Published in final edited form as:

Rheum Dis Clin North Am. 2013 November ; 39(4): 701–734. doi:10.1016/j.rdc.2013.08.001.

MONOGENIC AUTOINFLAMMATORY DISEASES: DISORDERS OF AMPLIFIED DANGER SENSING AND CYTOKINE DYSREGULATION

Gina A. Montealegre Sanchez*, Adriana Almeida De Jesus*, and Raphaela Goldbach-Mansky*

*Translational Autoinflammatory Diseases Section, National Institute of Arthritis, Musculoskeletal and Skin diseases (NIAMS), National Institutes of Health (NIH), Bethesda, MD, USA

Keywords

Autoinflammatory diseases; Cryopyrin associated periodic syndromes (CAPS); Neonatal-onset multisystem inflammatory disease (NOMID); Proteasome associated autoinflammatory syndrome (PRAAS); Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE); Deficiency of the IL-1 receptor antagonist (DIRA); Inflammasome; Hereditary fever syndromes; Intracellular pattern recognition receptors (PRR)

“OLD” and EMERGING “NEW” CONCEPTS

Monogenic autoinflammatory diseases can be defined as a group of immune dysregulatory conditions marked by excessive inflammation that is predominantly mediated by increased responses to known and unknown triggers by cells and molecules of the innate immune system (1). These illnesses typically present in childhood and can initially mimic infections or hematologic malignancies, but the inflammatory lesions are aseptic and non malignant. The discovery of single-gene defects in the IL-1 pathway that cause the spectrum of the cryopyrinopathies or cryopyrin associated periodic syndromes (CAPS) and the rare condition deficiency of the IL-1 receptor antagonist (DIRA), pointed to the pivotal role of IL-1 and provided us with deeper insights into the molecular bases that drives the inflammatory phenotypes. These findings translated into therapeutic approaches using IL-1 blocking agents, which have become standard of care for the cryopyrinopathies and DIRA, and their use has been expanded to other monogenic disorders, the periodic fever syndromes, and to disorders without yet identified genetic causes, including aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome, systemic-onset juvenile idiopathic arthritis (SJIA), adult-onset Still’s disease (AOSD), and Behçet’s disease.

The exciting journey of deciphering inflammatory phenotypes started with the discovery of the genetic cause of familial Mediterranean fever (FMF), the most prevalent autoinflammatory disease worldwide, in 1997 (2, 3), followed by two other periodic fever syndromes, TNF-receptor associated periodic syndrome (TRAPS) (4) and hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) (5–7). These three syndromes share the episodic nature of fever and periods of remission and can be grouped as “classic” hereditary periodic fever syndromes. The cryopyrinopathies, comprising familial

cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous and articular (CINCA) syndrome; and DIRA are caused by single-gene mutations in loci regulating IL-1 processing, secretion, and signaling. Interestingly, therapeutic interventions blocking IL-1 in an autoinflammatory bone disease with clinical similarities to DIRA, namely Majeed syndrome, confirmed a prominent role for IL-1 in this condition as well.

A group of recently described autoinflammatory syndromes that are unresponsive to IL-1 blocking therapy include the proteasome-associated autoinflammatory syndromes (PRAAS) or chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), an autoinflammatory condition presenting with lipodystrophy and myositis; deficiency of IL-36 receptor antagonist (DITRA) and CARD14 mediated psoriasis (CAMPS), two conditions presenting with pustular skin disease; and early-onset inflammatory bowel disease (IBD). Studies of the disease pathogenesis are pointing to a role of cytokine dysregulation in pathways not involving IL-1. The complex clinical and laboratory features, that in some novel conditions can overlap with those seen in patients with autoimmune diseases, illustrate that innate and adaptive immune responses can be dysregulated in a patient and need to be viewed as a continuum. Mutant protein in CAMPS and DITRA is mainly expressed in keratinocytes, which points to a role of primary keratinocyte dysregulation in pustular, neutrophilic dermatitis, and provides us with clues to tissue specific factors that lead to organ specific disease manifestations.

Summary of Implications on our Understanding of Disease Pathogenesis

1. Novel conditions add evidence to the hypothesis that autoinflammatory syndromes are caused by “exaggerated/increased” sensing of extracellular and intracellular “danger”

The genetic defect in a number of autoinflammatory disorders is in components of cytosolic pattern recognition receptors (PRRs) (NLRP3, NOD2, Pyrin), affecting their function, or in molecules involved in their mediator pathways (8) (Fig.2, Table 2).

The innate immune response evolved to protect organisms from exogenous and endogenous dangers that threaten harm/destroy the organism. The ultimate purpose of the immune response is to remove or sequester the source of the disturbance, and to restore functionality and tissue homeostasis (9). To do that the innate immune system utilizes a finite number of germline encoded PRRs that recognize exogenous, non-self and endogenous, self-molecules. The first PRRs identified and characterized were the toll-like receptors (TLRs) and later others including RIG-I-like helicase receptors (RLR) and the C-type lectin receptors (CLRs), which mainly sense exogenous pathogen associated molecular patterns (PAMPs) (10). More recently, PRRs that also recognize endogenous cytoplasmic damage associated molecular patterns (DAMPs) have been discovered. A “generic” immune response to extracellular and intracellular triggers has the following components: a “trigger” that is recognized by a “molecular sensor” that elicits “mediators” that lead to cytokine and chemokine production with the goal to recruit immune cells into the tissue and to coordinate a tissue “defense”. The immune response is tissue specific (9) (Fig.1).

The discovery that mutations in the NLRP3 inflammasome, the first identified human intracellular PRR in humans (11, 12), cause the disease spectrum of CAPS, provided a molecular mechanism that links intracellular stress recognition with the initiation of a cytokine response (inflammatory mediator). This response occurs through caspase-1 mediated IL-1 and IL-18 activation and thus provided a conceptual framework to understand the episodic inflammatory events that underlie autoinflammation (13). Since the discovery of cryopyrin/NLRP3, 23 structurally similar NOD-like receptors (NLRs) have been found in

humans (14). Interestingly, pediatric granulomatous arthritis (PGA) is caused by autosomal dominant gain of function mutations in the NACHT domain (exon 4) of one of these NLRs, *NOD2/CARD15*, but the inflammatory cytokine responses induced by the triggers to NOD2 are more complex, not clearly tied to IL-1 release, and involve NF κ B activation.

Recently, an increasing number of sensors that are triggered not only by viral DNA and RNA, but also by self DNA and RNA, has been found to be coupled to the transcription of Type 1 interferons (IFN Type I), and the induction of interferon response genes (15). A growing number of inflammatory conditions, including the autoimmune condition systemic lupus erythematosus (SLE) (16) and the monogenic condition Aicardi-Goutieres syndrome (AGS), which is caused by mutations in enzymes associated with the digestion of single-stranded or mispaired dsDNA, RNA/DNA hybrids, and deoxynucleotide triphosphates (17), presents with an increase in IFN response genes and raises the question whether novel autoinflammatory conditions presenting the induction of interferon response genes are associated with dysregulation in these IFN Type I coupled sensor pathways.

2. The inability to downregulate unopposed cytokine signaling leads to the development of “vicious cytokine cycles” that amplify and perpetuate inflammatory responses

The absence of functional receptor antagonists in two IL-1 receptor family members, *IL1RN* and *IL1F5/IL36RN*, generates cytokine amplification loops in response to triggered events that cannot be downregulated and can escalate to a systemic inflammatory response syndrome and death. The clinical consequences of the absence of a negative regulator counteracting cytokine signaling on the IL-1 and IL-36 receptor are illustrated in the disease expression of DIRA and DITRA respectively.

3. Primary dysregulation of keratinocyte activation can initiate the recruitment of hematopoietic cells into the tissue and initiate inflammatory amplification loops that lead to pustular dermatoses

The proteins encoded by mutated *CARD14* in CAMPS, and mutated *IL36RN/IL1F5* in DITRA, namely CARD14 and the IL-36 receptor antagonist respectively, are both mainly expressed in keratinocytes, and the fact that these diseases can present with generalized pustulosis, fever and/or systemic inflammation point to the primary dysregulation in keratinocytes as the “instigator” of an inflammatory immune response localized to the skin.

The molecular targets mutated in existing and emerging new autoinflammatory syndromes suggest a unifying hypothesis that the increased systemic and tissue specific inflammatory response seen in these patients may constitute a heightened immune response to extracellular and/or intracellular triggers, either because of enhanced sensor function, or umulation of triggers/inducers, or increased production of mediates, all contributing to the development of “amplification loops” of proinflammatory cytokine production and signaling.

I. IL-1 MEDIATED AUTOINFLAMMATORY DISEASES

The clinical disease manifestations of the cryopyrinopathies (FCAS, MWS and NOMID/CINCA), the “classic” autoinflammatory syndromes (FMF, TRAPS, HIDS), and the monogenic autoinflammatory bone diseases DIRA and Majeed syndrome significantly respond to IL-1 blocking therapies, suggesting a key pathogenic role of IL-1 in the disease pathogenesis. As our understanding of the disease pathogenesis in most of these disorders is centered around IL-1 β activation by the NLRP3 inflammasome, their pathogenesis is discussed together.

Pathogenesis Considerations in IL-1 mediated conditions

The NLRP3 inflammasome integrates sensing of a trigger and IL-1 maturation and secretion (Fig.2). The *NLRP3* gene encodes the protein cryopyrin, which together with the adapter proteins, ASC (apoptosis-associated speck-like protein containing a CARD) and CARDINAL, and 2 procaspase-1 molecules forms the NLRP3 inflammasome a caspase-1/IL-1 β activating platform. Upon stimulation, the NLRP3 inflammasome activates the proteolytic enzyme caspase-1 that cleaves inactive pro-IL-1 β and pro-IL-18 into their active forms (Fig.2) (18–20). Inflammasome activation requires a priming (first) signal, through for example a TLR, that leads to the transcription and translation of pro-IL-1 β ; and a second signal that leads to inflammasome and caspase-1 activation. Signal 1 is delivered through exogenous triggers that include whole pathogens (such as *S.aureus*, *L.monocytogenes* and *C.albicans*), PAMPs, such as LPS, (viral) nucleic acids, muramyl dipeptide (MDP), and bacterial toxins. Caspase-1 activation in response to bacterial infections also induces a rapid pro-inflammatory cell death termed pyroptosis (21).

Endogenous triggers released during cellular injury or death (i.e. extracellular ATP and hyaluronan), as well as indicators of metabolic stress [i.e. glucose, monosodium urate (MSU), calcium pyrophosphate dehydrate (CPPD) crystals, amyloid- β fibrils, cholesterol crystals] and phagocytosed environmental, large insoluble inorganic crystalline structures likely provide signal 2. These chemically diverse triggers cannot possibly bind directly to the inflammasome, which spurred the search for a common NLRP3 inflammasome activating final pathway.

Potential mechanisms of inflammasome activation may involve production of mitochondrial reactive oxygen species (ROS); ion fluxes such as K⁺ efflux from the cell and Ca²⁺ release from the endoplasmic reticulum; and protein kinase activation (recently reviewed in (22)). Two molecules that directly bind to the NLRP3 inflammasome have been described so far, the oxidized mitochondrial (oxi-mito) DNA that is released by dysfunctional mitochondria, and cyclic AMP (cAMP). Both are attractive candidates for a converging mechanism and while binding of oxi-mito DNA activates the inflammasome (23), cAMP binding is inhibitory (24). Interestingly, *NLRP3* mutations affect binding of the negative regulator cAMP to the NACHT domain (24), which leaves mutant NLRP3 inflammasomes more amenable to activation and may help to explain the constitutive activation of the mutant NLRP3 inflammasome in patients with CAPS.

Many factors contribute to the activation and function of the NLRP3 inflammasome and mutations in the 3 genes causing the hereditary fever syndromes are thought to affect factors that enhance/influence NLRP3 inflammasome mediated IL-1 activation and secretion.

MEFV, the FMF gene, encodes pyrin that can bind to the ASC adapter protein (25). One hypothesis is that the interaction between the wildtype pyrin and ASC may inhibit the NLRP3 inflammasome assembly (25). Mutant pyrin is thought to be a less effective inhibitor, which may lead to increased inflammasome activity. This is consistent with data in animal models where pyrin knockout mice or mice expressing a truncated protein have increased caspase-1 activation, increased IL-1 β maturation and a defect in macrophage apoptosis (20). Data from a knock-in mouse model also suggest that pyrin can form a NLRP3-independent pyrin inflammasome that activates IL-1 (26). How these models integrate *in vivo* in patients remains to be sorted out in the future.

Mutations in mevalonate kinase cause IDS and constitute an enzymatic block that leads to a shortage in isoprenoids, which are products of the cholesterol biosynthesis pathway, that subsequently leads to a decrease in post-translational prenylation (27). *In vitro* data from HIDS patients suggest that farnesol or geranylgeraniol compounds can reverse entu

IL-1 β secretion, and that inhibitors of sterol biosynthesis, which favor nonsterol isoprenoid biosynthesis, also reduce IL-1 β secretion by HIDS leukocytes (28), thus suggesting that HIDS patients with a shortage in isoprenoids have increased IL-1 β secretion. However, the search for molecular mechanisms that link a shortage in isoprenoids to IL-1 production and secretion is an area of ongoing research.

Mechanistic studies in TRAPS have recently shifted the focus from TNF as the pivotal cytokine to intracellular mechanisms ultimately leading to increase of multiple cytokines including IL-1 production. Mutant TNFR1 receptors fail to bind to TNF and are not transported to the cell surface but remain trapped in endoplasmic reticulum (ER) of the cells, where they umulate to ten-fold higher than wild-type levels, while cell surface receptor levels of wild-type and mutant protein are greatly reduced (29, 30). Cells from patients with TRAPS mutations spontaneously activate JNK and p38 MAP kinases (MAPKs); which may also lead to ROS-dependent increase in IL-1 production or provide a first signal for IL-1 transcription and promote the presence of pro-IL-1 β .

While NLRP3 mutations in patients with CAPS lead to overproduction and secretion of active IL-1 β upon stimulation, the mutations in DIRA reflect the effects of an inability to block and terminate IL-1 signaling. The IL-1 receptor antagonist (IL-1Ra), which is absent or non-functional in DIRA, usually competes with the proinflammatory cytokines IL-1 α and IL-1 β for binding to the IL-1 type I receptor (IL-1RI). Stimulation of patients' cells with IL-1 α or β , or LPS leads to increased production of a number of proinflammatory cytokines and chemokines including IL-6, IL-8, MIP-1 α , and TNF, suggesting that IL-1 signaling cannot be blocked in these patients and remains hyperactive (31, 32). (Fig. 2)

Majeed syndrome is a very rare condition that has only once been reported outside of Jordan, however the disease pathogenesis may tie in with inflammasome activation. Mutations in *LPIN2* cause loss of function of the Mg²⁺-dependent phosphatidate phosphatase (PAP) activity of the enzyme, Lipin-2, that is involved in the phospholipid biosynthesis pathway. Lipin-2 associates with the nuclear/ER membrane and catalyzes the conversion of phosphatidate (PA) to diacylglycerol (DAG), a precursor for the production of phospholipids that are components of cell membranes, essential for the absorption, transport and storage of lipids, and serve as reservoir for signaling molecules. The Majeed mutation, S734L, in human Lipin-2 alters a highly conserved serine residue in the C-LIP domain that leads to loss of Lipin-2 phosphatidate phosphatase activity (33, 34). The effect of mutant lipin-2 might be compensated for in tissues with high expression of Lipin-1 and 3 (in liver and fat), but not in monocytes where Lipin-2 is most highly expressed. Lipin-2 dampens the pro-inflammatory signaling that is produced by macrophages when exposed to excessive saturated fatty acids (35), the umulation of free fatty acids in monocytes and macrophages may lead to activation of the NLRP3 inflammasome a possible mechanism that needs further exploration.

A case report of a rapid and complete response to IL-1 blockade with anakinra and canakinumab in 2 patients with Majeed syndrome strongly suggests an IL-1 β mediated pathology and may link another dysregulated lipid biosynthesis pathway (HIDS being the other) to IL-1 possibly through NLRP3 inflammasome activation.

Clinical Features and Therapeutic Considerations for IL-1 mediated Conditions

i. The Cryopyrinopathies or Cryopyrin Associated Periodic Syndromes (CAPS) (including: FCAS, MWS and NOMID)—The term cryopyrinopathies or cryopyrin associated periodic syndromes (CAPS) encompasses the three historically described diseases: FCAS, MWS and NOMID/CINCA, all caused by autosomal dominant

gain of function mutations in *NLRP3/CIA1*. While FCAS is at the clinically mild end of the spectrum, NOMID is at the most severe end.

Genetics and epidemiology: Over 130 disease-causing mutations in *NLRP3/CIA1*, 90% are located in exon 3 (12, 36). The inheritance pattern in FCAS and MWS is usually familial (12), and the sporadic nature in patients with NOMID/CINCA (37, 38) is attributed to the severe phenotype of untreated patients, which results in their inability to reproduce. The face of NOMID has dramatically changed with IL-1 blocking therapy, so that more familial cases of NOMID will likely be seen in the future. Although genetic testing is confirmatory, the diagnosis needs to be made on clinical grounds. Approximately 50% of NOMID/CINCA patients and a much smaller percentage of FCAS and MWS patients do not have germline mutations in *NLRP3* detected by Sanger sequencing, which is a technique used to search for mutations in clinical assays. Of those “Sanger mutation negative” patients, about 70% have evidence of somatic mosaicism (39), which can currently only be detected by cell cloning and deep sequencing in research settings.

A rapid and complete clinical response to a treatment trial with an IL-1 blocking agent in patients with suspected CAPS can help to confirm the clinical diagnosis.

Based on estimates by centers treating these patients, the prevalence of CAPS is 1–2 patients per 1,000,000 people in Europe and the US.

Clinical manifestations: In general all CAPS patients present with episodes of fever, neutrophilic urticaria, conjunctivitis, arthralgia and elevated acute phase reactants (40). Onset, frequency, severity of overlapping symptoms, as well as degree of multiorgan involvement, long-term morbidity and mortality differ among FCAS, MWS and NOMID/CINCA patients.

In FCAS the febrile attacks are triggered by cold exposure. Attacks often start within 2 hours of cold exposure, peak at 2 to 6 hours, and last 12 to 48 hours. FCAS symptoms typically present in early childhood, but first presentations later in life are also seen. In FCAS, permanent organ damage is rare and secondary amyloidosis may occur in less than 2 % of patients (41).

MWS is of intermediate-severity. In patients with MWS, the febrile attacks are usually more frequent and can persist at a low-grade level with exacerbations (42). In addition to conjunctivitis, eye inflammation can involve the sclera (episcleritis) and anterior chamber (uveitis). During severe attacks, patients often complain of headache and present with aseptic meningitis or papilledema. In MWS, the most concerning disability is sensorineural hearing loss that typically develops in the second to third decade of life as a consequence of chronic inner ear inflammation which leads to damage of the Corti organ (43, 44). Secondary amyloidosis is frequently observed in patients living in Europe where it is found in 25% to 33% of the untreated patients (45). The percentage of patients developing amyloidosis is lower in the US for all amyloidosis conditions in general, suggesting that environmental factors can contribute to risk of disease independently of the genetics.

In NOMID, systemic and organ inflammation is constant and low-grade fevers, rashes, aseptic meningitis and arthropathy often start in the first weeks of life, with frequent exacerbations (46) (Fig.3A–E). Older children present with persistent low-grade fever, neutrophilic urticaria, arthropathy and aseptic meningitis, which leads to headaches and increased intracranial pressure, with early-morning nausea and vomiting. Symptoms mentioned above can undulate in severity but acute phase reactants never normalize and the disease is poorly responsive to steroids, and DMARDs.

Untreated NOMID patients develop permanent organ damage early in life (47). Chronic aseptic neutrophilic meningitis that presents as irritability, headaches and seizures, leads to the development of increased intracranial pressure, hydrocephalus and papilledema, brain atrophy, and cognitive impairment. Ongoing cochlear inflammation seen as cochlear enhancement on magnetic resonance imaging (MRI), leads to sensorineural hearing loss within the first years of life. Chronic papilledema results in optic nerve atrophy and progressive vision loss usually in the third decade of life, but anterior and rarely posterior uveitis can also contribute to the blindness (46). Cognitive delay is multifactorial, due to perinatal insult and the degree of central nervous system (CNS) inflammation.

About 50 to 70% of NOMID patients present with a deforming arthropathy that results in abnormal epiphyseal calcification, cartilage overgrowth and joint deformities. Premature patellar ossification and patellar overgrowth is a typical finding in NOMID (48).

Treatment of CAPS: Despite clinical heterogeneity, all patients with FCAS, MWS and NOMID respond dramatically and invariably to IL-1 blockade. The rapid improvement in clinical and laboratory parameters and safety data in all CAPS patients, led to the FDA approval of three anti-IL-1 agents for the treatment of CAPS: the long acting IL-1 inhibitors rilonacept (49, 50) and canakinumab (51), and the short acting IL-1 receptor antagonist anakinra (47) in the US, while rilonacept and canakinumab are approved by the EMA in Europe.

While preventing cold exposure improves the cold induced symptoms, optimal treatment with IL-1 blockage leads to complete resolution of symptoms in most cases and is the treatment of choice in FCAS patients (51, 52). In patients with MWS and NOMID, optimal IL-1 inhibiting therapy needs to be initiated early to prevent the development and progression of organ damage (47). Careful monitoring of CNS disease and inner ear inflammation is required in order to establish optimal treatment doses.

Sustained responses to IL-1 blocking therapies such as rilonacept (50) and canakinumab (53) are seen, while treatment with anakinra may require some dose adjustment with prolonged use (47, 54),

ii. The “classic” Periodic Fever Syndromes (FMF, TRAPS, HIDS)

Familial Mediterranean Fever (FMF)

Genetics and Epidemiology: FMF is caused by autosomal recessive mutations in the *MEFV* gene (2, 3). However, the description of patients with clinical FMF and only one single *MEFV* mutation suggests the possibility that a dominant inheritance is possible (55). The most common missense mutations detected in FMF patients are M694V, M680I, M694I and E726 (2) (36), and almost half of the mutations described so far are located in exon 10.

FMF is the most prevalent monogenic autoinflammatory disease, affecting more than 100,000 individuals worldwide (56), primarily eastern Mediterranean populations, including Sephardic Jews, Armenian, Arabian and Turkish descendants.

Clinical Manifestations: Most patients have disease onset before the third decade of life. FMF attacks typically last 1 to 3 days and flares recur periodically between once a week and once every few years, with symptom free intervals between flares (57, 58)

The acute attacks of FMF are characterized by recurrent episodes of fever, abdominal pain secondary to an acute generalized peritonitis, arthritis (mainly non-erosive oligoarthritis) and skin rash (erysipelas-like erythema). Episodes of abdominal pain can mimic an acute abdomen often leading to appendectomy or cholecystectomy. In a small percentage of

patients, episodes of myalgias can be prolonged (up to 6 weeks), debilitating, associated with fever, elevated erythrocyte sedimentation rate (ESR) but normal creatinine kinase (CK) (59). This "protracted febrile myalgia" in FMF patients is thought to be due to vasculitis (59). Other symptoms are serosal inflammation presenting as pleuritis, pericarditis and scrotal pain, and rarely aseptic meningitis (60). FMF patients may have an increased risk of sacroiliitis, irrespective of HLA-B27 status or colchicine prophylaxis.

Type AA secondary amyloidosis is the most frequent complication of FMF, occurring in 13% of Turkish patients (61). Frequency of amyloidosis differs between countries and, in a multicenter study, the country of recruitment was the most important risk factor for the occurrence of renal amyloidosis (62). Kidneys are the most affected organs and patients present with progressive proteinuria, nephrotic syndrome and chronic renal failure (61). Secondary AA amyloidosis is caused by persistently elevated serum amyloid A (SAA) levels. The development of AA amyloidosis is unlikely with low serum concentrations of this protein (<4mg/L) (63). All FMF patients should be regularly screened for amyloidosis by urinalysis.

Treatment: Since 1972, when colchicine was introduced as a treatment option, it has remained the standard of care for prophylaxis of attacks and prevention of amyloidosis. Doses of 1–2 mg per day of colchicine prevent the acute inflammatory attacks and the development of systemic amyloidosis (64). Given the cytokine profile reported in FMF, and the interactions of IL-1 β and pyrin, IL-1 inhibition needs to be considered for those patients with severe side effects or unresponsive to colchicine (65). A recent randomized placebo-controlled trial has suggested rilonacept, a long acting IL-1 inhibitor, as a treatment option for patients who are refractory or intolerant to colchicine. In this study enrolling 14 FMF patients during 12 months, rilonacept reduced the frequency of FMF attacks more significantly than placebo (66). Case series and case reports have also described the efficacy of the other IL-1 inhibitors, anakinra (67, 68) and canakinumab (67, 69), for FMF treatment. There are also anecdotal data supporting the use of TNF inhibitors in this disease (70, 71).

TNF receptor associated periodic syndrome (TRAPS)

Genetics and epidemiology: TRAPS is caused by autosomal dominant mutations in the *TNFRSF1A* gene, which encodes the TNF receptor type 1 (TNFR1). Over 100 mutations have been found to cause TRAPS (36).

Clinical manifestations and diagnosis: Clinical manifestations usually present in childhood and adolescence, but in about 20% of patients it appears first in adulthood. The mean length of the fever episodes is around 14 days but can last from 1 to 4 weeks.

TRAPS patients usually present with recurrent fever, abdominal pain, pleuritis, myalgias, arthralgias, and periorbital edema or conjunctivitis. Myalgias are frequently associated with an overlying tender erythematous skin rash that migrates from proximal-to-distal accompanying the myalgia pain. MRI shows segmental muscle edema, and on biopsy, a monocytic fasciitis is present (72). Periorbital edema is more common in TRAPS than in the other periodic fever syndromes and recurrent conjunctivitis or anterior uveitis can be present in up to half of the patients (73). Neurological manifestations are rare and include headaches, aseptic meningitis, optic neuritis and behavioral alterations. Amyloidosis is the most serious long-term complication of TRAPS and develops in 14–24% of patients (74). Given the overlapping symptoms with other autoinflammatory diseases, a definite diagnosis of TRAPS can only be made in the presence of a mutation in *TNFRSF1A*.

Treatment: TNF inhibition is effective in some cases. In a prospective study, etanercept reduced but not completely normalized the frequency and severity of the attacks and abnormal inflammatory markers (75). There are other studies that suggest that etanercept efficacy diminishes over time. In some centers, anakinra and canakinumab have become the treatment of choice (76) (77). However, individual cases of anakinra failure have been reported (78).

Hyperimmunoglobulinemia D with Periodic Fever Syndrome (HIDS) / Mevalonate Kinase deficiency

Genetics and epidemiology: HIDS is caused by autosomal recessive mutations in the *MVK* gene (mevalonate kinase gene) (6, 7). Currently, about 30 disease-causing variants have been identified and most of the mutation positive HIDS patients have at least one copy of the substitution V377I (79). The substitution I268T is the second most common variant (79) in HIDS patients in Western Europe (36)

Clinical manifestations and diagnosis: Typically, HIDS presents very early in life, usually before 1 year of age. HIDS episodes last 3 to 7 days and occur every 4–6 weeks. HIDS patients present with recurrent episodes of fever, that is often preceded by malaise and chills. Polyarthralgia or arthritis (non-erosive arthritis of large joints), as well as marked bilateral, tender, cervical lymphadenopathy are seen. Other symptoms include abdominal pain, vomiting, diarrhea, splenomegaly and a variety of skin lesions, including maculopapular, urticarial, nodular or purpuric rashes. Childhood vaccinations can precipitate an attack; other provocative factors include trauma, surgery, emotional stress and infections (80).

During febrile episodes, patients may present with elevated acute phase reactants (ESR and CRP), elevated urinary mevalonic acid levels and increased IgD and IgA levels. However, IgD concentrations are nonspecific and should not be used to make a diagnosis, especially in children under 3 years of age, since they can be elevated in other conditions, such as FMF and TRAPS (81). Genetic testing in children below the age of 5 years with recurrent fevers may be indicated. Amyloidosis is uncommon in HIDS patients.

Treatment: Initial suggestions to use simvastatin proved ineffective (82–84). However there are reports of patients responding to etanercept (85), and the IL-1 blocking agents anakinra (86, 87) and canakinumab (87).

iii. The Monogenic Autoinflammatory Bone Diseases (DIRA, Majeed syndrome)—Deficiency of interleukin 1 receptor antagonist (DIRA) and Majeed syndrome are two monogenic autoinflammatory disorders caused by loss of function mutations in the IL-1 receptor antagonist, *IL1RN*, in DIRA, and *LPIN2* in Majeed syndrome (88). Both conditions present early in life with sterile bone inflammation involving the ribs, long bones, and proximal femur (Fig. 3G–K); rarely CNS vasculitis can be seen (Fig. 3L) DIRA patients typically have pustular skin lesions (Fig. 3F)(31, 32), while in Majeed syndrome, the skin lesions are more variable and seem to be less prominent (89, 90). Founder mutations causing DIRA are seen in Newfoundland, the Netherlands, Lebanon, Northern Puerto Rico, Brazil (91) and, most recently, Turkey, while disease causing mutations in Majeed syndrome have, with one exception, only been seen in Jordanian patients.

Treatment: Treatment for DIRA is IL-1 blockade with anakinra; other IL-1 blocking therapies have not been evaluated. In Majeed syndrome, IL-1 inhibition was used

successfully in 2 patients but more data is needed to determine if this should be treatment of choice (92).

The monogenic inflammatory bone diseases are discussed in detail in a chapter by Ferguson et al.

II. AUTOINFLAMMATORY-SYNDROMES WITH VARIABLE RESPONSES TO IL-1 BLOCKAGE

Clinical and Therapeutic Considerations

Blau syndrome / early onset sarcoidosis (pediatric granulomatous arthritis, PGA)

Epidemiology and Genetics: PGA, pediatric granulomatous arthritis, is caused by autosomal dominant gain of function mutations in the NACHT domain (exon 4) of *NOD2/CARD15*, but the inflammatory cytokines responses are more complex, involve NFκB activation and are not clearly tied to IL-1 release (93, 94).

PGA can be inherited in an autosomal dominant pattern and familial cases have traditionally been called Blau syndrome. However, mutations can occur sporadically and, in these instances, the disease has historically been referred to as early-onset sarcoidosis (95, 96). The identification of overlapping mutations led to the recognition that these two disorders are the same disease. So far, 12 disease-causing mutations in *NOD2* gene have been reported to cause PGA. PGA symptoms include granulomatous inflammation of eyes, joints and skin, leading to an early-onset (before 4 years of age) classical triad of disease manifestations comprising chronic uveitis, arthritis and dermatitis.

Clinical Presentation and Diagnosis: Chronic arthritis is seen in 100% of patients, who mainly present with polyarthritis (96%). A symmetric hypertrophic tenosynovitis is observed in approximately 40% of the patients. Chronic, persistent eye involvement is present in most patients (84%) (97). Most patients have bilateral panuveitis (50%), while 25% of the subjects have anterior uveitis (97). Cataract, glaucoma and synechiae (Fig 3N) in 50% and 30% of patients respectively, represent damage from chronic inflammation and steroid treatment (96), and up to 40% of untreated patients develop irreversible blindness (97). The typical PGA exanthema is ichthyosis-like and occurs in 88% of the patients (95, 96). Less commonly observed findings include fever, camptodactyly and central neuropathy (95).

Laboratory exams demonstrate persistent leukocytosis, thrombocytosis and increased ESR and CRP. Synovial, skin and liver biopsies may show non-caseating granulomas, even though a definitive diagnosis is only achieved with DNA sequencing showing *NOD2/CARD15* mutations (97).

Treatment: Optimal therapy for PGA has not been established. NSAIDs can be used for mild clinical manifestations, whereas severe symptoms are treated with systemic corticosteroids. Immunosuppressant (methotrexate and cyclosporine) and biologics targeting TNF and IL-1 (etanercept, infliximab and anakinra) have been reported to result in clinical benefit, especially in patients with refractory uveitis (96, 97).

Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome

Genetics and epidemiology: PAPA syndrome is caused by autosomal dominant mutations in *PTSPIP1* (98). The disease is exceedingly rare, with less than 10 families identified so far.

Pathogenesis: The pathogenesis of PAPA is not well understood. *PSTPIP1* encodes CD2-binding protein-1, a cytoskeletal protein that is designated proline-serine-threonine-phosphatase interacting protein-1 (PSTPIP1). PSTPIP1 is an adaptor protein that interacts with PEST-type protein tyrosine phosphatases (PEST-PTPs), Wiskott-Aldrich syndrome protein (WASP) and pyrin, the protein encoded by *MEFV*, the FMF gene (99, 100). Disease causing *PSTPIP1* mutations are thought to diminish the interactions with PEST-type protein, which results in increased phosphorylation of mutated PSTPIP1 and increased interaction with pyrin (100). Four disease-causing variants have been described in *PTSPIP1*. It is suggested that PSTPIP1 mutants increase activation of the pyrin inflammasome associated IL-1 β activation (101), even though PSTPIP1 does not seem to be an essential regulator of the NLRP3, AIM2 or NLRC4 IL-1 β activating inflammasomes in a mouse model (102). Additional studies are needed to provide clues to better therapies, as IL-1 inhibiting approaches are only partially effective (i.e. for the treatment of pyogenic arthritis but less for severe skin disease).

Clinical manifestations: PAPA syndrome is a pyogenic autoinflammatory disease that presents with pyogenic arthritis (Fig. 3O), pyoderma gangrenosum (Fig. 3P) and severe cystic acne. PAPA patients present with early-onset episodes of painful sterile and deforming arthritis, cutaneous ulcers (pyoderma gangrenosum) and pathergy; cystic lesions or skin abscesses are seen at needle injection sites (98). Cystic acne and hidradenitis suppurativa of the axilla and groin can develop around puberty. Fever is rarely observed in these patients. Symptoms usually persist into adulthood with significant joint destruction and impaired quality of life related to physical disability (103). Other clinical findings/ complications from disease and treatment in PAPA patients include osteomyelitis, recurrent otitis, lymphadenopathy, splenomegaly, thrombocytopenia, hemolytic anemia, pharyngeal papillomatosis and large granular T cell lymphocytosis (103).

Treatment: Treatment of PAPA syndrome is challenging and corticosteroids, thalidomide, cyclosporine, dapsone, tacrolimus and IVIG have been used with variable responses (103). Several case reports indicate positive responses to TNF inhibition with etanercept, infliximab, and adalimumab in two patients and to IL-1 inhibition with anakinra in one case (103) but poor responses to anakinra, infliximab and etanercept have also been seen (103). In general, monoclonal anti-TNF antibodies (infliximab and adalimumab) were considered more effective in treating skin manifestations of PAPA syndrome while IL-1 inhibition seems to be more effective for the joint disease (103).

III. NON-IL-1 MEDIATED AUTOINFLAMMATORY SYNDROMES

Pathogenesis Considerations for non- IL-1 mediated conditions, PRAAS/CANDLE

The finding that mutations in *PSMB8* cause a severe inflammatory phenotype in humans, PRAAS/CANDLE, was unexpected given that *psmb8/lmp7* knockout mice lack spontaneous development of systemic symptoms, muscle inflammation or lipodystrophy (104). Proteasomes are ATP dependent protein degradation systems that target intracellular polyubiquitinated proteins derived from self-structures or foreign structures for proteolytic destruction (105, 106). Proteasome cleavage of proteins leads to the production of peptides for antigen presentation, but failure of mutant proteasome to clear immature proteins can

lead to an increased inflammatory response (107) (Fig. 2). In patients homozygous for *PSMB8* mutations, the assembly of the inducible proteasome complex is defective (108–110) and polyubiquitinated proteins umulate in tissues from these patients. Serum cytokine analysis in NNS and CANDLE patients showed elevation in IL-6, IFN γ -inducible protein 10, (IP-10, also called CXCL10), monocyte chemoattractant protein (MCP)-1 (CCL2) and IL-1 receptor antagonist (109) (111). Gene expression profiling using whole blood microarray identified the IFN pathway as the most differentially regulated pathway in CANDLE patients (111) and signal transducers and activators of transcription (STAT)-1, a downstream mediator of IFN Type I and type II signaling, showed higher constitutive phosphorylation and was more highly induced upon IFN γ stimulation in patients' monocytes compared to healthy controls. Inhibition with the Janus kinase (JAK) inhibitor, tofacitinib decreased the STAT-1 phosphorylation and IFN γ -induced IP-10 (111). Increased p38 MAPK responses have also been observed in PRAAS (109, 110). These observations suggest that a putative intracellular stress response might lead to an IFN response signature, which is very similar to the IFN response signature seen in SLE. The IFN response signature has also been seen in patients with Aicardi Goutieres syndrome (AGS), who present with a non-infectious, viral encephalitis like disease resulting in rapid demyelination often within the first years of life and basal ganglia calcifications (112). Whether targeting IFN signaling constitutes a therapeutic strategy in PRAAS/CANDLE patients is currently being assessed (clinical trials identifier NCT01724580). We suggest that a transient increase in DRiPs and polyubiquitylated proteins umulate and trigger a proteotoxic response through yet unknown sensors that are possibly IFN Type I induced (Fig. 2). Alternatively, similarly to AGS, where loss of function mutations in the exonuclease *TREX1* and other enzymes associated with the digestion of single-stranded or mispaired dsDNA, RNA/DNA hybrids, and deoxynucleotide triphosphates, lead to a self nucleotide induced Type I IFN associated signature (17), the interferon signature in CANDLE may also be induced by yet unknown triggers.

Proteasome associated autoinflammatory syndromes (PRAAS)/CANDLE

Genetics and epidemiology: The first description of Japanese patients presenting with “nodular erythema, elongated and thickened fingers and emaciation” date back to a report from Nakajo in 1939 (113). Nishimura et al, reported three similar patients in 1950 (114), the disease was later named Nakajo-Nishimura syndrome (NNS) in Japan.

The first reports of non-Japanese patients were on a Palestinian patient reported by Megarbane A (115), two Mexican siblings and one Portuguese patient reported by Garg et al (116). The presence of joint contractures, muscular atrophy, microcytic anemia and panniculitis-induced lipodystrophy lead to the term for joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy (JMP) syndrome.

In 2010, Torrelo et al. proposed the acronym chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE) (117)

In 2011, several studies showed that JMP syndrome (108), Nakajo-Nishimura syndrome (NNS) (109), Japanese autoinflammatory syndrome with lipodystrophy (JASL) (110), and CANDLE (111) are all caused by autosomal recessive mutations in the proteasome subunit β type 8 (*PSMB8*) gene, indicating that these disorders are phenotypes along the same disease spectrum (111, 117). Currently four mutations in *PSMB8* (T75M, A92T, C135X and G201V) have been described, but genetic heterogeneity is present (111).

Clinical manifestations (Fig. 3. Q–U): Common clinical features seen in PRAAS/CANDLE include high fevers, violaceous skin rashes varying from small nodules to violaceous plaques, also described as ‘pernio-like’ lesions covering trunk and extremities,

facial rashes leading to various degrees of edema, mimicking heliotrope rashes in some patients, drumstick like widening of the distal fingers tips, arthritis with variable degrees of joint contractures, and progressive lipodystrophy affecting initially the face and extremities but can be generalized. Other common clinical findings are myositis, hepatosplenomegaly, basal ganglia calcification, microcytic anemia and increased acute phase reactants (ESR and CRP). More variable symptoms include muscle atrophy, dyspnea, seizures, lymphadenopathy, low weight and height and metabolic abnormalities including truncal obesity and hyperlipidemias, insulin resistance and acanthosis nigricans (111, 116). They seem to be exaggerated in patients on steroids (109, 110). Severe inflammatory attacks are more pronounced in childhood than later in life. They can escalate in a systemic inflammatory syndrome resulting in organ failure and sudden death. The spectrum of organ damage that can be observed includes severe lipodystrophy, calcifications in vessels and soft tissues and rarely cardiomyopathy and cardiac arrhythmias (116).

Treatment: In the 9 patients who have been reported, most clinical symptoms partially responded to high doses of steroids (1–2 mg/kg/day) (111), while NSAIDs, colchicine, dapsone, methotrexate, tacrolimus and azathioprine were not effective in most of the patients (111). A variable response was observed to anti-TNF, anti-IL-1 and anti-IL-6 agents, but complete disease remission was not achieved with any of the therapies described (111). Lipodystrophy progressed in all patients despite immunosuppressive and cytokine targeted therapy (111). The increase in STAT-1 phosphorylation and the strong interferon response suggest that interference with IFN signaling may be a therapeutic strategy for the treatment of CANDLE/PRAAS.

Pathogenesis Considerations for non- IL-1 mediated conditions, DITRA, CAMPS

Two pustular psoriasis-like conditions were recently shown to be caused by monogenic defects, including the autosomal recessive loss of function mutations in the IL-36 receptor antagonist causing DITRA, and the autosomal dominant gain of function mutations in *CARD14* causing CAMPS.

In both instances, the mutated protein is highly expressed in keratinocytes. *IL36RN* encodes the IL-36-receptor antagonist (IL-36Ra), which binds to IL-36 receptor, and completely blocks binding by IL-36 α , - β and - γ and further downstream prevents NF-KB activation in response to TLR agonist stimulation (118, 119). The absence of the IL-36 receptor antagonist in DITRA patients leads to constitutively enhanced IL-36 receptor signaling in keratinocytes and hematopoietic cells. In patients with *CARD14* mutations, hematopoietic cells do not even express *CARD14*. Transfection of mutant *CARD14* into a keratinocyte cell line leads to increased NFkB 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 (120) (121).

Deficiency of interleukin 36 receptor antagonist (DITRA)

Genetics and epidemiology: Recently 16 family members of nine Tunisian families with generalized pustular psoriasis and fever flares were found to be homozygous for a mutation in *IL36RN* gene, L27P, indicating a founder mutation in Tunisia leading to this disease (118). Additionally, three unrelated English patients with a similar phenotype presented with mutations in *IL36RN* (119).

Clinical manifestations and diagnosis: More than 70% of the patients described developed the disease during childhood (7 days to 11 years of age) (118). DITRA patients present with recurrent and sudden onset generalized erythematous and pustular skin rashes, associated

with high fevers up to 40–42°C, asthenia, increased CRP and leucocytosis (118, 119). Secondary skin infections and sepsis may also occur (118). In all patients, the disease flares were thought to be triggered by viral or bacterial infections (14/16 patients), withdrawal of retinoid therapy (n=7), menstruation (n=6), and pregnancy in (n=4) (118, 119).

Treatment: Definitive treatment for this disease has not been established yet. Acitretin was used as treatment in 12 of the 19 patients described so far (118, 119). Other therapeutic regimens tried with variable individual responses included oral steroids in 4 patients, methotrexate in 3 patients, cyclosporine in 3 patients, adalimumab in 2 patients, infliximab in 2 and etanercept in one subject (118, 119). Topical steroids were used in 3 patients (118). IL-1 blocking therapy has not been reported in these patients. However, data from a mouse model mimicking IL36 signaling through a transcript, leads to a psoriasis like phenotype while knocking out the IL-1 receptor in this model suggests that IL-36 mediated keratinocyte activation does not require IL-1 signaling (122).

CARD14 mediated psoriasis (CAMPS)

Genetics and epidemiology—Autosomal dominant gain-of-function mutations in *CARD14* gene cause a spectrum of more localized plaque psoriasis or more generalized pustular psoriasis in two large kindreds, and severe generalized pustular psoriasis in an unrelated child who had a sporadic, *de novo* mutation in *CARD14* (121). Mutations in *CARD14* were also shown to cause a familial syndrome described as *pityriasis rubra pilaris* in 15 members of 3 families (120).

Clinical manifestations—The skin lesions in patients with *CARD14* mutations range from typical localized plaque psoriasis to generalized disease, involving 100% of the body surface area (Fig. 3M) (120, 121). Fever and other systemic manifestations are generally not present but can occur with super-infections of the skin in patients with CAMPS. The fact that *CARD14* mutations provoke a disease spectrum from localized plaque psoriasis to generalized pityriasis rubra pilaris, and pustular psoriasis, indicates that this disease at different levels of severity can be induced by one common pathogenic pathway.

Treatment—The therapeutic approach in CAMPS is very similar to the treatment of moderate-to-severe psoriasis, using methotrexate, cyclosporine and anti-TNF agents. Familial pityriasis rubra pilaris is considered refractory to the standard therapies and a partial response has been described with retinoids, cyclosporine and etanercept (120, 123). The similarities in gene expression studies in CAMPS and non-allelic psoriasis suggests that newer drugs targeting IL-12/23 and likely IL-17 may be of benefit.

Pathogenesis Considerations for non-IL-1 mediated conditions, EO-IBD

The loss of IL-10 signaling in mouse models and humans leads to an early-onset inflammatory bowel phenotype as the main organ manifestation with severe systemic inflammation, EO-IBD. These 'lack of function' mutations result in the loss of IL-10 signaling, as demonstrated by deficient signal transduction and activator of transcription-3 (STAT3) phosphorylation after stimulation with IL-10 and proves that loss of signaling of the anti-inflammatory cytokine IL-10 is sufficient to cause enterocolitis as the main clinical feature. Levels of TNF α and other inflammatory cytokines, including IL-1 α , IL-1 β and IL-6, are also increased in these patients. These data suggest a major role for IL-10 in counteracting commensal bacterial activation of the gut mucosa.

Early onset inflammatory bowel disease (EO-IBD)

Epidemiology and Genetics: Infantile IBD is caused by autosomal recessive mutations in IL-10R and IL-10 encoding genes (124). Four out of 9 patients with severe IBD presented with symptoms in the first year of life (124). In 2010, an autosomal recessive mutation in *IL10* gene in two unrelated patients with refractory early-onset IBD was found. Six disease-causing mutations in each of the IL-10 receptor genes (*IL10RA* and *IL10RB*) and two mutations in the IL-10 gene have been described.

Clinical Presentation and Diagnosis: Symptoms in patients with EO-IBD usually start in the first year of life, before 3 months of age, and include severe enterocolitis, characterized by bloody diarrhea, colonic abscesses, perianal fistulas, oral ulcers, failure to thrive and recurrent fever (124, 125). Musculoskeletal manifestations include acute recurrent arthritis of large joints, especially affecting knees (125). Remarkably, recurrent folliculitis has been observed in 75% of the patients (125). Recurrent infections, such as otitis media, bronchitis, pneumonia, septic arthritis and renal abscesses may indicate immunodeficiency in patients with EO-IBD (124, 125).

Treatment: Because EO-IBD is a severe disease and frequently refractory to standard immunosuppressants, hematopoietic stem cell transplantation (HSCT) has been proposed as a curative treatment (126). HSCT was performed in 9 out of the 29 patients with described IL-10 deficiency and complete clinical remission was achieved in all but one of the patients (125, 126).

Many of the primary immunodeficiencies present with infections but also with features of autoimmunity or autoinflammation. Recently conditions with prominent fever episodes that also present with immunodeficiencies were described, thus illustrating that an immune defect may have different effects in different cell types (127, 128).

CONCLUDING REMARKS – SYNOPSIS

An underlying theme in the pathogenesis of monogenic autoinflammatory diseases is an excessive sensing by altered PRR pathways that is even confirmed by the recognition of novel diseases. The excessive/increased extracellular or intracellular PRR response can be triggered by abnormally increased metabolites that umulate in the cell/ tissue (i.e CANDLE, and possibly Majeed and HIDS), or by mutations in sensors leading to constitutive over-activation (as in CAPS and PGA), or through variants in the associated mediator cytokine pathways that lead to their amplification and inability to downregulate an inflammatory disease pathway (as in DIRA and DITRA).

Lastly, the altered immune sensor function can be in non-hematopoietic cells. Gain-offunction mutations affecting NFkB mediated signaling in keratinocytes lead to chronic pustular skin lesions and to the subsequent recruitment of hematopoietic cells to the site. Thus, dysregulation in inflammatory pathways in non-hematopoietic cells can explain organ specificity. The study of sterile inflammation in patients with autoinflammatory syndromes does not fail to surprise us with new diseases that guide us to explore novel inflammatory pathways.

REFERENCES

1. Kastner DL, Aksentijevich I, Goldbach-Mansky R. Autoinflammatory disease reloaded: a clinical perspective. *Cell*. 2010; 140:784–790. [PubMed: 20303869]
2. Consortium FF. A candidate gene for familial Mediterranean fever. *Nat Genet*. 1997; 17:25–31. [PubMed: 9288094]

3. Consortium TIF. 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]
4. McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, Mansfield E, Gadina M, Karenko L, Pettersson T, McCarthy J, Frucht DM, Aringer M, Torosyan Y, Teppo AM, Wilson M, Karaarslan HM, Wan Y, Todd I, Wood G, Schlimgen R, Kumarajeewa TR, Cooper SM, Vella JP, Amos CI, Mulley J, Quane KA, Molloy MG, Ranki A, Powell RJ, Hitman GA, O'Shea JJ, Kastner DL. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell*. 1999; 97:133–144. [PubMed: 10199409]
5. Drenth JP, Cuisset L, Grateau G, Vasseur C, van de Velde-Visser SD, de Jong JG, Beckmann JS, van der Meer JW, Delpech M. Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. *Nat Genet*. 1999; 22:178–181. [PubMed: 10369262]
6. Frenkel J, Houten SM, Waterham HR, Wanders RJ, Rijkers GT, Kimpfen JL, Duran R, Poll-The BT, Kuis W. Mevalonate kinase deficiency and Dutch type periodic fever. *Clin Exp Rheumatol*. 2000; 18:525–532. [PubMed: 10949735]
7. Houten SM, Kuis W, Duran M, de Koning TJ, van Royen-Kerkhof A, Romeijn GJ, Frenkel J, Dorland L, de Barse MM, Huijbers WA, Rijkers GT, Waterham HR, Wanders RJ, Poll-The BT. Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinaemia D and periodic fever syndrome. *Nat Genet*. 1999; 22:175–177. [PubMed: 10369261]
8. Henderson C, Goldbach-Mansky R. Monogenic autoinflammatory diseases: new insights into clinical aspects and pathogenesis. *Curr Opin Rheumatol*. 2010; 22:567–578. [PubMed: 20671522]
9. Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008; 454:428–435. [PubMed: 18650913]
10. Janeway CA Jr, Medzhitov R. Innate immune recognition. *Annu Rev Immunol*. 2002; 20:197–216. [PubMed: 11861602]
11. Martinon F, Tschopp J. Inflammatory caspases: linking an intracellular innate immune system to autoinflammatory diseases. *Cell*. 2004; 117:561–574. [PubMed: 15163405]
12. 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; 29:301–305. [PubMed: 11687797]
13. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol*. 2009; 27:519–550. [PubMed: 19302047]
14. Ting JP, Williams KL. The CATERPILLER family: an ancient family of immune/apoptotic proteins. *Clin Immunol*. 2005; 115:33–37. [PubMed: 15870018]
15. Atianand MK, Fitzgerald KA. Molecular basis of DNA recognition in the immune system. *J Immunol*. 2013; 190:1911–1918. [PubMed: 23417527]
16. Bennett L, Palucka AK, Arce E, Cantrell V, Borvak J, Banchereau J, Pascual V. Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J Exp Med*. 2003; 197:711–723. [PubMed: 12642603]
17. Crow YJ. Type I interferonopathies: a novel set of inborn errors of immunity. *Ann N Y Acad Sci*. 2011; 1238:91–98. [PubMed: 22129056]
18. Mariathasan S, Newton K, Monack DM, Vucic D, French DM, Lee WP, Roose-Girma M, Erickson S, Dixit VM. Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. *Nature*. 2004; 430:213–218. [PubMed: 15190255]
19. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. *Mol Cell*. 2002; 10:417–426. [PubMed: 12191486]
20. Chae JJ, Komarow HD, Cheng J, Wood G, Raben N, Liu PP, Kastner DL. 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]
21. Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: host cell death and inflammation. *Nat Rev Microbiol*. 2009; 7:99–109. [PubMed: 19148178]

22. 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]
23. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, Ramanujan VK, Wolf AJ, Vergnes L, Ojcius DM, Rentsendorj A, Vargas M, Guerrero C, Wang Y, Fitzgerald KA, Underhill DM, Town T, Arditi M. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity.* 2012; 36:401–414. [PubMed: 22342844]
24. Lee GS, Subramanian N, Kim AI, Aksentijevich I, Goldbach-Mansky R, Sacks DB, Germain RN, Kastner DL, Chae JJ. The calcium-sensing receptor regulates the NLRP3 inflammasome through Ca^{2+} and cAMP. *Nature.* 2012; 492:123–127. [PubMed: 23143333]
25. Richards N, Schaner P, Diaz A, Stuckey J, Sheldon E, Wadhwa A, Gumucio DL. Interaction between pyrin and the apoptotic speck protein (ASC) modulates ASC-induced apoptosis. *J Biol Chem.* 2001; 276:39320–39329. [PubMed: 11498534]
26. Chae JJ, Cho YH, Lee GS, Cheng J, Liu PP, Feigenbaum L, Katz SI, Kastner DL. Gain-of-function Pyrin mutations induce NLRP3 protein-independent interleukin-1 β activation and severe autoinflammation in mice. *Immunity.* 2011; 34:755–768. [PubMed: 21600797]
27. Kuijk LM, Beekman JM, Koster J, Waterham HR, Frenkel J, Coffey PJ. HMG-CoA reductase inhibition induces IL-1 β release through Rac1/PI3K/PKB-dependent caspase-1 activation. *Blood.* 2008; 112:3563–3573. [PubMed: 18684863]
28. Mandey SH, Kuijk LM, Frenkel J, Waterham HR. A role for geranylgeranylation in interleukin-1 β secretion. *Arthritis Rheum.* 2006; 54:3690–3695. [PubMed: 17075828]
29. Lobito AA, Kimberley FC, Muppidi JR, Komarow H, Jackson AJ, Hull KM, Kastner DL, Screaton GR, Siegel RM. Abnormal disulfide-linked oligomerization results in ER retention and altered signaling by TNFR1 mutants in TNFR1-associated periodic fever syndrome (TRAPS). *Blood.* 2006; 108:1320–1327. [PubMed: 16684962]
30. Simon A, Park H, Maddipati R, Lobito AA, Bulua AC, Jackson AJ, Chae JJ, Ettinger R, de Koning HD, Cruz AC, Kastner DL, Komarow H, Siegel RM. Concerted action of wild-type and mutant TNF receptors enhances inflammation in TNF receptor 1-associated periodic fever syndrome. *Proc Natl Acad Sci U S A.* 2010; 107:9801–9806. [PubMed: 20457915]
31. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, van Royen-Kerkhoff A, Laxer R, Tedgard U, Cowen EW, Pham TH, Booty M, Estes JD, Sandler NG, Plass N, Stone DL, Turner ML, Hill S, Butman JA, Schneider R, Babyn P, El-Shanti HI, Pope E, Barron K, Bing X, Laurence A, Lee CC, Chapelle D, Clarke GI, Ohson K, Nicholson M, Gadina M, Yang B, Korman BD, Gregersen PK, van Hagen PM, Hak AE, Huizing M, Rahman P, Douek DC, Remmers EF, Kastner DL, Goldbach-Mansky R. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *N Engl J Med.* 2009; 360:2426–2437. [PubMed: 19494218]
32. Reddy S, Jia S, Geoffrey R, Lorier R, Suchi M, Broeckel U, Hessner MJ, Verbsky J. An autoinflammatory disease due to homozygous deletion of the IL1RN locus. *N Engl J Med.* 2009; 360:2438–2444. [PubMed: 19494219]
33. Donkor J, Zhang P, Wong S, O'Loughlin L, Dewald J, Kok BP, Brindley DN, Reue K. 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; 284:29968–29978. [PubMed: 19717560]
34. Fakas S, Qiu Y, Dixon JL, Han GS, Ruggles KV, Garbarino J, Sturley SL, Carman GM. Phosphatidate phosphatase activity plays key role in protection against fatty acid-induced toxicity in yeast. *J Biol Chem.* 2011; 286:29074–29085. [PubMed: 21708942]
35. Valdearcos M, Esquinas E, Meana C, Pena L, Gil-de-Gomez L, Balsinde J, Balboa MA. Lipin-2 reduces proinflammatory signaling induced by saturated fatty acids in macrophages. *J Biol Chem.* 2012; 287:10894–10904. [PubMed: 22334674]
36. Infefers: an online database for autoinflammatory mutations. Copyright. Available at <http://fmf.igh.cnrs.fr/ISSAID/infefers/> Accessed (date of access).
37. Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, Hofmann SR, Stein L, Russo R, Goldsmith D, Dent P, Rosenberg HF, Austin F, Remmers EF, Balow JE Jr, Rosenzweig S, Komarow H, Shoham NG, Wood G, Jones J, Mangra N, Carrero H, Adams BS, Moore TL, Schikler K, Hoffman H, Lovell DJ, Lipnick R, Barron K, O'Shea JJ, Kastner DL, Goldbach-

- Mansky R. 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 Rheum.* 2002; 46:3340–3348. [PubMed: 12483741]
38. Feldmann J, Prieur AM, Quartier P, Berquin P, Certain S, Cortis E, Teillac-Hamel D, Fischer A, de Saint Basile G. 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]
 39. Tanaka N, Izawa K, Saito MK, Sakuma M, Oshima K, Ohara O, Nishikomori R, Morimoto T, Kambe N, Goldbach-Mansky R, Aksentjevich I, de Saint Basile G, Neven B, van Gijn M, Frenkel J, Arostegui JI, Yague J, Merino R, Ibanez M, Pontillo A, Takada H, Imagawa T, Kawai T, Yasumi T, Nakahata T, Heike T. High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome: results of an International Multicenter Collaborative Study. *Arthritis Rheum.* 2011; 63:3625–3632. [PubMed: 21702021]
 40. Arostegui JI, Aldea A, Modesto C, Rua MJ, Arguelles F, Gonzalez-Ensenat MA, Ramos E, Rius J, Plaza S, Vives J, Yague J. Clinical and genetic heterogeneity among Spanish patients with recurrent autoinflammatory syndromes associated with the CIAS1/PYPAF1/NALP3 gene. *Arthritis Rheum.* 2004; 50:4045–4050. [PubMed: 15593220]
 41. Stych B, Dobrovolny D. Familial cold auto-inflammatory syndrome (FCAS): characterization of symptomatology and impact on patients' lives. *Curr Med Res Opin.* 2008; 24:1577–1582. [PubMed: 18423104]
 42. Dode C, Le Du N, Cuisset L, Letourneur F, Berthelot JM, Vaudour G, Meyrier A, Watts RA, Scott DG, Nicholls A, Granel B, Frances C, Garcier F, Edery P, Boulinguez S, Domergues JP, Delpech M, Grateau G. New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. *Am J Hum Genet.* 2002; 70:1498–1506. [PubMed: 11992256]
 43. Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum.* 2004; 50:607–612. [PubMed: 14872505]
 44. Muckle TJ, Wellsm. Urticaria, deafness, and amyloidosis: a new heredo-familial syndrome. *Q J Med.* 1962; 31:235–248. [PubMed: 14476827]
 45. Aganna E, Martinon F, Hawkins PN, Ross JB, Swan DC, Booth DR, Lachmann HJ, Bybee A, Gaudet R, Woo P, Feighery C, Cotter FE, Thome M, Hitman GA, Tschopp J, McDermott MF. Association of mutations in the NALP3/CIAS1/PYPAF1 gene with a broad phenotype including recurrent fever, cold sensitivity, sensorineural deafness, and AA amyloidosis. *Arthritis Rheum.* 2002; 46:2445–2452. [PubMed: 12355493]
 46. Goldbach-Mansky R, Dailey NJ, Canna SW, Gelabert A, Jones J, Rubin BI, Kim HJ, Brewer C, Zalewski C, Wiggs E, Hill S, Turner ML, Karp BI, Aksentjevich I, Pucino F, Penzak SR, Haverkamp MH, Stein L, Adams BS, Moore TL, Fuhlbrigge RC, Shaham B, Jarvis JN, O'Neil K, Vehe RK, Beitz LO, Gardner G, Hannan WP, Warren RW, Horn W, Cole JL, Paul SM, Hawkins PN, Pham TH, Snyder C, Wesley RA, Hoffmann SC, Holland SM, Butman JA, Kastner DL. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. *N Engl J Med.* 2006; 355:581–592. [PubMed: 16899778]
 47. Sibley CH, Plass N, Snow J, Wiggs EA, Brewer CC, King KA, Zalewski C, Kim HJ, Bishop R, Hill S, Paul SM, Kicker P, Phillips Z, Dolan JG, Widemann B, Jayaprakash N, Pucino F, Stone DL, Chapelle D, Snyder C, Butman JA, Wesley R, Goldbach-Mansky R. 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 Rheum.* 2012; 64:2375–2386. [PubMed: 22294344]
 48. 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; 37:145–152. [PubMed: 17136361]
 49. Hoffman HM, Throne ML, Amar NJ, Cartwright RC, Kivitz AJ, Soo Y, Weinstein SP. Long-term efficacy and safety profile of rilonacept in the treatment of cryopyrin-associated periodic

- syndromes: results of a 72-week open-label extension study. *Clin Ther.* 2012; 34:2091–2103. [PubMed: 23031624]
50. Goldbach-Mansky R, Shroff SD, Wilson M, Snyder C, Plehn S, Barham B, Pham TH, Pucino F, Wesley RA, Papadopoulos JH, Weinstein SP, Mellis SJ, Kastner DL. A pilot study to evaluate the safety and efficacy of the long-acting interleukin-1 inhibitor rilonacept (interleukin-1 Trap) in patients with familial cold autoinflammatory syndrome. *Arthritis Rheum.* 2008; 58:2432–2442. [PubMed: 18668591]
 51. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, Gitting X, Widmer A, Patel N, Hawkins PN. Use of canakinumab in the cryopyrin-associated periodic syndrome. *N Engl J Med.* 2009; 360:2416–2425. [PubMed: 19494217]
 52. Hoffman HM, Throne ML, Amar NJ, Sebai M, Kivitz AJ, Kavanaugh A, Weinstein SP, Belomestnov P, Yancopoulos GD, Stahl N, Mellis SJ. Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. *Arthritis Rheum.* 2008; 58:2443–2452. [PubMed: 18668535]
 53. Kuemmerle-Deschner JB, Hachulla E, Cartwright R, Hawkins PN, Tran TA, Bader-Meunier B, Hoyer J, Gattorno M, Gul A, Smith J, Leslie KS, Jimenez S, Morell-Dubois S, Davis N, Patel N, Widmer A, Preiss R, Lachmann HJ. Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes. *Ann Rheum Dis.* 2011; 70:2095–2102. [PubMed: 21859692]
 54. Neven B, Marvillet I, Terrada C, Ferster A, Boddaert N, Couloignier V, Pinto G, Pagnier A, Bodemer C, Bodaghi B, Tardieu M, Prieur AM, Quartier P. Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome. *Arthritis Rheum.* 2010; 62:258–267. [PubMed: 20039428]
 55. Stoffels M, Szperl A, Simon A, Netea MG, Plantinga TS, van Deuren M, Kamphuis S, Lachmann HJ, Cuppen E, Kloosterman WP, Frenkel J, van Diemen CC, Wijmenga C, van Gijn M, van der Meer JW. MEFV mutations affecting pyrin amino acid 577 cause autosomal dominant autoinflammatory disease. *Ann Rheum Dis.* 2013
 56. Heller H, Sohar E, Pras M. Ethnic distribution and amyloidosis in familial Mediterranean fever (FMF). *Pathol Microbiol (Basel).* 1961; 24:718–723.
 57. Ben-Chetrit E, Levy M. Familial Mediterranean fever. *Lancet.* 1998; 351:659–664. [PubMed: 9500348]
 58. Chae JJ, Aksentijevich I, Kastner DL. Advances in the understanding of familial Mediterranean fever and possibilities for targeted therapy. *Br J Haematol.* 2009; 146:467–478. [PubMed: 19466978]
 59. Langevitz P, Zemer D, Livneh A, Shemer J, Pras M. Protracted febrile myalgia in patients with familial Mediterranean fever. *J Rheumatol.* 1994; 21:1708–1709. [PubMed: 7799354]
 60. Gedalia A, Zamir S. Neurologic manifestations in familial Mediterranean fever. *Pediatr Neurol.* 1993; 9:301–302. [PubMed: 8216544]
 61. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, Tutar E, Ozen S, Topaloglu R, Yilmaz E, Arici M, Bakkaloglu A, Besbas N, Akpolat T, Dinc A, Erken E. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Medicine (Baltimore).* 2005; 84:1–11. [PubMed: 15643295]
 62. Touitou I, Sarkisian T, Medlej-Hashim M, Tunca M, Livneh A, Cattani D, Yalcinkaya F, Ozen S, Majeed H, Ozdogan H, Kastner D, Booth D, Ben-Chetrit E, Pugnere D, Michelon C, Seguret F, Gershoni-Baruch R. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. *Arthritis Rheum.* 2007; 56:1706–1712. [PubMed: 17469185]
 63. Lachmann HJ, Goodman HJ, Gilbertson JA, Gallimore JR, Sabin CA, Gillmore JD, Hawkins PN. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med.* 2007; 356:2361–2371. [PubMed: 17554117]
 64. 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; 314:1001–1005. [PubMed: 3515182]

65. Moser C, Pohl G, Haslinger I, Knapp S, Rowczenio D, Russel T, Lachmann HJ, Lang U, Kovarik J. Successful treatment of familial Mediterranean fever with Anakinra and outcome after renal transplantation. *Nephrol Dial Transplant*. 2009; 24:676–678. [PubMed: 19033248]
66. Hashkes PJ, Spalding SJ, Giannini EH, Huang B, Johnson A, Park G, Barron KS, Weisman MH, Pashinian N, Reiff AO, Samuels J, Wright DA, Kastner DL, Lovell DJ. Riloncept for colchicine-resistant or -intolerant familial Mediterranean fever: a randomized trial. *Ann Intern Med*. 2012; 157:533–541. [PubMed: 23070486]
67. Meinzer U, Quartier P, Alexandra JF, Hentgen V, Retornaz F, Kone-Paut I. Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. *Semin Arthritis Rheum*. 2011; 41:265–271. [PubMed: 21277619]
68. Ozen S, Bilginer Y, Aktay Ayaz N, Calguneri M. Anti-interleukin 1 treatment for patients with familial Mediterranean fever resistant to colchicine. *J Rheumatol*. 2011; 38:516–518. [PubMed: 21159830]
69. Mitroulis I, Skendros P, Oikonomou A, Tzioufas AG, Ritis K. The efficacy of canakinumab in the treatment of a patient with familial Mediterranean fever and longstanding destructive arthritis. *Ann Rheum Dis*. 2011; 70:1347–1348. [PubMed: 21345814]
70. Seyahi E, Ozdogan H, Celik S, Ugurlu S, Yazici H. Treatment options in colchicine resistant familial Mediterranean fever patients: thalidomide and etanercept as adjunctive agents. *Clin Exp Rheumatol*. 2006; 24:S99–S103. [PubMed: 17067437]
71. Ozcakar ZB, Yuksel S, Ekim M, Yalcinkaya F. Infliximab therapy for familial Mediterranean fever-related amyloidosis: case series with long term follow-up. *Clin Rheumatol*. 2012; 31:1267–1271. [PubMed: 22673790]
72. Hull KM, Drewe E, Aksentijevich I, Singh HK, Wong K, McDermott EM, Dean J, Powell RJ, Kastner DL. The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. *Medicine (Baltimore)*. 2002; 81:349–368. [PubMed: 12352631]
73. Jesus AA, Oliveira JB, Aksentijevich I, Fujihiro E, Carneiro-Sampaio MM, Duarte AJ, Silva CA. TNF receptor-associated periodic syndrome (TRAPS): description of a novel TNFRSF1A mutation and response to etanercept. *Eur J Pediatr*. 2008; 167:1421–1425. [PubMed: 18408954]
74. Aksentijevich I, Galon J, Soares M, Mansfield E, Hull K, Oh HH, Goldbach-Mansky R, Dean J, Athreya B, Reginato AJ, Henrickson M, Pons-Estel B, O'Shea JJ, Kastner DL. The tumor-necrosis-factor receptor-associated periodic syndrome: new mutations in TNFRSF1A, ancestral origins, genotype/phenotype studies, and evidence for further genetic heterogeneity of periodic fevers. *Am J Hum Genet*. 2001; 69:301–314. [PubMed: 11443543]
75. Bulua AC, Mogul DB, Aksentijevich I, Singh H, He DY, Muenz LR, Ward MM, Yarboro CH, Kastner DL, Siegel RM, Hull KM. Efficacy of etanercept in the tumor necrosis factor receptor-associated periodic syndrome: a prospective, open-label, dose-escalation study. *Arthritis Rheum*. 2012; 64:908–913. [PubMed: 22006113]
76. Gattorno M, Pelagatti MA, Meini A, Obici L, Barcellona R, Federici S, Buoncompagni A, Plebani A, Merlini G, Martini A. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. *Arthritis Rheum*. 2008; 58:1516–1520. [PubMed: 18438813]
77. Sacre K, Brihaye B, Lidove O, Papo T, Pocard MA, Cuisset L, Dode C. Dramatic improvement following interleukin 1beta blockade in tumor necrosis factor receptor-1-associated syndrome (TRAPS) resistant to anti-TNF-alpha therapy. *J Rheumatol*. 2008; 35:357–358. [PubMed: 18260167]
78. Quillinan N, Mannion G, Mohammad A, Coughlan R, Dickie LJ, McDermott MF, McGonagle D. Failure of sustained response to etanercept and refractoriness to anakinra in patients with T50M TNF-receptor-associated periodic syndrome. *Ann Rheum Dis*. 2011; 70:1692–1693. [PubMed: 21378401]
79. Cuisset L, Drenth JP, Simon A, Vincent MF, van der Velde Visser S, van der Meer JW, Grateau G, Delpech M. Molecular analysis of MVK mutations and enzymatic activity in hyper-IgD and periodic fever syndrome. *Eur J Hum Genet*. 2001; 9:260–266. [PubMed: 11313769]
80. Drenth JP, Haagsma CJ, van der Meer JW. Hyperimmunoglobulinemia D and periodic fever syndrome. The clinical spectrum in a series of 50 patients. *International Hyper-IgD Study Group. Medicine (Baltimore)*. 1994; 73:133–144. [PubMed: 8190036]

81. Ammouri W, Cuisset L, Rouaghe S, Rolland MO, Delpech M, Grateau G, Ravet N. Diagnostic value of serum immunoglobulinaemia D level in patients with a clinical suspicion of hyper IgD syndrome. *Rheumatology (Oxford)*. 2007; 46:1597–1600. [PubMed: 17804452]
82. Simon A, Drewe E, van der Meer JW, Powell RJ, Kelley RI, Stalenhoef AF, Drenth JP. Simvastatin treatment for inflammatory attacks of the hyperimmunoglobulinemia D and periodic fever syndrome. *Clin Pharmacol Ther*. 2004; 75:476–483. [PubMed: 15116060]
83. Bader-Meunier B, Florkin B, Sibilia J, Acquaviva C, Hachulla E, Grateau G, Richer O, Farber CM, Fischbach M, Hentgen V, Jegou P, Laroche C, Neven B, Lequerre T, Mathian A, Pellier I, Touitou I, Rabier D, Prieur AM, Cuisset L, Quartier P. Mevalonate kinase deficiency: a survey of 50 patients. *Pediatrics*. 2011; 128:e152–e159. [PubMed: 21708801]
84. van der Hilst JC, Bodar EJ, Barron KS, Frenkel J, Drenth JP, van der Meer JW, Simon A. Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome. *Medicine (Baltimore)*. 2008; 87:301–310. [PubMed: 19011501]
85. 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 Rheum*. 2003; 48:2645–2651. [PubMed: 13130485]
86. Rigante D, Ansuini V, Bertoni B, Pugliese AL, Avallone L, Federico G, Stabile A. Treatment with anakinra in the hyperimmunoglobulinemia D/periodic fever syndrome. *Rheumatol Int*. 2006; 27:97–100. [PubMed: 16871408]
87. Galeotti C, Meinzer U, Quartier P, Rossi-Semerano L, Bader-Meunier B, Pillet P, Kone-Paut I. Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency. *Rheumatology (Oxford)*. 2012; 51:1855–1859. [PubMed: 22740624]
88. Ferguson PJ, Chen S, Tayeh MK, Ochoa L, Leal SM, Pelet A, Munnich A, Lyonnet S, Majeed HA, El-Shanti H. Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). *J Med Genet*. 2005; 42:551–557. [PubMed: 15994876]
89. Majeed HA, Kalaawi M, Mohanty D, Teebi AS, Tunjekar MF, al-Gharbawy F, Majeed SA, al-Gazzar AH. Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet syndrome in two siblings. *J Pediatr*. 1989; 115:730–734. [PubMed: 2809904]
90. Ferguson PJ, El-Shanti HI. Autoinflammatory bone disorders. *Curr Opin Rheumatol*. 2007; 19:492–498. [PubMed: 17762617]
91. Jesus AA, Osman M, Silva CA, Kim PW, Pham TH, Gadina M, Yang B, Bertola DR, Carneiro-Sampaio M, Ferguson PJ, Renshaw BR, Schooley K, Brown M, Al-Dosari A, Al-Alami J, Sims JE, Goldbach-Mansky R, El-Shanti H. A novel mutation of IL1RN in the deficiency of interleukin-1 receptor antagonist syndrome: description of two unrelated cases from Brazil. *Arthritis Rheum*. 2011; 63:4007–4017. [PubMed: 22127713]
92. Herlin T, Fiirgaard B, Bjerre M, Kerndrup G, Hasle H, Bing X, Ferguson PJ. Efficacy of anti-IL-1 treatment in Majeed syndrome. *Ann Rheum Dis*. 2012
93. Miceli-Richard C, Lesage S, Rybojad M, Prieur AM, Manouvrier-Hanu S, Hafner R, Chamailard M, Zouali H, Thomas G, Hugot JP. CARD15 mutations in Blau syndrome. *Nat Genet*. 2001; 29:19–20. [PubMed: 11528384]
94. Kanazawa N, Okafuji I, Kambe N, Nishikomori R, Nakata-Hizume M, Nagai S, Fuji A, Yuasa T, Manki A, Sakurai Y, Nakajima M, Kobayashi H, Fujiwara I, Tsutsumi H, Utani A, Nishigori C, Heike T, Nakahata T, Miyachi Y. Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor kappaB activation: common genetic etiology with Blau syndrome. *Blood*. 2005; 105:1195–1197. [PubMed: 15459013]
95. Rose CD, Arostegui JI, Martin TM, Espada G, Scalzi L, Yague J, Rosenbaum JT, Modesto C, Cristina Arnal M, Merino R, Garcia-Consuegra J, Carballo Silva MA, Wouters CH. NOD2-associated pediatric granulomatous arthritis, an expanding phenotype: study of an international registry and a national cohort in Spain. *Arthritis Rheum*. 2009; 60:1797–1803. [PubMed: 19479837]
96. Rose CD, Martin TM, Wouters CH. Blau syndrome revisited. *Curr Opin Rheumatol*. 2011; 23:411–488. [PubMed: 21788900]

97. Arostegui JI, Arnal C, Merino R, Modesto C, Antonia Carballo M, Moreno P, Garcia-Consuegra J, Naranjo A, Ramos E, de Paz P, Rius J, Plaza S, Yague J. 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 Rheum.* 2007; 56:3805–3813. [PubMed: 17968944]
98. Wise CA, Gillum JD, Seidman CE, Lindor NM, Veile R, Bashardes S, Lovett M. Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. *Hum Mol Genet.* 2002; 11:961–969. [PubMed: 11971877]
99. 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; 273:5765–5770. [PubMed: 9488710]
100. Shoham NG, Centola M, Mansfield E, Hull KM, Wood G, Wise CA, Kastner DL. Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc Natl Acad Sci U S A.* 2003; 100:13501–13506. [PubMed: 14595024]
101. Yu JW, Fernandes-Alnemri T, Datta P, Wu J, Juliana C, Solorzano L, McCormick M, Zhang Z, Alnemri ES. Pyrin activates the ASC pyroptosome in response to engagement by autoinflammatory PSTPIP1 mutants. *Mol Cell.* 2007; 28:214–227. [PubMed: 17964261]
102. Wang D, Hoing S, Patterson HC, Ahmad UM, Rathinam VA, Rajewsky K, Fitzgerald KA, Golenbock DT. Inflammation in mice ectopically expressing human Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome-associated PSTPIP1 A230T mutant proteins. *J Biol Chem.* 2013; 288:4594–4601. [PubMed: 23293022]
103. Demidowich AP, Freeman AF, Kuhns DB, Aksentijevich I, Gallin JI, Turner ML, Kastner DL, Holland SM. Brief report: genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). *Arthritis Rheum.* 2012; 64:2022–2027. [PubMed: 22161697]
104. 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; 383:109–113. [PubMed: 8612775]
105. Ciechanover A. Intracellular protein degradation: from a vague idea through the lysosome and the ubiquitin-proteasome system and onto human diseases and drug targeting. *Neurodegener Dis.* 2012; 10:7–22. [PubMed: 22327508]
106. Goldberg AL. Functions of the proteasome: from protein degradation and immune surveillance to cancer therapy. *Biochem Soc Trans.* 2007; 35:12–17. [PubMed: 17212580]
107. Seifert U, Bialy LP, Ebstein F, Bech-Otschir D, Voigt A, Schroter F, Prozorovskii T, Lange N, Steffen J, Rieger M, Kuckelkorn U, Aktas O, Kloetzel PM, Kruger E. Immunoproteasomes preserve protein homeostasis upon interferon-induced oxidative stress. *Cell.* 2010; 142:613–624. [PubMed: 20723761]
108. Agarwal AK, Xing C, DeMartino GN, Mizrachi D, Hernandez MD, Sousa AB, Martinez de Villarreal L, dos Santos HG, Garg A. PSMB8 encoding the beta5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. *Am J Hum Genet.* 2010; 87:866–872. [PubMed: 21129723]
109. Arima K, Kinoshita A, Mishima H, Kanazawa N, Kaneko T, Mizushima T, Ichinose K, Nakamura H, Tsujino A, Kawakami A, Matsunaka M, Kasagi S, Kawano S, Kumagai S, Ohmura K, Mimori T, Hirano M, Ueno S, Tanaka K, Tanaka M, Toyoshima I, Sugino H, Yamakawa A, Tanaka K, Niikawa N, Furukawa F, Murata S, Eguchi K, Ida H, Yoshiura K. Proteasome assembly defect due to a proteasome subunit beta type 8 (PSMB8) mutation causes the autoinflammatory disorder, Nakajo-Nishimura syndrome. *Proc Natl Acad Sci U S A.* 2011; 108:14914–14919. [PubMed: 21852578]
110. Kitamura A, Maekawa Y, Uehara H, Izumi K, Kawachi I, Nishizawa M, Toyoshima Y, Takahashi H, Standley DM, Tanaka K, Hamazaki J, Murata S, Obara K, Toyoshima I, Yasutomo K. A mutation in the immunoproteasome subunit PSMB8 causes autoinflammation and lipodystrophy in humans. *J Clin Invest.* 2011; 121:4150–4160. [PubMed: 21881205]
111. Liu Y, Ramot Y, Torrelo A, Paller AS, Si N, Babay S, Kim PW, Sheikh A, Lee CC, Chen Y, Vera A, Zhang X, Goldbach-Mansky R, Zlotogorski A. Mutations in proteasome subunit beta

type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis Rheum.* 2012; 64:895–907. [PubMed: 21953331]

112. Livingston JH, Stivaros S, van der Knaap MS, Crow YJ. Recognizable phenotypes associated with intracranial calcification. *Dev Med Child Neurol.* 2013; 55:46–57. [PubMed: 23121296]
113. Nakajo A. Secondary hypertrophic osteoperiostosis with pernio. *J. Derm. Urol.* 1939; 45:77–86.
114. Nishimura N, Deki T, Kato S. Hypertrophic pulmonary osteoarthropathy with pernio-like eruption in the two families: report of the three cases. *Jpn. J. Derm. Venereol.* 1950; 60:136–141.
115. Megarbane A, Sanders A, Chouery E, Delague V, Medlej-Hashim M, Torbey PH. An unknown autoinflammatory syndrome associated with short stature and dysmorphic features in a young boy. *J Rheumatol.* 2002; 29:1084–1087. [PubMed: 12022327]
116. Garg A, Hernandez MD, Sousa AB, Subramanyam L, Martinez de Villarreal L, dos Santos HG, Barboza O. An autosomal recessive syndrome of joint contractures, muscular atrophy, microcytic anemia, and panniculitis-associated lipodystrophy. *J Clin Endocrinol Metab.* 2010; 95:E58–E63. [PubMed: 20534754]
117. Torrello A, Patel S, Colmenero I, Gurbindo D, Lendinez F, Hernandez A, Lopez-Robledillo JC, Dadban A, Requena L, Paller AS. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. *J Am Acad Dermatol.* 2010; 62:489–495. [PubMed: 20159315]
118. Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, Zribi J, Bal E, Cluzeau C, Chrabieh M, Towne JE, Douangpanya J, Pons C, Mansour S, Serre V, Makni H, Mahfoudh N, Fakhfakh F, Bodemer C, Feingold J, Hadj-Rabia S, Favre M, Genin E, Sahbatou M, Munnich A, Casanova JL, Sims JE, Turki H, Bachelez H, Smahi A. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med.* 2011; 365:620–628. [PubMed: 21848462]
119. Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, Knight J, Spain SL, Nestle FO, Burden AD, Capon F, Trembath RC, Barker JN. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *Am J Hum Genet.* 2011; 89:432–437. [PubMed: 21839423]
120. Fuchs-Telem D, Sarig O, van Steensel MA, Isakov O, Israeli S, Nussbeck J, Richard K, Winpenning V, Vernooij M, Shomron N, Uitto J, Fleckman P, Richard G, Sprecher E. Familial pityriasis rubra pilaris is caused by mutations in CARD14. *Am J Hum Genet.* 2012; 91:163–170. [PubMed: 22703878]
121. Jordan CT, Cao L, Roberson ED, Pierson KC, Yang CF, Joyce CE, Ryan C, Duan S, Helms CA, Liu Y, Chen Y, McBride AA, Hwu WL, Wu JY, Chen YT, Menter A, Goldbach-Mansky R, Lowes MA, Bowcock AM. PSORS2 is due to mutations in CARD14. *Am J Hum Genet.* 2012; 90:784–795. [PubMed: 22521418]
122. Blumberg H, Dinh H, Trueblood ES, Pretorius J, Kugler D, Weng N, Kanaly ST, Towne JE, Willis CR, Kuechle MK, Sims JE, Peschon JJ. Opposing activities of two novel members of the IL-1 ligand family regulate skin inflammation. *J Exp Med.* 2007; 204:2603–2614. [PubMed: 17908936]
123. Medlej-Hashim M, Delague V, Chouery E, Salem N, Rawashdeh M, Lefranc G, Loiselet J, Megarbane A. Amyloidosis in familial Mediterranean fever patients: correlation with MEFV genotype and SAA1 and MICA polymorphisms effects. *BMC Med Genet.* 2004; 5:4. [PubMed: 15018633]
124. Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schaffer AA, Noyan F, Perro M, Diestelhorst J, Allroth A, Murugan D, Hatscher N, Pfeifer D, Sykora KW, Sauer M, Kreipe H, Lacher M, Nustede R, Woellner C, Baumann U, Salzer U, Koletzko S, Shah N, Segal AW, Sauerbrey A, Buderus S, Snapper SB, Grimbacher B, Klein C. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med.* 2009; 361:2033–2045. [PubMed: 19890111]
125. Kotlarz D, Beier R, Murugan D, Diestelhorst J, Jensen O, Boztug K, Pfeifer D, Kreipe H, Pfister ED, Baumann U, Puchalka J, Bohne J, Egritas O, Dalgic B, Kolho KL, Sauerbrey A, Buderus S, Gungor T, Enninger A, Koda YK, Guariso G, Weiss B, Corbacioglu S, Socha P, Uslu N, Metin A, Wahbeh GT, Husain K, Ramadan D, Al-Herz W, Grimbacher B, Sauer M, Sykora KW, Koletzko S, Klein C. Loss of interleukin-10 signaling and infantile inflammatory bowel disease:

- implications for diagnosis and therapy. *Gastroenterology*. 2012; 143:347–355. [PubMed: 22549091]
126. Engelhardt KR, Shah N, Faizura-Yeop I, Kocacik Uygun DF, Frede N, Muise AM, Shteyer E, Filiz S, Chee R, Elawad M, Hartmann B, Arkwright PD, Dvorak C, Klein C, Puck JM, Grimbacher B, Glocker EO. Clinical outcome in IL-10-and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. *J Allergy Clin Immunol*. 2012
127. Zhou Q, Lee GS, Brady J, Datta S, Katan M, Sheikh A, Martins MS, Bunney TD, Santich BH, Moir S, Kuhns DB, Long Priel DA, Ombrello A, Stone D, Ombrello MJ, Khan J, Milner JD, Kastner DL, Aksentijevich I. A hypermorphic missense mutation in PLCG2, encoding phospholipase Cgamma2, causes a dominantly inherited autoinflammatory disease with immunodeficiency. *Am J Hum Genet*. 2012; 91:713–720. [PubMed: 23000145]
128. Boisson B, Laplantine E, Prando C, Giliani S, Israelsson E, Xu Z, Abhyankar A, Israel L, Trevejo-Nunez G, Bogunovic D, Cepika AM, Macduff D, Chrabieh M, Hubeau M, Bajolle F, Debre M, Mazzolari E, Vairo D, Agou F, Virgin HW, Bossuyt X, Rambaud C, Facchetti F, Bonnet D, Quartier P, Fournet JC, Pascual V, Chaussabel D, Notarangelo LD, Puel A, Israel A, Casanova JL, Picard C. Immunodeficiency, autoinflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency. *Nat Immunol*. 2012; 13:1178–1186. [PubMed: 23104095]

Key points

- Monogenic autoinflammatory diseases are caused by single-gene defects in innate immune regulatory pathways. They present in childhood with sterile inflammation and can mimic infections.
- Gain of function mutations in *NLRP3/CIAS1*, encoding the first “intracellular danger sensor” identified in humans, cause the clinical spectrum of the cryopyrinopathies and link “danger recognition” to the activation of the proinflammatory “alarm” cytokine IL-1.
- The pivotal role of IL-1 in the cryopyrinopathies was confirmed in clinical studies using IL-1 blocking therapies and encouraged their use in the classic periodic fever syndromes, FMF, TRAPS, and HIDS.
- Novel autoinflammatory conditions with poor responses to IL-1 blocking therapies include the proteasome-associated autoinflammatory syndromes (PRAAS), the deficiency of IL-36 receptor antagonist (DITRA), CARD14 mediated psoriasis (CAMPS) and early-onset IBD, and suggest a role of cytokine dysregulation beyond IL-1.
- Early diagnosis of these syndromes is essential because effective therapies, particularly for the IL-1 mediated conditions, can change patients’ lives and disease outcomes.
- An emerging theme in our understanding of the pathogenesis of exaggerated sterile inflammatory responses in autoinflammatory syndromes converges on dysregulation in intracellular innate immune sensing, and on the amplification of pro-inflammatory cytokine circuits that cannot be downregulated.

Components of an inflammatory response

Figure 1. Components of an inflammatory response

An immune response is triggered by exogenous or endogenous triggers that are sensed by a molecular sensor, a pattern recognition receptor (PRR) that can be located on the cell surface or in the cytoplasm. A triggering event is linked to the activation of mediators that lead to the stimulation and secretion of cytokines and chemokines which lead to the recruitment of immune cells into the tissue and the coordination of an immune response. The immune response is often tissue specific and may explain the difference in organ manifestations in autoinflammatory diseases. Some mutations that lead to cytokine dysregulation also influence cell growth and differentiation and/or cell death often in a cell specific manner

Figure 2. Proposed mechanisms of activation of proinflammatory 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 adapter molecules apoptotic speck protein (ASC) and CARDINAL to form an active catalytic complex with two pro-caspase-1 molecules. Via autocatalysis, this complex generates active caspase-1, which cleaves inactive pro-interleukin(IL)-1 β into its active form, IL-1 β . **B. Familial Mediterranean fever (FMF).** (b.1). Wild-type pyrin can inhibit inflammasome activation by direct binding to caspase-1. Mutated pyrin cannot exert its inhibitory effect on the inflammasome, leading to unopposed inflammasome activation. (b.2) Wild-type pyrin can also interact directly with ASC forming the "pyrin inflammasome", which is activated in the presence of FMF-causing mutations. **C. Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS).** TNFR1 molecules are transported from endoplasmic reticulum (ER) to the Golgi and then to the cell surface. Wild type TNFR1 complexes are bound to extracellular TNF, leading to NF- κ B activation. Receptor cleavage from the cell surface abrogates receptor signaling and the soluble receptor can buffer soluble TNF. Mutated TNFR1 (which causes TRAPS) is misfolded and cannot be transported to the cell surface. Misfolded TNFR1 is sequestered in the ER, where it may lead to abnormal signaling through increased mitochondrial reactive oxygen species (ROS) production. **D. Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS).** Mevalonate kinase, a

critical enzyme in the biosynthesis of sterol and non-sterol isoprenoids, catalyzes the conversion of mevalonate to mevalonate phosphate. In HIDS, activity of this enzyme is reduced, resulting in a decreased concentration of mevalonate phosphate, geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP), leading to decreased activity of geranylgeranyltransferase and impaired geranylgeranylation of a number of proteins. Through an unknown mechanism, the reduced geranylgeranylation would lead to an increased pro-caspase-1 activation and consequent caspase-1 activation with resulting overproduction of IL-1 β . **E.** Deficiency of the interleukin-1 receptor antagonist (DIRA). Deficiency of IL-1Ra leads to unopposed IL-1 α and IL-1 β signaling. **F.** Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE). Proteasomes are an ATP dependent protein degradation system that targets intracellular polyubiquitinated proteins derived from self structures or foreign structures for proteolytic destruction. Patients who are homozygous for *PSMB8* mutations show various assembly defects, with impaired proteolytic activity which is proposed to lead to an increase in, i.e polyubiquitylation of defective ribosomal products (DRiPs) which might umulate in tissues from these patients and induce an increased inflammatory response. Serum cytokine analysis in CANDLE and gene expression profiling identified the IFN signaling pathway as the most differentially regulated cytokine pathway. **G.** CARD14 mediated psoriasis (CAMPS). Mutated CARD14 protein is mainly expressed in keratinocytes and leads to NF- κ B activation and increased chemokine production. **H.** Deficiency of the interleukin-36 receptor antagonist (DITRA). Deficiency of IL-36Ra in the keratinocyte leads to unopposed IL-36 signaling. **I.** Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA). Wild-type PSTPIP1, a regulatory molecule of the NLRP3 inflammasome, binds to pyrin. Mutated PSTPIP1 is proposed to not dissociate from its binding to pyrin, leading to uninhibited inflammasome and “pyrin inflammasome” activities.

ASC (apoptotic speck protein); BCL10 (B-cell lymphoma/leukemia 10); CARD14 (caspase recruitment domain-containing protein 14); DAMPs (damage associated molecular patterns); IFN (interferon); IL-1 β (interleukin-1 β); IL-1 α/β (interleukin-1 α/β); IL-1Ra (interleukin-1 receptor antagonist); IL-6 (interleukin-6); IL-36 (interleukin-36); IL36Ra (interleukin-36 receptor antagonist); IFN γ - inducible protein 10 (IP-10); JAK1 (Janus kinase 1); JAK2 (Janus kinase 2); MALT1 (mucosa-associated lymphoid tissue lymphoma translocation protein 1); MAPK (mitogen-activated protein kinase); PAMPs (pathogen associated molecular patterns)p-JNK (phosphorylated-JNK); ROS (reactive oxygen species); STAT1 (signal transducer and activator of transcription 1); TNFR (tumor necrosis factor receptor); TNF (tumor necrosis factor); TYK2 (tyrosine kinase 2).

Figure 3.

- A. Urticarial rash in a patient with CAPS - Muckle-Wells syndrome
- B. Severe hydrocephalus and cerebral atrophy in neonatal-onset multisystem inflammatory disease (NOMID)
- C. Papilledema in NOMID
- D. Patellar overgrowth in NOMID
- E. Knee MRI showing cartilaginous proliferation and widening of the growth plate of the distal femur in a patient with CAPS-NOMID
- F. Pustulosis in deficiency of the interleukin-1 receptor antagonist (DIRA)
- G. Metaphyseal osteolytic lesions in distal and proximal tibia in a very young DIRA patient, periosteal elevation is also seen
- H. Bony overgrowth in a DIRA patient (rare)
- I. Widening of multiple ribs (asterisk) and clavicles (arrows) in DIRA osteomyelitis
- J. Chest deformities in DIRA
- K. Block vertebral formation following osteolytic vertebral lesions in DIRA
- L. Enhancement in the right post-central and pre-central gyrus in a patient with vasculitis in DIRA
- M. Generalized psoriasis in CARD14 mediated psoriasis (CAMPS)
- N. Anterior synechiae and cataract with chronic uveitis in a patient with Blau syndrome

- O. Sagittal image of a fat suppressed T2 weighted sequence showing synovial thickening and enhancement with moderate fluid in the right elbow joint in pyogenic arthritis
- P. Extensive pyoderma gangrenosum lesion in a patient with pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome.
- Q. Finger swelling in chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE)
- R. Erythematous annular and nodular rash in CANDLE syndrome
- S. Characteristic facial lipodystrophy (red arrows) in CANDLE syndrome
- T. Basal ganglia calcifications in CANDLE syndrome
- U. Myositis in CANDLE syndrome

Table 1

Demographic, genetic and clinical features of the monogenic autoinflammatory diseases (AID)

		Inheritance / Ethnic Distribution	Gene / Protein	Clinical Manifestations					Treatment		
				Skin	CNS	Eye	Inner ear	MSK		Systemic inflammation	
IL-1-Mediated Diseases	Cryopyrinopathies	FCAS	<i>NLRP3</i> (1q44) / Cryopyrin (NLRP3)	Cold-induced neutrophilic urticaria	Headache	Conjunctivitis	None	Myalgia, arthralgia	Fever, ↑ acute phase reactants <i>Complications:</i> Amyloidosis is uncommon (~2%)	Anti-IL1 agents: anakinra, canakinumab, rilonacept (only for FCAS and MWS)	
		MWS	<i>NLRP3</i> (1q44) / Cryopyrin (NLRP3)	Neutrophilic urticaria	Headache	Conjunctivitis, episcleritis, optic disk edema <i>Complications:</i> corneal opacification	Cochlear edema <i>Complications:</i> SNHL, hearing loss	Myalgia, arthralgia, oligo-arthritis	Fever, ↑ acute phase reactants, occasional lymphadenopathy Pericarditis, pleuritis and peritonitis are rare <i>Complications:</i> Amyloidosis is observed in ~25% of cases. Peritoneal adhesions		
		NOMID	<i>NLRP3</i> (1q44) / Cryopyrin (NLRP3)	Neutrophilic urticaria	Headache, chronic aseptic meningitis <i>Complications:</i> Developmental delay	Conjunctivitis, Uveitis <i>Complications:</i> Papilledema, progressive vision loss, corneal opacification	Cochlear edema <i>Complications:</i> SNHL, hearing loss	Arthralgia and chronic arthritis <i>Complications:</i> epiphyseal overgrowth, joint contractures	Fever, ↑ acute phase reactants, occasional lymphadenopathy, hepatosplenomegaly Pericarditis, pleuritis and peritonitis are rare. <i>Complications:</i> Amyloidosis in untreated patients who achieve adulthood	Daily oral colchicine, anti-IL1 agents (anakinra, rilonacept and canakinumab)	
	Classic Periodic Fever Syndromes	FMF	AR or AD / Jewish, Arab, Armenian, Turkish, Italian	<i>MEFV</i> (16p13.3) / Pyrin	Erysipelas-like erythema (ELE)	Aseptic meningitis (rare)	Uncommon	None	Exercise-induced myalgia, protracted febrile myalgia, arthritis <i>Complications:</i> sacroiliitis, joint anhrrosis, hip arthritis & erosions	Fever and ↑ acute phase reactants Serositis: peritonitis, pleuritis, pericarditis, epididymitis <i>Complications:</i> Peritoneal adhesions Amyloidosis risk varies according with genotype and environment.	
		TRAPS	AD / Broad ethnic distribution Originally Irish/ Scottish	<i>TNFRSF1A</i> (12p13) / 55kDaTNF receptor	Migratory erythema often associated myalgia, ELE	Headache; aseptic meningitis (rare)	Periorbital edema, conjunctivitis Uveitis	None	Migratory myalgia, arthralgia, non-erosive arthritis	Fever, ↑ acute phase reactants and occasional lymphadenopathy Serositis: peritonitis, pleuritis, pericarditis, scrotal pain <i>Complications:</i> Amyloidosis is observed in ~14% of cases. Peritoneal adhesions	Etanercept, anti-IL1 agents (anakinra)
		HIDS	AR / Dutch, Northern European	<i>MVK</i> (12q24) / Mevalonate kinase	Maculo-papular purpuric exanthema, aphthous oral ulcers	Uncommon	Uncommon	Uncommon	None	Arthralgia, non-erosive acute polyarthritis; myalgia (rare)	Fever, ↑ acute phase reactants, cervical lymphadenopathy hepatosplenomegaly Peritonitis is uncommon. Pericarditis is rare.

			Clinical Manifestations						Treatment
			Eye	Inner ear	MSK	Systemic inflammation			
Autoinflammatory Bone Diseases	DIRA	AR / Newfoundland, Puerto Rican, Brazilian, Dutch, Palestinian	IL1RN (2q14.2) / IL1RA	Pustular dermatitis	Rare CNS vasculitis <i>Complications:</i> Rare encephalomalacia	Conjunctivitis is rare	None	Recurrent multifocal aseptic osteomyelitis peristostitis <i>Complications:</i> Vertebral and odontoid destruction	Anti-IL1 agents (anakinra)
		Majeed	LPN2 (18p11.31) / Lipin2	Pustular dermatoses	Uncommon	Uncommon	Uncommon	Hematologic manifestations: dyserythropoietic anemia	
	PRAAS	CANDLE	AR / Originally Japan Any race or ethnicity	PSMB8 (6p21.3) /	Nodular exanthema, panniculitis, lipodystrophy, periorbital erythema	Aseptic meningitis <i>Complications:</i> Basal ganglia calcification	Conjunctivitis	None	Arthralgias, arthritis, myalgias, myositis <i>Complications:</i> Joint contractures
NF-κB Mediated Diseases	CAMPS	AD	CARD14/CARD14	Plaque or pustular psoriasis	Uncommon	Uncommon	None	Arthritis in 30% of patients	MTX, CsA, anti-TNF agents, psoriasis medications
	DITRA	AR / Originally Tunisia - England	IL36RN (2q14) / IL36RA	Generalized pustular psoriasis Oral mucosa involvement	Uncommon	Uncommon	None	Uncommon	Cs, CsA, retinoids, anti-TNF agents
Other Pathogenesis Pathways	PAPA	AD / Originally Caucasian, any ethnicity	PSTPIP1 (12q24-q25.1) / PSTPIP1	Pyoderma gangrenosum pathergy, skin abscesses, cystic acne, hidradenitis	Uncommon	Uncommon	None	Deforming aseptic pyogenic arthritis <i>Complications:</i> Joint destruction Impaired QOL related to physical disability	CS, anti-TNF agents, anti-IL1 agents (anakinra)
	PGA	AD, sporadic / Originally Caucasian but other ethnicities also seen	NOD2 / CARD15 (16q12.1-13)	Ilethysis-like exanthema non-casecting granulomata	Rare, central neuropathy, stroke, and hearing loss	Chronic ivetitis, cataract, glaucoma, blindness, <i>Complications:</i> Blindness	None	Polyarthritis, hypertrophic tenosynovitis	CS, methotrexate, azathioprine, cyclosporine, anti-TNF agents
	EO-IBD	AR / Originally Lebanese and Turkish	IL10 (1q31-q32); IL10RA (11q23); IL10RB (21q22.11) / IL-10; IL-10RA / IL-10RB	Folliculitis	Uncommon	Uncommon	Uncommon	None	Arthritis

FMF: familial Mediterranean fever; TRAPS: TNF receptor associated periodic syndrome; HIDS: hyperimmunoglobulinemia D syndrome with periodic fever; CAPS: cryopyrin associated periodic syndrome; NOMID: neonatal-onset multisystem inflammatory disease; MWS: Muckle-Wells syndrome; FCAS: familial cold autoinflammatory syndrome; PGA: pediatric granulomatous arthritis; DIRA: deficiency of interleukin 1 receptor antagonist; PAPA: pyogenic arthritis, pyoderma gangrenosum and acne syndrome; EO-IBD: early-onset inflammatory bowel disease; DITRA: deficiency of interleukin 36 receptor antagonist; CAMP5: CARD14 mediated psoriasis; PRAAS: proteasome associated autoinflammatory syndromes;
AD: autosomal dominant; AR: autosomal recessive, CNS: central nervous system; MSK: musculoskeletal; SNHL: sensorineural hearing loss, IVIG: intravenous immunoglobulin; NSAIDs: non-steroidal anti-inflammatory drugs; CS: corticosteroids; CsA: cyclosporine; AZA: azathioprine; MTX: methotrexate; TAC: tacrolimus; HSCT: hematopoietic stem cell transplantation; JAK: Janus Kinase; TNF: tumor necrosis factor; Acute phase reactants: C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Table 2

Known and putative proinflammatory mechanisms of cryopyrin associated periodic syndromes (CAPS); familial Mediterranean fever (FMF); tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS); hyperimmunoglobulinemia D with periodic fever syndrome (HIDS); deficiency of the interleukin-1 receptor antagonist (DIRA); Majeed syndrome; chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE); CARD14 mediated psoriasis (CAMPs); deficiency of the interleukin-36 receptor antagonist (DITRA); pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome and pediatric granulomatous arthritis (PGA). CNS (central nervous system); DAMPs (damage associated molecular patterns); ERK (extracellular signal-regulated kinases); GI (gastrointestinal tract); IFN (interferon); IL-1 β (interleukin 1 β); IL-1 (interleukin 1 α and β); IL-1Ra (interleukin 1 receptor antagonist); IL-36 (interleukin 36); MAPK (mitogen-activated protein kinase); NLRs [nucleotide oligomerization domain (NOD)-like receptors]; PAMPs (pathogen associated molecular patterns); p-JNK (phosphorylated-JNK); RIG-I-like (retinoic acid-inducible gene 1); RIP2 (receptor interacting protein kinase 2); ROS (reactive oxygen species); TLR (toll-like receptor); TNFR (tumor necrosis factor receptor); TNF (tumor necrosis factor).

Disease Gene/Protein	Trigger	Sensor	Mediator pathway / Cytokine amplification loop	Target organ	Therapeutic Targets
CAPS <i>NLRP3</i> / Cryopyrin	TLR stimulants (PAMPs), NLR stimulants (DAMPs), Cold in FCAS pts.	Constitutive <i>NLRP3</i> inflammasome activation	IL-1 β secretion is increased	Skin, CNS, eye, inner ear, joints and bone	IL-1, IL-1 β , (future targets caspase-1, Inflammasome activity)
FMF <i>MEFV</i> / Pyrin	Stress (DAMPs), Infection (PAMPs)	Increased/constitutive pyrin inflammasome function, decreased <i>NLRP3</i> inhibition	IL-1 β secretion is increased, neutrophil activation	Skin, joints, muscles, serositis, CNS, and eye	IL-1
TRAPS <i>TNFRSF1A</i> / 55kDaTNF receptor	Stress (DAMPs), Infections (PAMPs)	TLRs, NLRs, s other	Increase ROS production due to trapped mutant TNFR and MAPK activation (p-p38, p-JNK)	Skin, eye, joints, serositis, CNS	IL-1 and TNF
HIDS <i>MVK</i> / Mevalonate kinase	Possible accumulation of non isoprenylated protein?, vaccinations, infections, stress	NLRP3 inflammasome?	Increase in NLRP3 dependent IL-1 production (largely unknown mechanisms)	Skin, joints, muscle, GI, CNS, eye	IL-1
DIRA <i>IL1RN</i> / IL1RA	Stress (DAMPs), Infections (PAMPs), mechanical stress on skin	TLRs, NLRs, other?	Unopposed IL-1 α β signaling	Skin, bone, CNS, and eye	IL-1
Majeed <i>LPIN2</i> / Lipin2	Accumulation of fatty acids that may trigger <i>NLRP3</i> inflammasome?	NLRP3 inflammasome?	Increased IL-1 production?	Skin, bone, and bone marrow	IL-1 mediated (?)
CANDLE <i>PSMB8</i> /β5i	Accumulation of polyubiquitinated proteins, other?	Intracellular receptor coupled to IFN response gene stimulation?	IFN mediated and other including pERK	Skin, joints, muscle, GI, eye, adipose tissue, CNS, and bone marrow	IFN + unknown pathways
CAMPs <i>CARD14</i> / <i>CARD14-CARMA2</i>	PAMPs, mechanical irritation, infection	TLRs, RIG-I-like, other?	Constitutive NFKB activation in keratinocytes	Skin and joints	NF-κB + unknown pathways

Disease Gene/Protein	Trigger	Sensor	Mediator pathway / Cytokine amplification loop	Target organ	Therapeutic Targets
DITRA <i>IL36RN</i> / <i>IL36RA</i>	Infections (PAMPs), Stress (DAMPs)	TLR, NLR, other	Unopposed IL-36 signaling	Skin	(future target IL-36) + unknown pathways
PAPA <i>PSTPIP1</i> / <i>PSTPIP1</i>	Skin puncture, acne lesion, unknown	TLRs, NLRs, other	NLRP3 dependent IL-1 release and unknown	Skin, joints	IL-1 (arthritis) + unknown pathways
PGA <i>NOD2</i> / <i>CARD15</i>	Stress (DAMPs), Infections (PAMPs)	Constitutive NOD2 and NFKB activation	RIP2 kinase mediated NFKB activation	Skin, eye, joints, CNS	NF-κB + unknown pathways
EO-IBD <i>IL10RA</i> , <i>IL10RB</i> , <i>IL10</i> / <i>IL10RA</i> , <i>IL10RB</i> , <i>IL10</i>	Commensal bacteria	TLRs, NLRs in colon, other	Decreased antinflammatory signaling through IL-10 receptor	GI tract, colon, skin	Reconstitute IL-10 signaling

In blue are the primary defects induced by the genetic mutation.