson HC, Ahmad UM, Rathinam VA, et al. Inflammation in mice ectopically expressing human Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome-associated PSTPIP1 A230T mutant proteins. J Biol Chem. 2013; 288:4594–601. [PubMed: 23293022]
195. Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med. 2014; 370:911–20. [PubMed: 24552284]
196. Navon Elkan P, Pierce SB, Segel R, Walsh T, Barash J, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med. 2014; 370:921–31. [PubMed: 24552285]
197. Wiseman DH, May A, Jolles S, Connor P, Powell C, et al. A novel syndrome of congenital sideroblastic anemia, B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD). Blood. 2013; 122:112–23. [PubMed: 23553769]
198. Chakraborty PK, Schmitz-Abe K, Kennedy EK, Mamady H, Naas T, et al. Mutations in *TRNT1* cause congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD). Blood. 2014; 124:2867–71. [PubMed: 25193871]
199. Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, et al. Interleukin-36–receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med. 2011; 365:620–28. [PubMed: 21848462]
200. Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet. 2011; 89:432–37. [PubMed: 21839423]
201. Blumberg H, Dinh H, Trueblood ES, Pretorius J, Kugler D, et al. Opposing activities of two novel members of the IL-1 ligand family regulate skin inflammation. J Exp Med. 2007; 204:2603–14. [PubMed: 17908936]
202. Engelhardt KR, Shah N, Faizura-Yeop I, Kocacik Uygun DF, Frede N, et al. Clinical outcome in IL-10– and IL-10 receptor–deficient patients with or without hematopoietic stem cell transplantation. J Allergy Clin Immunol. 2013; 131:825–30. [PubMed: 23158016]
203. Kotlarz D, Beier R, Murugan D, Diestelhorst J, Jensen O, et al. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. Gastroenterology. 2012; 143:347–55. [PubMed: 22549091]

204. Mosser DM, Zhang X. Interleukin-10: new perspectives on an old cytokine. Immunol Rev. 2008; 226:205–18. [PubMed: 19161426]
205. Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schaffer AA, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med. 2009; 361:2033–45. [PubMed: 19890111]
206. Kuhn R, Lohler J, Rennick D, Rajewsky K, Muller W. Interleukin-10-deficient mice develop chronic enterocolitis. Cell. 1993; 75:263–74. [PubMed: 8402911]
207. Begue B, Verdier J, Rieux-Laucat F, Goulet O, Morali A, et al. Defective IL10 signaling defining a subgroup of patients with inflammatory bowel disease. Am J Gastroenterol. 2011; 106:1544–55. [PubMed: 21519361]
208. Glocker EO, Frede N, Perro M, Sebire N, Elawad M, et al. Infant colitis—it's in the genes. Lancet. 2010; 376:1272. [PubMed: 20934598]
209. Roers A, Siewe L, Strittmatter E, Deckert M, Schluter D, et al. T cell–specific inactivation of the interleukin 10 gene in mice results in enhanced T cell responses but normal innate responses to lipopolysaccharide or skin irritation. J Exp Med. 2004; 200:1289–97. [PubMed: 15534372]
210. Zigmond E, Bernshtein B, Friedlander G, Walker CR, Yona S, et al. Macrophage-restricted interleukin-10 receptor deficiency, but not IL-10 deficiency, causes severe spontaneous colitis. Immunity. 2014; 40:720–33. [PubMed: 24792913]
211. Zhou Q, Lee GS, Brady J, Datta S, Katan M, et al. A hypermorphic missense mutation in *PLCG2*, encoding phospholipase Cγ2, causes a dominantly inherited autoinflammatory disease with immunodeficiency. Am J Hum Genet. 2012; 91:713–20. [PubMed: 23000145]
212. Hibbs ML, Harder KW, Armes J, Kountouri N, Quilici C, et al. Sustained activation of Lyn tyrosine kinase in vivo leads to autoimmunity. J Exp Med. 2002; 196:1593–604. [PubMed: 12486102]
213. Ueki Y, Tiziani V, Santanna C, Fukai N, Maulik C, Garfinkle J, et al. Mutations in the gene encoding c-Abl-binding protein SH3BP2 cause cherubism. Nat Genet. 2001; 28:125–26. [PubMed: 11381256]
214. Reichenberger EJ, Levine MA, Olsen BR, Papadaki ME, Lietman SA. The role of SH3BP2 in the pathophysiology of cherubism. Orphanet J Rare Dis. 2012; 7(Suppl 1):S5. [PubMed: 22640988]
215. Ueki Y, Lin CY, Senoo M, Ebihara T, Agata N, Onji M, et al. Increased myeloid cell responses to M-CSF and RANKL cause bone loss and inflammation in SH3BP2 "cherubism" mice. Cell. 2007; 128:71–83. [PubMed: 17218256]
216. Hero M, Suomalainen A, Hagström J, Stoor P, Kontio R, Alapulli H, et al. Anti-tumor necrosis factor treatment in cherubism—clinical, radiological and histological findings in two children. Bone. 2013; 52:347–53. [PubMed: 23069372]
217. Kadlub N, Vazquez MP, Galmiche L, L'Herminé AC, Dainese L, Ulinski T, et al. The calcineurin inhibitor tacrolimus as a new therapy in severe cherubism. J Bone Miner Res. 2014 In press.
218. Setta-Kaffetzi N, Simpson MA, Navarini AA, Patel VM, Lu HC, et al. AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. Am J Hum Genet. 2014; 94:790–97. [PubMed: 24791904]
219. Blaydon DC, Biancheri P, Di WL, Plagnol V, Cabral RM, et al. Inflammatory skin and bowel disease linked to ADAM17 deletion. N Engl J Med. 2011; 365:1502–8.10.1056/NEJMoa1100721 [PubMed: 22010916]
220. Jéru I, Duquesnoy P, Fernandes-Alnemri T, Cochet E, Yu JW, et al. Mutations in *NALP12* cause hereditary periodic fever syndromes. PNAS. 2008; 105:1614–19. [PubMed: 18230725]
221. Borghini S, Tassi S, Chiesa S, Caroli F, Carta S, et al. Clinical presentation and pathogenesis of cold-induced autoinflammatory disease in a family with recurrence of an NLRP12 mutation. Arthritis Rheumatol. 2011; 63:830–39.
222. Jéru I, Le Borgne G, Cochet E, Hayrapetyan H, Duquesnoy P, et al. Identification and functional consequences of a recurrent NLRP12 missense mutation in periodic fever syndromes. Arthritis Rheumatol. 2011; 63:1459–64.
223. Jéru I, Cochet E, Duquesnoy P, Hentgen V, Copin B, et al. Brief Report: involvement of *TNFRSF11A* molecular defects in autoinflammatory disorders. Arthritis Rheumatol. 2014; 66:2621–27. [PubMed: 24891336]

224. Molho-Pessach V, Ramot Y, Camille F, Doviner V, Babay S, et al. H syndrome: the first 79 patients. J Am Acad Dermatol. 2014; 70:80–88. [PubMed: 24172204]

225. Melki I, Lambot K, Jonard L, Couloigner V, Quartier P, et al. Mutation in the *SLC29A3* gene: a new cause of a monogenic, autoinflammatory condition. Pediatrics. 2013; 131:e1308–13. [PubMed: 23530176]

226. Cheng LE, Kanwar B, Tcheurekdjian H, Grenert JP, Muskat M, et al. Persistent systemic inflammation and atypical enterocolitis in patients with NEMO syndrome. Clin Immunol. 2009; 132:124–31. [PubMed: 19375390]

227. Boisson B, Laplantine E, Prando C, Giliani S, Israelsson E, et al. Immunodeficiency, autoinflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency. Nat Immunol. 2012; 13:1178–86. [PubMed: 23104095]

228. Kanneganti TD, Lamkanfi M, Nunez G. Intracellular NOD-like receptors in host defense and disease. Immunity. 2007; 27:549–59. [PubMed: 17967410]

229. Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. PNAS. 2013; 110:3507–12. [PubMed: 23401516]

230. Brydges SD, Mueller JL, McGeough MD, Pena CA, Misaghi A, et al. Inflammasome-mediated disease animal models reveal roles for innate but not adaptive immunity. Immunity. 2009; 30:875–87. [PubMed: 19501000]

231. Brydges SD, Broderick L, McGeough MD, Pena CA, Mueller JL, Hoffman HM. Divergence of IL-1, IL-18, and cell death in NLRP3 inflammasomopathies. J Clin Investig. 2013; 123:4695–705. [PubMed: 24084736]

232. Meng G, Zhang F, Fuss I, Kitani A, Strober W. A mutation in the *Nlrp3* gene causing inflammasome hyperactivation potentiates Th17 cell-dominant immune responses. Immunity. 2009; 30:860–74. [PubMed: 19501001]

233. Chae JJ, Cho YH, Lee GS, Cheng J, Liu PP, et al. Gain-of-function pyrin mutations induce NLRP3 protein-independent interleukin-1β activation and severe autoinflammation in mice. Immunity. 2011; 34:755–68. [PubMed: 21600797]

234. Hager EJ, Tse HM, Piganelli JD, Gupta M, Baetscher M, et al. Deletion of a single mevalonate kinase (*Mvk*) allele yields a murine model of hyper-IgD syndrome. J Inherit Metab Dis. 2007; 30:888–95. [PubMed: 18008182]

235. Komarow HD, Chae JJ, Raben N, Wood G, Kastner DL. Mice with mutations of TNFRSF1A may reveal insights into pathogenesis of TRAPS, a dominantly inherited autoinflammatory disease. J Allergy Clin Immunol. 2004; 113(2 Suppl):S205.

236. Horai R, Saijo S, Tanioka H, Nakae S, Sudo K, et al. Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin 1 receptor antagonist-deficient mice. J Exp Med. 2000; 191:313–20. [PubMed: 10637275]

237. Nicklin MJ, Hughes DE, Barton JL, Ure JM, Duff GW. Arterial inflammation in mice lacking the interleukin 1 receptor antagonist gene. J Exp Med. 2000; 191:303–12. [PubMed: 10637274]

238. Fehling HJ, Swat W, Laplace C, Kühn R, Rajewsky K, et al. MHC class I expression in mice lacking the proteasome subunit LMP-7. Science. 1994; 265:1234–37. [PubMed: 8066463]

239. Czar MJ, Kersh EN, Mijares LA, Lanier G, Lewis J, et al. Altered lymphocyte responses and cytokine production in mice deficient in the X-linked lymphoproliferative disease gene *SH2D1A/DSHP/SAP*. PNAS. 2001; 98:7449–54. [PubMed: 11404475]

240. Wu C, Nguyen KB, Pien GC, Wang N, Gullo C, et al. SAP controls T cell responses to virus and terminal differentiation of T_H2 cells. Nat Immunol. 2001; 2:410–14. [PubMed: 11323694]

241. Yin L, Al-Alem U, Liang J, Tong WM, Li C, et al. Mice deficient in the X-linked lymphoproliferative disease gene *sap* exhibit increased susceptibility to murine gammaherpesvirus-68 and hypogammaglobulinemia. J Med Virol. 2003; 71:446–55. [PubMed: 12966553]

242. Harlin H, Reffey SB, Duckett CS, Lindsten T, Thompson CB. Characterization of XIAP-deficient mice. Mol Cell Biol. 2001; 21(10):3604–8. [PubMed: 11313486]

243. Olayioye MA, Kaufmann H, Pakusch M, Vaux DL, Lindeman GJ, et al. XIAP-deficiency leads to delayed lobuloalveolar development in the mammary gland. Cell Death Differ. 2005; 12:87–90. [PubMed: 15540113]

244. Harder KW, Parsons LM, Armes J, Evans N, Kountouri N, et al. Gain- and loss-of-function Lyn mutant mice define a critical inhibitory role for Lyn in the myeloid lineage. Immunity. 2001; 15:603–15. [PubMed: 11672542]

245. Hibbs ML, Harder KW, Armes J, Kountouri N, Quilici C, et al. Sustained activation of Lyn tyrosine kinase in vivo leads to autoimmunity. J Exp Med. 2002; 196:1593–604. [PubMed: 12486102]

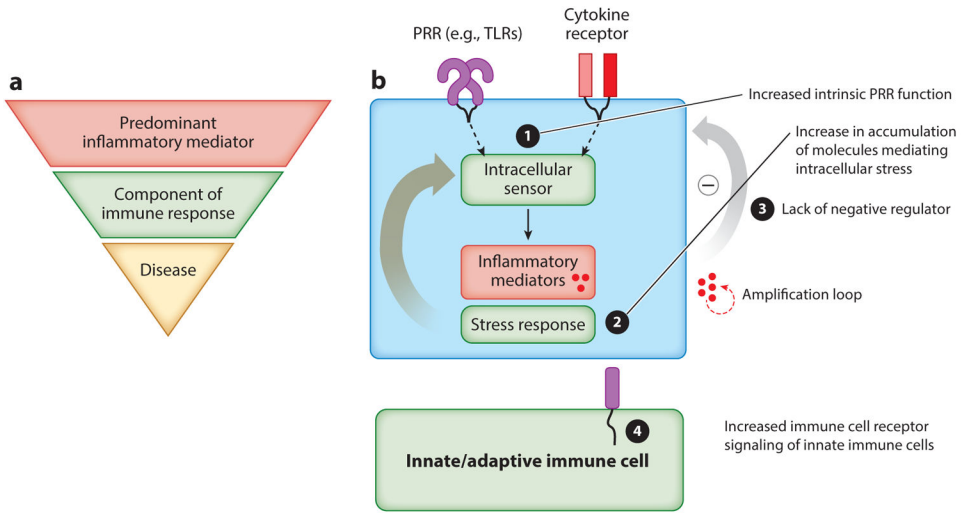

Figure 1.

Principles of immune dysregulation in autoinflammatory diseases. (*a*) Each genetically defined autoinflammatory disease (*yellow*) can be classified based on the predominant proinflammatory mediator that is upregulated, where known, (*red*) and the component of the innate immune response that is affected by the disease-causing mutations (*green*). (*b*) Dysregulation in four components of the immune response are found to cause autoinflammatory diseases. (Table 1 presents a complete list of genes that are mutated in autoinflammatory diseases and the corresponding components of the innate immune response that are affected.) ❶ Gain-of-function mutations (autosomal dominant, often sporadic/de novo) in genes encoding intracellular PRRs or their adaptor molecules result in constitutively increased innate immune sensor function and increased or continued production of proinflammatory mediators. ❷ Loss-of-function mutations or haploinsufficiency of molecules/enzymes critical for maintaining cell homeostasis can result in accumulation of intracellular stressors that stimulate intracellular sensor/PRR activation and the production of proinflammatory mediators. ❸ Loss-of-function mutations in genes encoding negative regulators that downregulate proinflammatory responses also lead to autoinflammatory diseases. The mutations observed so far lead to loss of function of a cytokine receptor antagonist, or an antiinflammatory cytokine, or failure to terminate the release of inflammatory mediators by inflammatory cells (e.g, cytotoxic dysfunction causing persistent macrophage activation). ❹ Mutations that alter immune receptor signaling cause a group of diseases presenting with often more complex clinical phenotypes that can include autoinflammatory, immunodeficient, and autoimmune features depending on their effect on innate or adaptive immune cells. (Abbreviations: PRR, pattern-recognition receptor; TLR, Toll-like receptor.)

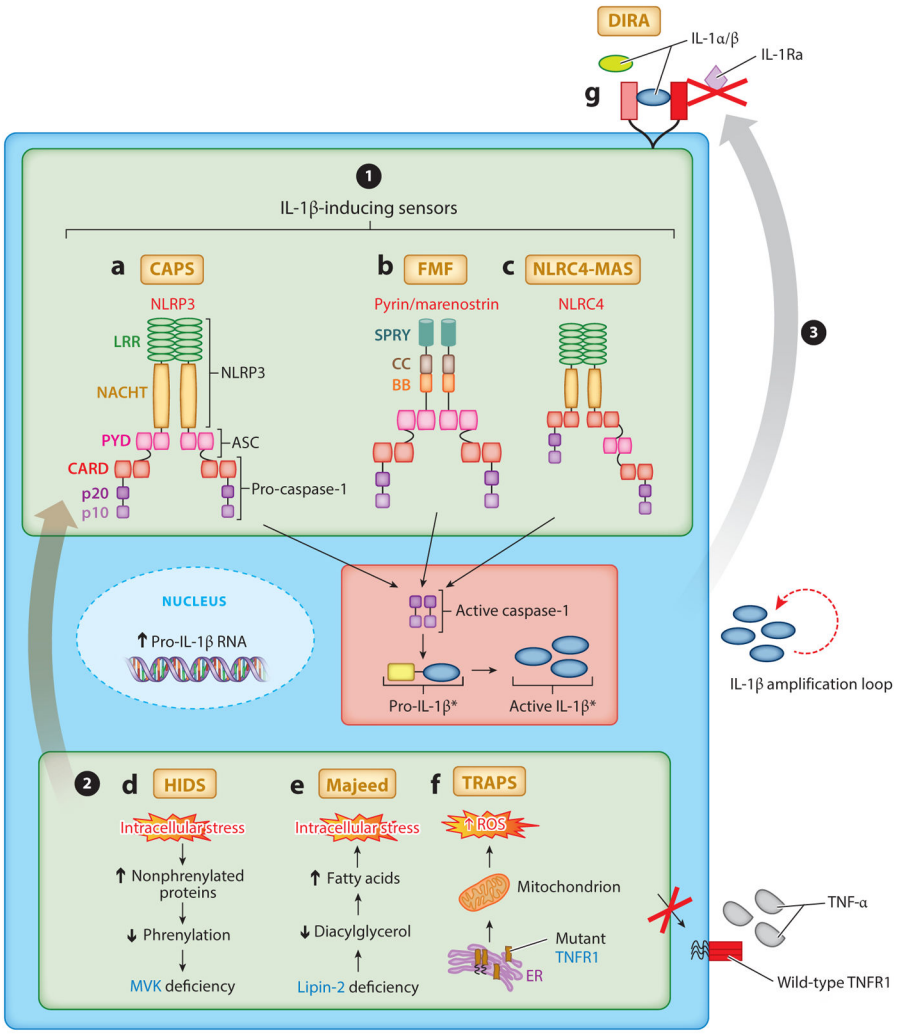

Figure 2.

Proposed mechanisms of activation of IL-1-signaling pathways in autoinflammatory diseases. (*a*) Cryopyrinopathies (CAPS). Unlike wild-type NLRP3, mutated NLRP3 (which causes CAPS) is constitutively activated and thought to oligomerize and bind to the adapter molecule ASC (apoptosis-associated speck-like protein containing a CARD) to form an active catalytic complex with two pro-caspase-1 molecules. Via autocatalysis, this complex generates active caspase-1, which cleaves inactive pro-IL-1β into its active form, IL-1β. (*b*) Familial Mediterranean fever (FMF). Wild-type pyrin can interact directly with ASC, forming the pyrin inflammasome, which is activated in the presence of FMF-causing mutations. (*c*) NLRC4-MAS. Mutations in the NACHT domain of NLRC4 cause autoinflammatory diseases that predispose to the development of macrophage-activating syndrome (MAS). The asterisk (*) indicates that caspase-1 activation also leads to IL-18 activation that is highest in NLRC4 inflammasome activation. (*d*) Hyper-IgD syndrome (HIDS). Mevalonate kinase (MVK), a critical enzyme in the biosynthesis of sterol and nonsterol isoprenoids, catalyzes the conversion of mevalonate to mevalonate phosphate. In HIDS, activity of this enzyme is reduced, resulting in decreased concentrations of

mevalonate phosphate, geranylgeranyl pyrophosphate, and farnesyl pyrophosphate, and impaired geranylgeranylation of a number of proteins. Through an unknown mechanism, the reduced geranylgeranylation would lead to an increased procaspase-1 activation and consequent caspase-1 activation, with resulting overproduction of IL-1β. (*e*) Majeed syndrome. Lipin-2 catalyzes the conversion of phosphatidate to diacylglycerol, a precursor for the production of phospholipids. Mutations in *LPIN2* are thought to lead to an accumulation of fatty acids and intracellular stress that induces inflammasome activation. (*f*) TNF receptor–associated periodic syndrome (TRAPS). TNFR1 molecules are transported from the endoplasmic reticulum (ER) to the Golgi apparatus and then to the cell surface. Mutated TNFR1 (which causes TRAPS) is misfolded and cannot be transported to the cell surface. Misfolded TNFR1 is sequestered in the ER, where it causes intracellular stress through increased mitochondrial reactive oxygen species (ROS) production that leads to inflammasome activation and increased signaling, including NF-κB activation. (*g*) Deficiency of IL-1Ra (DIRA). Deficiency of IL-1Ra leads to unopposed IL-1α and IL-1β signaling. The structure of the inflammasomes was adapted from Reference 28. Numbers in black circles indicate disease caused by ❶ increased sensor function, ❷ generation of cell stress, or ❸ loss of negative regulator. (Other abbreviations: IL-1Ra, IL-1 receptor antagonist; PYD, pyrin domain.)

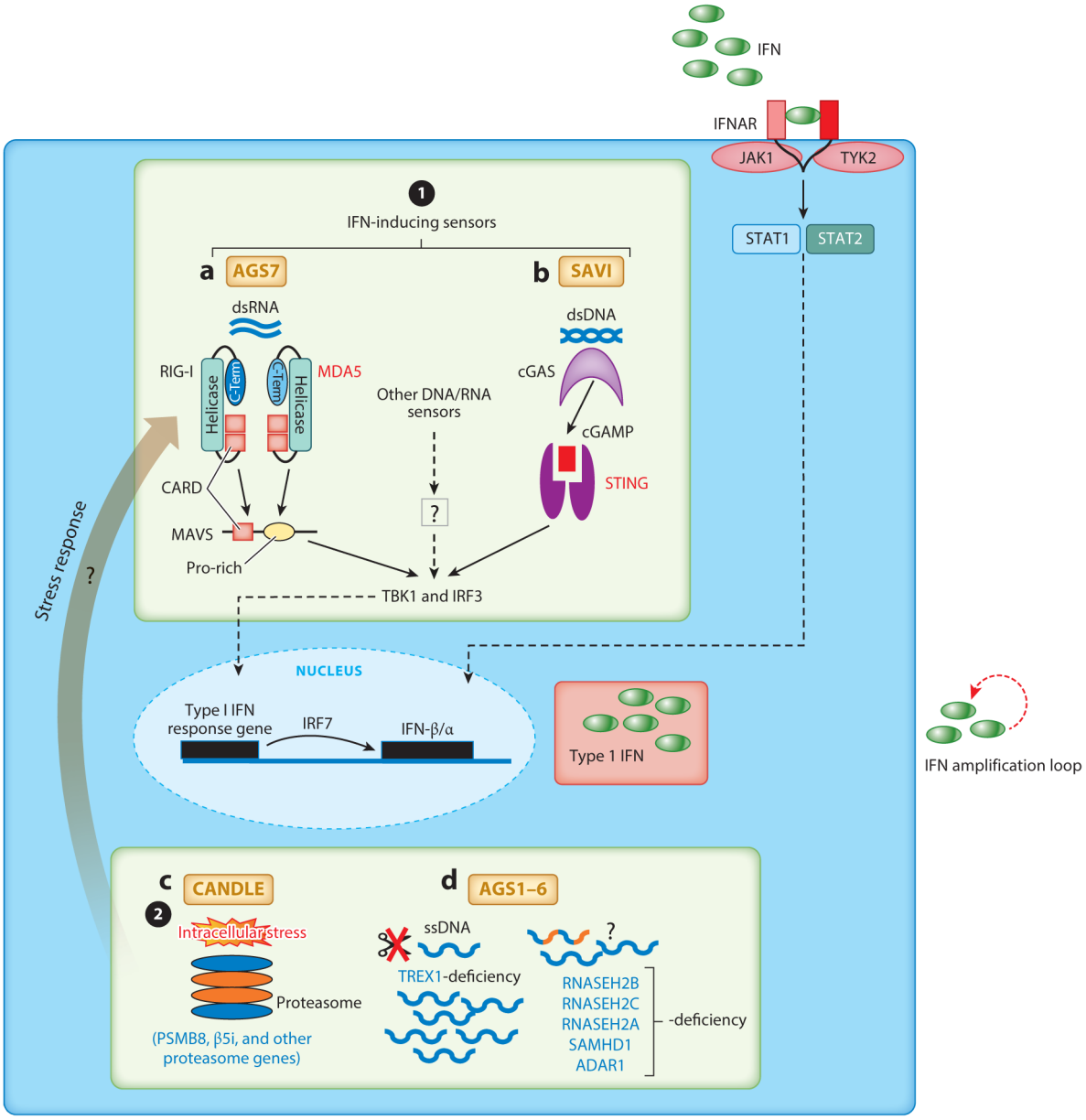

Figure 3.

Proposed mechanisms of activation of proinflammatory signaling pathways in IFN-mediated autoinflammatory diseases. Pathways of innate immune sensing of cytosolic nucleotide and stress lead to type I IFN production and a feed-forward loop of IFN signaling. The enzyme cGAS is a cytosolic sensor of dsDNA that, upon activation, generates a small-molecule second messenger, cGAMP, which binds and signals through the adaptor protein STING. Similarly, the RIG-I-like receptor sensors RIG-I and MDA5 are triggered by binding to dsRNA and signal through the adaptor protein MAVS. The common pathway downstream of STING and MAVS includes TBK1 and IRF3 phosphorylation/activation and IFN-β transcription. The disease-causing mutations cause a gain of function of an intracellular sensor (*red*) or a loss of function of a protein (*blue*), leading to generation of intracellular

stress. (*a*) Aicardi-Goutières syndrome 7 (AGS7). MDA5, encoded by *IFIH1*, is one of the dsRNA sensors. Gain-of-function mutation in MDA5 causes constitutive or enhanced IFN-β transcription, resulting in a clinical syndrome similar to that caused by TREX1 mutation. (*b*) STING-associated vasculopathy with onset in infancy (SAVI). Gain-of-function mutations in STING cause spontaneous or enhanced transcription of IFN-β, leading to the clinical syndrome SAVI. (*c*) PRAAS/CANDLE. Genetic mutations in proteasome subunits cause loss of function and cellular stress. Through a still unclear process, reduced proteasome function leads to type I IFN production and the inflammatory disease phenotype of CANDLE. Whether the stress response due to defective proteasome function that is triggered through the cytosolic nucleotide–sensing pathway or other sensors that are coupled to type I IFN production remains unknown. The transcription and secretion of type I IFN results in a cytokine amplification loop in the same cells or other bystander cells. *IRF7* is one of the IFN response genes, which further promote type I IFN transcription and amplification of the process. (*d*) Aicardi-Goutières syndrome 1–6 (AGS1–6). TREX1 loss-of-function mutations cause accumulation of ssDNA derived from an endogenous retroelement, resulting in STING-dependent type I IFN transcription (AGS1). Similarly, loss-of-function mutations in RNASEH2B, RNASEH2C, RNASEH2A, SAMHD1, and ADAR1 result in type I IFN transcription through still unknown signaling processes (AGS2–6). Numbers in black circles indicate disease caused by ❶ increased sensor/adaptor function or ❷ generation of cell stress. (Other abbreviations: AMP, adenosine monophosphate; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; cGAMP, cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase; GMP, guanosine monophosphate; MAVS, mitochondrial antiviral-signaling protein; PRAAS, proteasome-associated autoinflammatory syndromes; TREX1, three prime repair exonuclease 1.)

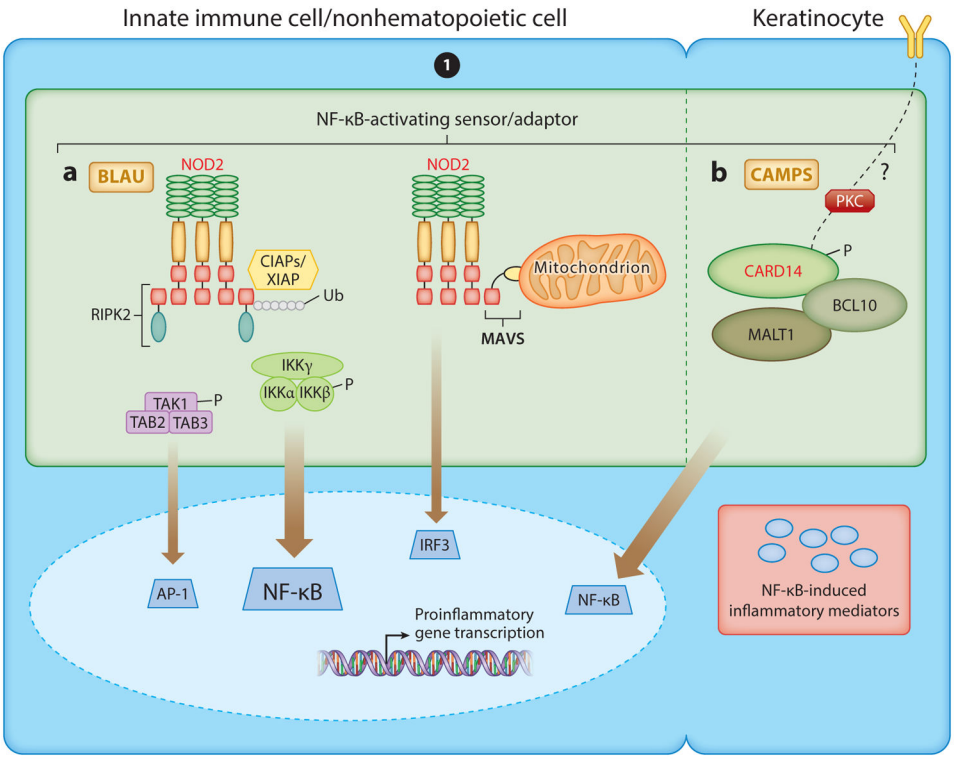

Figure 4.

Potential mechanisms of NF-κB-mediated diseases. (*a*) Pediatric granulomatous arthritis/Blau syndrome. Upon activation or when mutated, NOD2 oligomerizes and recruits the kinase RIPK2. IAP proteins then mediate the ubiquitylation of RIPK2, enabling it to initiate a signal pathway that results in transcriptional activation, most notably through the canonical NF-κB pathway. Oligomerized NOD2 can also associate with the mitochondrial adaptor protein MAVS to activate IFN production. (*b*) CARD14-mediated psoriasis (CAMPS). Expression of adaptor protein CARD14 is largely restricted to keratinocytes. Although it is unclear what signals drive CARD14 activation, activation of PKC results in CARD14 phosphorylation and activation. Upon activation or when mutated, as in patients with CAMPS, it associates with the BCL10/MALT1 complex, resulting in excessive NF-κB activation. NF-κB-associated gene transcription then drives neutrophil and lymphocyte chemotaxis and psoriasis-like skin inflammation. In general, the inflammatory mediators induced by excessive NF-κB activation vary by disease and cell type. Number in black circled indicates ❶ disease caused by increased sensor/adaptor function. (Other abbreviations: IAP, inhibitor of apoptosis; MAVS, mitochondrial antiviral-signaling protein; PKC, protein kinase C; XIAP, X-linked IAP.)

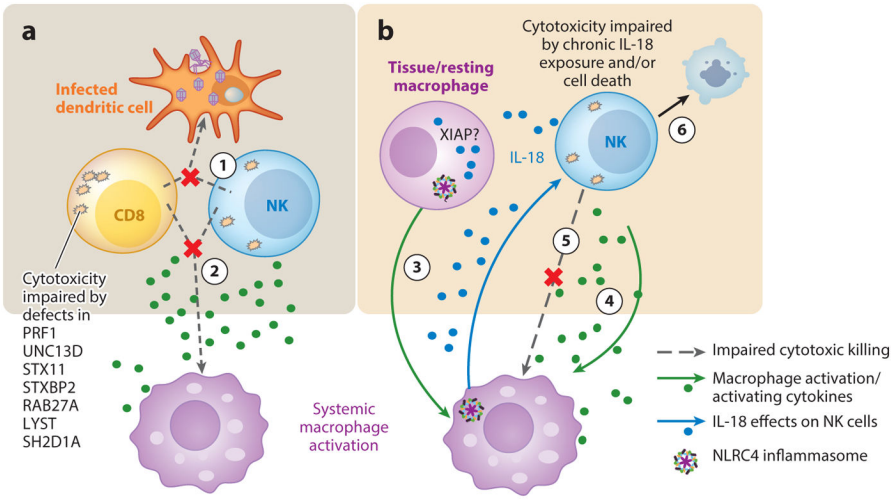

Figure 5.

Schematic of the mechanisms resulting in systemic macrophage activation. (*a*) In familial HLH, cytotoxic lymphocytes lack the ability to kill infected antigen-presenting cells. ① This results in failure to clear the infection and failure to terminate their own stimulation. With unrestrained stimulation, these lymphocytes produce extraordinary amounts of macrophage-stimulating cytokines, such as IFN-γ. They also lack the ability to kill activated macrophages. ② In MAS, intrinsic defects such as hyperactivity of the NLRC4 inflammasome could prime for macrophage activation directly, ③ but they could also cause constitutive IL-18 production that is enhanced upon macrophage activation. Upon infection or stress, lymphocytes (e.g., NK cells) chronically exposed to IL-18 could ④ prime for cytokine overproduction, ⑤ impair cytotoxicity, or ⑥ promote NK cell death. Systemic macrophage activation results in the release of a variety of potent inflammatory mediators (IL-1β, IL-6, TNF-α, IL-33, IL-1α, HMGB1, S100 proteins, etc.) that cause the shock-like symptoms associated with MAS and HLH. (Abbreviations: HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; XIAP, X-linked inhibitor of apoptosis.)

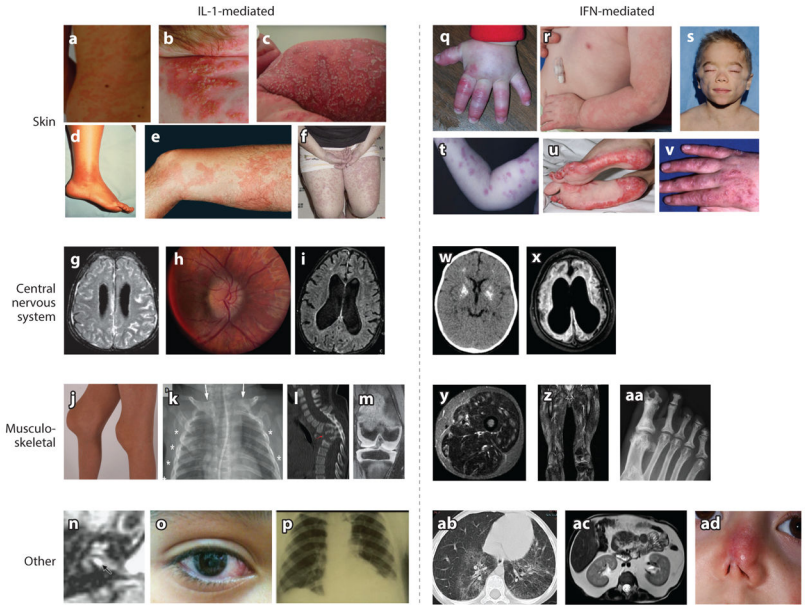

Figure 6.

Clinical manifestations of IL-1-mediated and IFN-mediated diseases. (*a*) Urticarial rash in NOMID. (*b*,*c*) Pustular rash in DIRA. (*d*) Erysipelas-like erythema in FMF. (*e*) Erythematous dermal macules (migratory during a disease flare) in a patient with TRAPS. (*f*) Purpuric rash in a patient with HIDS. (*g*) Leptomeningeal enhancement in NOMID. (*h*) Inflammation-induced chronic papilledema in NOMID. (*i*) Hydrocephalus and cerebral atrophy in NOMID. (*j*) Patella enlargement in NOMID. (*k*) Widening of multiple ribs (*asterisks*) and clavicles (*arrows*) in DIRA osteomyelitis. (*l*) Spine MRI showing destruction of vertebral bodies and severe kyphosis due to osteomyelitis in a patient with DIRA (*red arrow* indicates collapsed vertebra). (*m*) Metaphyseal bone overgrowth in NOMID. (*n*) Cochlear enhancement in NOMID. (*o*) Conjunctival erythema in a patient with TRAPS. (*p*) Pleural effusion in a patient with FMF. (*q*) Finger and hand swelling in CANDLE syndrome. (*r*) Erythematous-macular rash in AGS. (*s*) Characteristic lipodystrophy in a patient with CANDLE syndrome. (*t*) Erythematous-nodular rash in a patient with CANDLE. (*u*) Intense plantar erythema/vasculitis in a patient with SAVI. (*v*) Purpuric and papular rash in a patient with SAVI. (*w*) Basal ganglia calcifications in CANDLE syndrome. (*x*) Severe hydrocephalus and cerebral atrophy in AGS. (*y*) Patchy myositis in CANDLE syndrome. (*z*) Evidence of myositis and panniculitis in a bilateral thigh MRI of a CANDLE patient. (*aa*) Bone resorption in a patient with SAVI. (*ab*) Interstitial lung disease in a patient with SAVI. (*ac*) Intra-abdominal fat deposition in a patient with CANDLE syndrome. (*ad*) Telangiectasia, atrophy, and scarring of the skin with loss of deep tissue of the nose in a patient with SAVI. (Abbreviations: AGS, Aicardi-Goutières syndrome; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; DIRA, deficiency of the IL-1 receptor antagonist; FMF, familial Mediterranean fever; HIDS, hyper-IgD syndrome; IFN, interferon; NOMID, neonatal-onset multisystem inflammatory disease; SAVI, STING-associated vasculopathy with onset in infancy; TRAPS, TNF receptor–associated periodic syndrome.)

Table 1

Organization of autoinflammatory diseases by affected component of the immune response[1]

Component of immune response	Gene	Common aliases	Diseases	Functional impact of mutation	Cytokine dysregulation	Increased cytokine circuit
❶ **Increased intracellular sensor/pattern-recognition receptor or adaptor molecule function**						
NOD-like receptors	*NLRP3*	*NALP3, PYPAF1*	CAPS (NOMID, MWS, FCAS)	Constitutive NLRP3 inflammasome activation and IL-1β production and secretion	IL-1β	IL-1
	NLRC4	*CARD12*	NLRC4-MAS	Constitutive IL-1β and IL-18 production leading to macrophage activation	IL-1β/IL-18	IL-1/IL-18
	NOD2	*CARD15*	Blau syndrome, PGA	Constitutive RIP2K and NF-κB activation	TNF, IL-1, IL-6, and others	TNF, IL-1, others?
RIG-like receptor	*IFIH1*	*MDA5*	AGS7	Constitutive activation of dsRNA sensor linked to IFN production	IFN type I	IFN type I
TRIM-like intracellular PRR	*MEFV* or *MEFV*	Pyrin, marenostrin	FMF	Increased IL-1 activation in response to poorly defined cytoskeletal changes	IL-1β	IL-1, others?
Adaptor molecule	*TMEM173*	*STING*	SAVI	Constitutive STING activation leading to constitutive IFN-β transcription	IFN-β	IFN-β
Adaptor molecule	*CARD14*	*PSORS2*	CAMPS	Constitutive NF-κB activation	NF-κB	IL-17/IL-23
❷ **Accumulation of intracellular stressors that trigger PRR activation**						
Proteasome dysfunction with reduced clearance of ubiquitylated proteins	*PSMB8* and other genes	Proteasome subunit β5i and others	PRAAS/CANDLE	Proteasome dysfunction leading to accumulation of ubiquitylated proteins and IFN response gene induction	IFN type I	IFN type I
Protein-folding defect	*TNFRSF1A*	*TNFR1*	TRAPS	Trapping of mutant TNF receptor in Golgi apparatus leading to MAPK activation	IL-1, TNF, and others	IL-1, IL-6, and others
Inflammatory response to exposure of excess free fatty acids	*LPIN2*	*LPIN2*	Majeed	Decreased PA phosphatidase activity of lipin-2 leads to accumulation of PA	IL-1, others?	IL-1
Lack of prenylation leads to cytoskeletal changes and inflammasome activation	*MVK*	Mevalonate kinase	HIDS	Lack of prenylation leads to various protein modifications	IL-1β	

Component of immune response	Gene	Common aliases	Diseases	Functional impact of mutation	Cytokine dysregulation	Increased cytokine circuit
Accumulation of nucleic acids	*TREX1*	N/A	AGS1	Accumulation of nucleic acids	IFN type I	IFN type I, others?
Accumulation of nucleic acids	*RNASEH2A, B, C*	N/A	AGS2, 3, 4	Accumulation of nucleic acids	IFN type I	IFN type I, others?
Accumulation of nucleic acids	*SAMHD1*	N/A	AGS5	Accumulation of nucleic acids	IFN type I	IFN type I, others?
Accumulation of nucleic acids	*ADAR*	dsRNA-specific ADA	AGS6	Accumulation of nucleic acids	IFN type I	IFN type I, others?
Phosphatase	*ACP5*	TRAP/PPA5	SPENCDI	Lack of tartrate-resistant acid phosphatase 5 may lead to accumulation of osteopontin	IFN type I	IFN type I, unknown
Increased pyrin inflammasome assembly and cytoskeletal stress	*PSTPIP1*	*C2BP1*	PAPA	Cytoskeletal change stimulating inflammasome	IL-1β, TNF, and others	IL-1 and others
Adenosine deaminase deficiency causing immune hyperactivity and growth factor deficiency	*CERC1*	*ADA2*	DADA2	Lack of extracellular degradation of adenosine, lack of growth factor activity of ADA2, and stimulation of inflammatory macrophage response	TNF and others	TNF and others
Mitochondrial and cellular stress	*TRNT1*	*tRNA nucleotidyl transferase*	SIFD	Inability to generate functional tRNAs, abnormal stress response	Unknown	IL-1, IFN, unknown
Loss of negative regulator resulting in inability to attenuate proinflammatory cytokine responses						
Loss of cytokine receptor antagonism	*IL1RN*	N/A	DIRA	Lack of IL-1 receptor antagonist causing unopposed IL-1 signaling	Unblocked IL-1 signaling	IL-1α, IL-1β
Loss of cytokine receptor antagonism	*IL36RN*	N/A	DITRA	Lack of IL-36 receptor antagonist causing unopposed IL-36 signaling	Unblocked IL-36 signaling	IL-36α, β, γ
IL-10 receptor deficiency	*IL10RA*	N/A	EO-IBD	Lack of anti-inflammatory IL-10 signaling	No IL-10 signaling	Multiple cytokines and lack of regulatory T cells
IL-10 receptor deficiency	*IL10RB*	N/A	EO-IBD	Lack of anti-inflammatory IL-10 signaling	No IL-10 signaling	Multiple cytokines and lack of regulatory T cells
IL-10 deficiency	*IL10*	N/A	EO-IBD	Lack of anti-inflammatory IL-10 signaling	No IL-10 signaling	Multiple cytokines and lack of regulatory T cells
Loss of cytotoxic function	*LYST*	*CHS1*	Chediak-Higashi syndrome	Decreased cytotoxic granule formation	Increased macrophage activation and cytokine production	IL-18?, mixed

Component of immune response	Gene	Common aliases	Diseases	Functional impact of mutation	Cytokine dysregulation	Increased cytokine circuit
	AP3B1	*ADTB3A, HPS2*	Hermansky-Pudlak syndrome II	Cytotoxic granule formation impairment	Increased macrophage activation and cytokine production	IL-18?, mixed
	RAB27A	*RAB27, GS2*	Griscelli syndrome, type 2	Tethering impairment	Increased macrophage activation and cytokine production	IL-18?, mixed
	UNC13D	Munc 13–4	FHL3	Docking/priming impairment	Increased macrophage activation and cytokine production	IL-18?, mixed
	STX11	Syntaxin 11	FHL4	Membrane fusion impairment	Increased macrophage activation and cytokine production	IL-18?, mixed
	STXBP2	*UNC18B*, Munc 18-2	FHL5	Cytotoxic granule formation impairment	Increased macrophage activation and cytokine production	IL-18?, mixed
	PRF1	Perforin 1	FHL2	No perforin production	Increased macrophage activation and cytokine production	IL-18?, mixed
	SH2D1A	*SAP*	XLP1	Adaptor protein regulating intracellular signaling	Increased macrophage activation and cytokine production	IL-18?, mixed
❶ Increased signaling through receptors controlling innate immune cell function						
Phospholipase	*PLCG2*	N/A	PLAID/APLAID	Increased phospholipid activity leading to increased PIP2 conversion to IP3 and DAG and decreased B cell and NK cell receptor signaling	IL-1, others	Unknown
Tyrosine kinases	*LYN* or *LYN*	N/A	LAID	Increased or decreased Lyn signaling at B cell receptors and myeloid cells	Unknown	Unknown
Adaptor molecules	*SH3BP2*	N/A	Cherubism	Increased signaling through multiple pathways, enhanced NFATc1 activation, osteoclast differentiation	TNFα, others	Unknown
❺ Insufficient data to classify						
Apoptosis/signaling regulator	*XIAP*	*BIRC4*	XLP2	Increased apoptosis, defective NOD2 signaling	IL-18, other	IL-18, other
Adaptor molecule (component of AP1)	*AP1S3*	AP1 complex subunit σ-3	Pustular psoriasis	Decreased endosomal localization of TLR3 leads to inflammatory response; may be keratinocyte restricted	IL-1?	IL-1, unknown

Abbreviations: ADA, adenosine deaminase; APLAID, autoinflammation and PLAID; AGS, Aicardi-Goutières syndrome; AP1, adaptor protein complex 1; CAMPS, CARD14-mediated psoriasis; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPS, cryopyrin-associated periodic syndromes; DADA2, deficiency of adenosine deaminase 2; DAG, diacylglycerol; DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of IL-36 receptor antagonist; EO-IBD, early-onset inflammatory bowel disease; FCAS, familial cold autoinflammatory syndrome; FHL, familial hemophagocytic lymphohistiocytosis; FMF, familial Mediterranean fever; HIDS, hyper-IgD syndrome; LAID, LYN-associated autoinflammatory disease; MWS, Muckle-Wells syndrome; NISBD, neonatal inflammatory skin and bowel disease; NOMID, neonatal-onset multisystem inflammatory disease; PA, phosphatidate; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; PGA, pediatric granulomatous arthritis; PLAID, PLCγ2-associated antibody deficiency and immune dysregulation; PRAAS, proteasome-associated autoinflammatory syndromes; PRR, pattern-recognition receptor; SAVI, STING-associated vasculopathy with onset in infancy; SPENCDI, spondyloenchondrodysplasia with immune dysregulation; TRAPS, TNF receptor–associated periodic syndrome; TRIM, tripartite motif.

[1]Each genetically defined autoinflammatory disease (*yellow*) can be classified based on the predominant proinflammatory mediator that is upregulated, where known, and the component of the innate immune response that is affected by the disease-causing mutations (*green*).

Table 2

Currently approved anticytokine drugs

Target	Generic	Trade name
IL-1	Anakinra	Kineret
	Rilonacept	Arcalyst
	Canakinumab	Ilaris
TNF	Etanercept	Enbrel
	Infliximab	Remicade
	Adalimumab	Humira
	Golimumab	Simponi
	Certolizumab	Cimzia
IL-6	Tocilizumab	Actemra
	Tofacitinib	Xelians
IFN	Tofacitinib	Xelians
	Ruxolitinib	Jakafi
	Baricitinib	In clinical trials[1]
IL-17/IL-23	Ustekinumab	Stellara

[1] Not yet approved by the US Food and Drug Administration.

Table 3

Genetic and clinical features of autoinflammatory diseases[1]

			OMIM No.	Inheritance	Gene (chromosome region)	Protein (UniProtKB)	Clinical and laboratory findings										
							Systemic inflammation	Mucocutaneous	Musculoskeletal	Ocular	Pulmonary	GI	Liver	Spleen	Lymph nodes	CNS	Other/ specific features
IL-1 mediated autoinflammatory diseases (Group 1)																	
Increased intracellular sensor/PRR function	**CAPS**	**NOMID**	607115	AD	*NLRP3* (1q44)	NALP3	Fever, ↑acute phase reactants	Neutrophilic urticaria	Epiphyseal and patella enlargement, periostitis, chronic arthropathy	Conjunctivitis, uveitis, papilledema, progressive amaurosis	Uncommon	Abdominal pain	Enlarged during exacerbations	Enlarged during exacerbations	Occasional lymphadenopathy	Delayed mental development, chronic aseptic meningitis, headache	Sensorineural hearing loss
		MWS	191900	AD	*NLRP3* (1q44)	NALP3	Fever, ↑acute phase reactants	Neutrophilic urticaria	Myalgia, arthralgia, oligoarticular arthritis	Conjunctivitis, episcleritis, optic disk edema	Uncommon	Abdominal pain	Uncommon	Uncommon	Occasional lymphadenopathy	Headache	Sensorineural hearing loss
		FCAS	120100	AD	*NLRP3* (1q44)	NALP3	Fever, ↑acute phase reactants	Neutrophilic urticaria	Myalgia, arthralgia	Conjunctivitis	Uncommon	Nausea	Uncommon	Uncommon	Uncommon	Headache	Sensorineural hearing loss
	FMF		249100	AR/AD	*MEFV* (16p13.3)	MEFV/pyrin	Fever, ↑acute phase reactants	Erysipelas-like erythema	Large-joint episodic arthritis	Uncommon	Pleuritis	Aseptic peritonitis, diarrhea, constipation	Uncommon	Uncommon	Uncommon	Uncommon	Pericarditis, epididymitis
	NLRC4-MAS[1]		NA	AD	*NLRC4* (2p22.3)	NLRC4	Fever, ↑acute phase reactants	Rare dermographism/urticarial rash	Arthralgia	Uncommon	Uncommon	Early-onset nonspecific enterocolitis	Hepatomegaly, hepatitis	Splenomegaly	Occasional lymphadenopathy	Uncommon	Coagulopathy, pancytopenia, ↑ferritin, ↑triglycerides
Generation of intracellular stress	**HIDS/MKD**		260920	AR	*MVK* (12q24.11)	MK	Fever, ↑acute phase reactants	Maculopapular or purpuric exanthema	Arthralgia, nonerosive acute polyarthritis	Uncommon	Uncommon	Abdominal pain, vomiting, diarrhea	Hepatomegaly	Splenomegaly	Painful cervical adenopathy	Uncommon	Recurrent and/or severe infections in up to 30% of patients
	TRAPS		142680	AD	*TNFRSF1A* (12p13.31)	TNFR1A	Fever, ↑acute phase reactants	Erysipelas-like erythema	Migratory myalgia, arthralgia, nonerosive arthritis	Periorbital edema, conjunctivitis	Pleuritis	Abdominal pain, peritonitis, diarrhea, constipation	Uncommon	Uncommon	Occasional lymphadenopathy	Headache	Pericarditis, prolonged fever episodes
	Majeed syndrome		609628	AR	*LPIN2* (18p11.31)	Lipin-2	↑acute phase reactants	Pustular dermatitis	Recurrent multifocal aseptic osteomyelitis	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Dyserythropoietic anemia
Loss of a negative regulator	**DIRA**		612852	AR	*IL1RN* (2q13)	IL1-RA	Occasional fever, ↑acute phase reactants	Pustular dermatitis	Recurrent multifocal aseptic osteomyelitis	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	CNS vasculitis (rare)	Deformity of clavicles and ribs, absence of odontoid process, venous thrombosis
IFN-mediated autoinflammatory diseases (Group 2)																	
Increased intracellular sensor/adaptor function	**SAVI**		615934	AD	*TMEM173* (5q31.2)	STING	Fever, ↑acute phase reactants	Erythematous-purpuric lesions, ischemic ulcerative skin disease, necrosis of extremities, loss of tissue	Arthralgia, myositis	Uncommon	Interstitial lung disease, lung fibrosis, emphysema, paratracheal adenopathy	Uncommon	Uncommon	Uncommon	Occasional lymphadenopathy	Basal ganglia calcifications (rare)	Typical involvement of cheeks, earlobes, and tip of nose; flares triggered by cold; nasal septum perforation; anemia; lymphopenia; hypergamm aglobulinemia
	AGS7		615846	AD	*IFIH1* (2q24.2)	IFIH1/MDA5	Occasional fever	Chilblain lesions, livedo reticularis	Arthritis (rare)	Normal vision to cortical blindness, glaucoma	Uncommon	Uncommon	Hepatomegaly (rare)	Splenomegaly (rare)	Uncommon	Basal ganglia calcifications, white matter abnormalities and cerebral atrophy, bilateral involvement of deep white matter; poor head control, trunk hypotonia, pyramidal and extrapyramidal signs, tetraplegia, persistence of archaic reflexes, dystonic movements	Variable severity of CNS disease, thrombocytopenia
Generation of intracellular stress	**AGS1**		225750	AR/AD	*TREX1* (3p21.31)	TREX1	Occasional fever	Chilblain lesions, livedo reticularis	Uncommon	Normal vision to cortical blindness, glaucoma	Uncommon	Uncommon	Hepatomegaly (rare)	Splenomegaly (rare)	Uncommon		Thrombocytopenia, neonatal onset, higher mortality
	AGS2		610181	AR	*RNASEH2B* (13q14.3)	RNH2B	Occasional fever	Chilblain lesions, livedo reticularis	Uncommon	Normal vision to cortical blindness, glaucoma	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon		Later onset, lower morbidity and mortality
	AGS3		610329	AR	*RNASEH2C* (11q13.1)	RNH2C	Occasional fever	Chilblain lesions, livedo reticularis	Uncommon	Normal vision to cortical blindness, glaucoma	Uncommon	Uncommon	Hepatomegaly (rare)	Splenomegaly (rare)	Uncommon		Thrombocytopenia, neonatal onset, higher mortality
	AGS4		610333	AR	*RNASEH2A* (19p13.2)	RNH2A	Occasional fever	Chilblain lesions, livedo reticularis	Uncommon	Normal vision to cortical blindness, glaucoma	Uncommon	Uncommon	Hepatomegaly (rare)	Splenomegaly (rare)	Uncommon		Thrombocytopenia, neonatal onset; higher mortality
	AGS5		612952	AR	*SAMHD1* (20q11.23)	SAMH1	Occasional fever	Chilblain lesions, livedo reticularis	Uncommon	Normal vision to cortical blindness, glaucoma	Uncommon	Uncommon	Hepatomegaly (rare)	Splenomegaly (rare)	Uncommon		Later onset, lower morbidity and mortality; inflammatory intracranial large-vessel phenotype observed
	AGS6		615010	AR/AD	*ADAR* (1q21.3)	DSRAD	Occasional fever	Chilblain lesions, livedo reticularis	Uncommon	Normal vision to cortical blindness, glaucoma	Uncommon	Uncommon	Hepatomegaly (rare)	Splenomegaly (rare)	Uncommon		Later onset, lower morbidity and mortality
	PRAAS/CANDLE		256040	AR	*PSMB8*, others (6p21.32)	PSB8	Fever, ↑acute phase reactants	Nodular exanthema, panniculitis, lipodystrophy	Myositis, arthralgia, arthritis	Eyelids edema and erythema	Uncommon	Increased intra-abdominal fat	Hepatomegaly	Splenomegaly	Uncommon	Basal ganglia calcifications	Lipodystrophy, dyslipidemia, growth delay, pancreatic abnormalities, microcytic anemia, cytopenias
	SPENCDI		607944	AR	*ACP5* (19p13.2)	TRAP/PPA5	Can present with fever	Variable: can have Raynaud's	Inflammatory myopathy reported	Uncommon	Uncommon	Uncommon	Uncommon	Related to underlying autoimmunity	Related to underlying autoimmunity	Spasticity, developmental delay, cerebral calcifications	Autoimmunity
Autoinflammatory diseases caused by increased NF-κB signaling (Group 3)																	
Increased intracellular sensor/adaptor function	**PGA**		186580	AD	*NOD2/CARD 15* (16q12.1)	NOD2	Rare fever, ↑ acute-phase reactants	Ichthyosis-like exanthema	Polyarthritis, hypertrophic tenosynovitis	Chronic uveitis, cataract, glaucoma, amaurosis	Interstitial lung disease (rare)	Uncommon	Hepatomegaly	Splenomegaly (rare)	Occasional lymphadenopathy (rare)	Transient neuropathy	Parotitis, pericarditis, arterial hypertension
	CAMPS		602723	AD	*CARD14* (17q25.3)	CAR14	Fever can present with superinfections of the skin	Plaque or pustular psoriasis	Arthritis	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Rare systemic manifestations

			OMIM No.	Inheritance	Gene (chromosome region)	Protein (UniProtKB)	Clinical and laboratory findings										
							Systemic inflammation	Mucocutaneous	Musculoskeletal	Ocular	Pulmonary	GI	Liver	Spleen	Lymph nodes	CNS	Other/ specific features
Autoinflammatory diseases caused by persistent macrophage activation (Group 4)																	
Increased macrophage activation and IL-18 overproduction	**NLRC4-MAS**		NA	AD	*NLRC4* (2q22.3)	NLRC4	Fever, ↑acute phase reactants	Rare dermographism/urticarial rash	Arthralgia	Uncommon	Uncommon	Early-onset nonspecific enterocolitis	Hepatomegaly, hepatitis	Splenomegaly	Occasional lymphadenopathy	Uncommon	Coagulopathy, pancytopenia, ↑ ferritin, ↑ triglycerides
	XLP2-MAS		300635	X-linked	*XIAP* (Xq25)	XIAP	Fever, ↑acute phase reactants	Uncommon	Arthralgia	Uncommon	Uncommon	Risk for Crohn disease	Hepatomegaly, hepatitis	Splenomegaly	Frequent lymphadenopathy	Uncommon	Coagulopathy, pancytopenia, ↑ ferritin, ↑ triglycerides
Loss of the negative regulatory effects of cytotoxic killing	**Without albinism**	**FHL2**	603553	AR	*PRF1* (10q22.1)	PERF	Fever, ↑acute phase reactants	Uncommon	Uncommon	Uncommon	ARDS	Uncommon	Hepatomegaly, hepatitis	Splenomegaly	Frequent lymphadenopathy	Encephalitis, seizures, periventricular enhancement	Coagulopathy, pancytopenia, ↑ ferritin, ↑ triglycerides
		FHL3	608898	AR	*UNC13D* (17q25.1)	UN13D/Mun c13-4	Fever, ↑acute phase reactants	Uncommon	Uncommon	Uncommon	ARDS	Uncommon	Hepatomegaly, hepatitis	Splenomegaly	Frequent lymphadenopathy	Encephalitis, seizures, periventricular enhancement	Coagulopathy, pancytopenia, ↑ ferritin, ↑ triglycerides
		FHL4	603552	AR	*STX11* (6q24.2)	STX11	Fever, ↑acute phase reactants	Uncommon	Uncommon	Uncommon	ARDS	Uncommon		Splenomegaly	Frequent lymphadenopathy	Encephalitis, seizures, periventricular enhancement	Coagulopathy, pancytopenia, ↑ ferritin, ↑ triglycerides
		FHL5	613101	AR	*STXBP2* (19p13.2)	STXB2/Munc 18-2	Fever, ↑acute phase reactants	Uncommon	Uncommon	Uncommon	ARDS	Uncommon	Hepatomegaly, hepatitis	Splenomegaly	Frequent lymphadenopathy	Encephalitis, seizures, periventricular enhancement	Coagulopathy, pancytopenia, ↑ ferritin, ↑ triglycerides
	With albinism	**CHS**	214500	AR	*LYST* (1q42.3)	LYST	Variable, fever due to infections	Skin and hair hypopigmentation photosensitivity	Uncommon	Iris hypopigmentation; retinal hypopigmentation, nystagmus, vision impairment	Uncommon	Uncommon	Hepatomegaly, hepatitis	Splenomegaly	Frequent lymphadenopathy	Sensory and motor neuropathies, ataxia, tremor, areflexia, low cognitive abilities	Coagulopathy, pancytopenia, ↑ ferritin, ↑ triglycerides
		GS2	607624	AR	*RAB27A* (15q21.3)	RB27A	Variable, fever due to infections	Skin and hair hypopigmentation photosensitivity	Uncommon	Uncommon	Uncommon	Uncommon	Hepatomegaly, hepatitis	Splenomegaly	Frequent lymphadenopathy	Uncommon	Coagulopathy, pancytopenia, ↑ ferritin, ↑ triglycerides
		HPS2	608233	AR	*AP3B1* (5q14.1)	AP3B1	Variable, fever due to infections	Skin and hair hypopigmentation photosensitivity	Uncommon	Horizontal nystagmus, ocular hypopigmentation and vision impairment	Pulmonary fibrosis	Uncommon	Hepatomegaly, hepatitis	Splenomegaly	Frequent lymphadenopathy	Uncommon	Coagulopathy, pancytopenia, ↑ ferritin, ↑ triglycerides
Autoinflammatory diseases with yet-uncharacterized pivotal proinflammatory mediators (Group 5)																	
Generation of intracellular stress	**PAPA**		604416	AD	*PSTPIP1* (15q24.3)	PPIP1	Occasional fever, ↑acute phase reactants	Pyoderma gangrenosum, severe acne	Deforming aseptic pyogenic arthritis	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Thrombocytopenia and neutropenia (rare)
	DADA2		615688	AR	*CECR1* (22q11.1)	CECR1/ADAT	Fever, ↑acute phase reactants	Livedo reticularis, purpuric lesions, and ischemic and necrotic skin disease	Myalgia, arthralgia	Variable ophthalmologic involvement	Uncommon	Abdominal pain, diarrhea, ascites (rare)	Hepatomegaly	Splenomegaly	Occasional lymphadenopathy	Ischemic or hemorrhagic stroke	Testicular pain, portal hypertension, lymphopenia, low IgM, recurrent infections
	SIFD		616084	AR	*TRNT1* (3p26.2)	TRNT1	Periodic fevers	Uncommon	Uncommon	Uncommon	Sinopulmonary infections	Vomiting & diarrhea with fever episodes	Uncommon	Uncommon	Uncommon	Developmental delay, seizures	Severe sideroblastic anemia, B lymphopenia, CVID
Loss of negative regulation	**DITRA**		614204	AR	*IL36RN* (2q13)	I36RA	Fever, fatigue, and ↑acute phase reactants	Generalized pustular psoriasis	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Fever of elevated temperature, secondary skin infections
	EO-IBD28		613148	AR	*IL10RA* (11q23.3)	110R1/IL10RA	Fever, ↑acute phase reactants	Folliculitis	Arthritis	Uncommon	Uncommon	Severe colitis: bloody diarrhea, abscesses, perianal fistula, oral aphthous lesions	Uncommon	Uncommon	Occasional lymphadenopathy	Uncommon	Recurrent infections
	EO-IBD25		612567	AR	*IL10RB* (21q22.11)	110R2/IL10RB	Fever, ↑acute phase reactants	Folliculitis	Arthritis	Uncommon	Uncommon	Severe colitis: bloody diarrhea, abscesses, perianal fistula, oral aphthous lesions	Uncommon	Uncommon	Occasional lymphadenopathy	Uncommon	Recurrent infections
	EO-IBD with IL-10 deficiency		NA	AR	*IL10* (1q32.1)	IL10	Fever, ↑acute phase reactants	Folliculitis	Arthritis	Uncommon	Uncommon	Severe colitis: bloody diarrhea, abscesses, perianal fistula, oral aphthous lesions	Uncommon	Uncommon	Occasional lymphadenopathy	Uncommon	Recurrent infections
Increased immune cell receptor signaling	**PLAID**		614468	AD	*PLCG2* (16q23.3)	PLCG2	Variable, fever due to infections	Cold-induced urticaria and/or granulomatous skin rash	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Positive autoantibodies and autoimmune manifestations recurrent and/or severe infections, allergic disease
	APLAID		614878	AD	*PLCG2* (16q23.3)	PLCG2	Variable, fever due to infections	Erythematous plaques and vesicopustular lesions, cellulitis	Arthralgia	Corneal erosions, ulcerations, intraocular hypertension, cataracts	Interstitial lung disease	Abdominal pain and bloody diarrhea	Uncommon	Uncommon	Uncommon	Uncommon	Mild immunodeficiency
	LAID		NA	AD	*LYN* (8q12.1)	LYN	Fever, ↑acute phase reactants	Erythematous nodular and purpuric rash	Arthralgia	Periorbital erythema	Uncommon	Uncommon	Vanishing bile duct disease, ↑ LFTs	Massive splenomegaly	Occasional lymphadenopathy	Uncommon	Anemia, marked leukocytosis, autoantibodies
	Cherubism		118400	AD	*SH3BP2* (4p16.3)	SH3BP2	Uncommon	Edema related to underlying bone inflammation	Lytic jawbone lesions filled with expansive inflammatory tissue	Uncommon	Uncommon	Uncommon	Uncommon	Uncommon	Cervical lymphadenopathy	Uncommon	Spontaneous improvement with puberty

Abbreviations: AD, autosomal dominant; AGS, Aicardi-Goutières syndrome; APLAID, autoinflammation and PLAID; AR, autosomal recessive; ARDS, acute respiratory distress syndrome; CAMPS, CARD14-mediated psoriasis; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPS, cryopyrin-associated periodic syndrome; CHS, Chediak-Higashi syndrome; CNS, central nervous system; DADA2, deficiency of adenosine deaminase 2; DIRA, deficiency of interleukin 1 receptor antagonist; DITRA, deficiency of IL-36 receptor antagonist; EO-IBD, early-onset irritable bowel disease; FCAS, familial cold autoinflammatory syndrome; FHL, familial hemophagocytic lymphohistiocytosis; FMF, familial Mediterranean fever; GI, gastrointestinal; GS, Griscelli syndrome; HIDS, hyper-IgD syndrome; HPS2, Hermansky-Pudlak syndrome II; IBD, inflammatory bowel disease; LAID, LYN-associated autoinflammatory disease; LFT, liver function tests; MAS, macrophage activation syndrome; MKD, mevalonate kinase deficiency; MWS, Muckle-Wells syndrome; NA, not applicable; NOMID, neonatal-onset multisystem inflammatory disease; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; PGA, pediatric granulomatous arthritis; PLAID, PLCγ2-associated antibody deficiency and immune dysregulation; PRR, pattern-recognition receptor; SAVI, STING-associated vasculopathy with onset in infancy; STING, stimulator of IFN genes; SPENCDI, spondyloenchondrodysplasia with immune dysregulation; TRAPS, TNF receptor–associated periodic syndrome; XLP, X-linked lymphoproliferative disease.

[1] Each genetically defined autoinflammatory disease (*yellow*) can be classified based on the predominant proinflammatory mediator that is upregulated, where known, (*red*) and the component of the innate immune response that is affected by the disease-causing mutations (*green*).

[2] Also discussed in Group 4.

Table 4

Mouse models of human genetic autoinflammatory diseases

Human disease	Gene mutated	Animal model	Mouse phenotype	Differences with human disease manifestations	References
CAPS	*NLRP3*	*Nlrp3* knock-in mice with CAPS-associated mutants, by Hoffman (A350V and L351P)	Neonatal or perinatal onset, systemic inflammation, poor growth	Not recapitulated in mice: bony lesions, CNS inflammation, and hearing loss; inflammation depends on both IL-1 and IL-18 in mice; mouse with skin abscesses; patients with neutrophilic urticaria	230, 231
		Nlrp3 knock-in mice with MWS-associated mutant, by Strober (R258W)	Poor growth, systemic inflammation, Th17-dominant skin inflammation		232
FMF	*MEFV*	*Mefv* knock-in mice with mutant human B30.2 domain	Spontaneous bone marrow–dependent inflammation similar to but more severe than in humans	Not recapitulated in mice: serositis, pleuritis, or pericarditis	233
HIDS	*MVK*	*Mvk*-deficient mice heterozygote	Increased IgD level, hepatomegaly, splenomegaly, and changes in thermoregulation		234
		Mvk-deficient mice homozygote	Embryonic lethal		
TRAPS	*TNFRSF1A*	*Tnfrsf1a* knock-in mice with human T50M and C33Y mutations	Resistance to lethal dose of LPS	Not recapitulated in mice: intermittent fevers, serositis, arthritis	235
DIRA	*IL1RN*	*Il1rn*-deficient mice	Develop chronic inflammatory polyarthropathy on Balb/c background but not on C57BL/6 background	Not recapitulated in mice: osteomyelitis and pustular skin disease, no or minimal arthritis in patients	236
			Develop arterial inflammation on 129/MF1 background		237
PAPA	*PSTPIP1*	*Pstpip1* A230T transgenic expression in hemopoietic cells in mice	Healthy	Not recapitulated in mice: severe pyoderma gangrenosum skin lesions/ impaired healing and pyogenic arthritis in humans	194
		Pstpip1 A230T transgenic ubiquitous expression	Partial embryonic lethality, growth retardation, increased circulating proinflammatory cytokine level, but no sign of arthritis		
AGS	*TREX1*	*Trex1*-deficient mice	Mice do not have CNS disease; instead, they develop inflammatory myocarditis and kidney inflammation	Not recapitulated in mice: white matter disease; mouse develops myocarditis that is not seen in patients	114
CANDLE	*PSMB8*	*Psmb8*-deficient mice	Mice have no disease, just reduced expression of MHC-I and moderate defect in antigen presentation	Not recapitulated in mice; systemic inflammation, lipodystrophy, skin inflammation	238
DITRA	*IL36RN*	*Il36rn*-deficient mice	Healthy, but can exacerbate inflammation caused by IL-36A transgenic expression in keratinocytes in mice (skin acanthosis, hyperkeratosis)	Not recapitulated in mice; generalized pustular psoriasis	201
XLP1	*SH2D1A*	*Sh2d1a*-deficient mice	Increased number of CD8 and CD4 T cells in response to LCMV infection		239–241
XLP2	*XIAP*	*Xiap*-deficient mice	Largely healthy, with mammary gland development abnormality	Not recapitulated in mice; hemophagocytic lymphohistiocytosis,	242, 243

Human disease	Gene mutated	Animal model	Mouse phenotype	Differences with human disease manifestations	References
				splenomegaly, hypogammaglobulinemia, and hemorrhagic colitis	
				splenomegaly, hypogammaglobulinemia, and hemorrhagic colitis	
				splenomegaly, hypogammaglobulinemia, and hemorrhagic colitis	
EO-IBD	*IL10RA*, *IL10RB*, *IL10*	*Il10*-deficient mice	Growth retardation, anemia, and chronic enterocolitis		206
		Il10ra-deficient mice (in intestinal resident macrophage)	Colitis		210
		Il10-deficient mice (in intestinal resident macrophage)	Healthy		
LAID	*LYN*	*Lyn* knock-in mice with Y508F mutation	Autoantibody, lethal glomerulonephritis	No glomerulonephritis in patient	244, 245
Cherubism	*SH3BP2*	*SH3BP2* knock-in mice with P416R mutation	Cherubism-like lesions throughout skeleton and in spleen/liver	Human disease not ameliorated by TNF-α inhibition, no jaw tropism in mice	214, 215

Abbreviations: AGS, Aicardi-Goutières syndrome; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; CAPS, cryopyrin-associated periodic syndrome; DIRA, deficiency of IL-1 receptor antagonist; DITRA, deficiency of IL-36 receptor antagonist; EO-IBD, early-onset inflammatory bowel disease; FMF, familial Mediterranean fever; HIDS, hyper-IgD syndrome; LAID, LYN-associated autoinflammatory disease; LCMV, lymphocytic choriomeningitis virus; LPS, lipopolysaccharide; MWS, Muckle-Wells syndrome; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; TRAPS, TNF receptor–associated periodic syndrome; XLP, X-linked lymphoproliferative disease.