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The spectrum of autoinflammatory diseases: recent bench to bedside observations

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Abstract

Purpose of review—The autoinflammatory diseases are a group of conditions that include the hereditary fever syndromes, and result from upregulated innate immune responses. The discovery of the genetic basis for these conditions led to the description of novel intracellular receptors for infectious and noninfectious danger signals. This article focuses on recent progress in our understanding of autoinflammatory syndromes, and how insights into these conditions have triggered the exploration of the role of innate immunity in common rheumatologic diseases.

Recent findings—New models for the pathogenesis of several autoinflammatory syndromes have been proposed, including the role of pyrin and cryopyrin in regulating inflammation. Robust evidence has emerged that IL-1 β oversecretion is pivotal in cryopyrin-associated periodic syndromes, and that IL-1 inhibition ameliorates the clinical features of these syndromes. Monosodium urate crystals stimulate IL-1 β secretion via cryopyrin, which led to the addition of gout to the spectrum of autoinflammatory diseases.

Summary—Advances in our understanding of the autoinflammatory diseases have led to renewed interest in the innate immune system, and its role in the pathogenesis of more common rheumatic diseases.

Keywords

cryopyrin-associated periodic syndromes; familial Mediterranean fever; hyperimmunoglobulinemia-D with periodic fever syndrome; inflammasome; pyrin; tumor necrosis factor receptor-associated periodic syndrome

Introduction

The concept of autoinflammatory diseases was introduced in the 1990s [1]. This concept encompasses a group of hereditary recurrent fever syndromes characterized by recurrent episodes of inflammation without evidence of the typical features of autoimmune diseases

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such as high titer autoantibodies or autoreactive T-cells [1]. In clinical practice, many patients who are eventually diagnosed with a hereditary recurrent fever syndrome are initially diagnosed as having ‘fever of unknown origin’, after an extensive workup excludes infections and malignancies. The initially described hereditary fever syndromes include familial Mediterranean fever (FMF) (Online Mendelian Inheritance in Man, OMIM 249100) (website: <http://www.ncbi.nlm.nih.gov>), the cryopyrin-associated periodic syndromes (CAPS), namely, familial cold autoinflammatory syndrome (FCAS) (OMIM 120100), Muckle-Wells syndrome (MWS) (OMIM 191900) and neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic, cutaneous, articular (CINCA) syndrome (OMIM 607115), tumor necrosis factor (TNF) receptor associated periodic syndrome (TRAPS) (OMIM 191190) and hyperimmunoglobulinemia-D with periodic fever syndrome (HIDS) (OMIM 260920). Recently, the syndrome of pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) (OMIM 604416), Blau syndrome (OMIM 186580) and early-onset sarcoidosis (OMIM 609464) have been added as auto-inflammatory syndromes all, however, present without recurrent fevers. We therefore use the more inclusive term ‘monogenic autoinflammatory syndromes’ to refer to all of these conditions. A list of the currently identified monogenic autoinflammatory syndromes and their clinical presentation and treatment has been given elsewhere [2] and they are listed in Table 1.

Recent literature on the crystal-induced arthritides, gout and pseudogout, confirms initial speculation that autoinflammation plays a role in a wider spectrum of conditions (Table 2) [3]. Disease-based gene discovery in these rare conditions has led to the description of novel pathways in the innate immune system, and provides insights into the molecular and cellular mechanisms regulating infection, endogenous stress and autoinflammation. This review highlights recent advances in this field and the implications for our understanding and treatment of common rheumatologic disorders.

Update on the genetics underlying monogenic autoinflammatory conditions

The appropriate evaluation of patients with suspected autoinflammatory syndromes can prove challenging. Two recent studies suggest that genetic testing should be reserved for patients with a clinical picture suggestive of a specific syndrome. In a European study involving specialist centers, a detailed clinical history suggesting one of the autoinflammatory syndromes, followed by targeted genetic testing, confirmed the diagnosis in 84 out of 87 patients in whom a clinical diagnosis had been made. In contrast, in 60 patients where the clinical history did not suggest a specific syndrome, screening for mutations in all the genes causing febrile autoinflammatory syndromes yielded just one possible diagnosis of FMF, and two cases with genetic variants, polymorphisms, rather than disease-causing mutations [4•]. A French group [5] suggested that genetic screening for FMF should be considered only in patients of Mediterranean origin who meet the diagnosis of definite FMF based on the Israeli criteria [6]. Both of these studies reflect the extensive experience of clinicians in evaluating patients with potential autoinflammatory diseases. More significantly, they were conducted in countries with clearly defined ethnic groups, which may allow clinicians to identify specific autoinflammatory conditions with greater confidence based on clinical features alone. Indeed, it could be argued that in countries or

ethnic groups with a high prevalence of a specific condition, such as FMF, patients with typical symptoms and signs do not require confirmatory genetic testing. Applying these study findings to clinical practice in countries with mixed populations is more problematic, however. The expansion of the clinical phenotypes of each of the autoinflammatory conditions and the recognition of these syndromes in patients with nonclassic ethnic backgrounds suggest that, in some circumstances, more liberal genetic testing is useful in deriving a diagnosis. The search for genetic causes of disease is a rapidly evolving field of research, with new mutations and functional polymorphisms being identified in both classical monogenic autoinflammatory syndromes and nonclassical syndromes. No generally accepted guidelines for genetic testing currently exist, and clinicians should bear in mind that the indications for genetic testing will change according to our evolving knowledge of these conditions.

Familial Mediterranean fever—When the genetic mutations associated with FMF were initially identified, it was suspected that most were highly penetrant; however, not all variants of *MEFV* result in typical symptoms of FMF. Variants may represent decreased penetrance mutations, where not all patients with the mutation have clinical disease. Alternatively, they may be functional polymorphisms, relatively common variants in a population that do not result in clinical disease, but their biologic effect may confer a selective advantage. Controversy has surrounded the *MEFV* variant E148Q. The frequency of this variant is high (4–12%) in several ethnic populations who have a low prevalence of FMF. It has been suggested that when E148Q is found in association with ‘disease-causing’ mutations (i.e. M694V, etc.), it may result in clinical FMF. This led to the evaluation of 21 individuals with clinical FMF in 18 families with the E148Q variant. Using pedigree analysis, the transmission of E148Q did not correlate with clinical FMF [7]. The authors suggest that this variant is not implicated in FMF, and that its identification should not lead to a false-positive diagnosis of FMF. Further research will be required to determine if this variant represents a functional polymorphism.

Cryopyrin-associated periodic syndrome—NOMID, MWS and FCAS were traditionally considered distinct syndromes; however, their common genetic mutations in *CIAS1*, also called *NLRP3/NALP3* and *PYPAF1*, and their overlapping clinical features such as urticaria-like skin rash, and varying degrees of systemic inflammation, indicate that these conditions lie along a clinical continuum [8•]. NOMID has the most severe clinical phenotype and worst prognosis; FCAS is relatively mild with a good prognosis, and MWS lies in between. Only half of all patients with clinical NOMID have a demonstrable mutation in , and their overlapping clinical features such as urticaria-like skin rash, and varying degrees of systemic inflammation, indicate that these conditions lie along a clinical continuum [8•]. NOMID has the most severe clinical phenotype and worst prognosis; FCAS is relatively mild with a good prognosis, and MWS lies in between. Only half of all patients with clinical NOMID have a demonstrable mutation in , and their overlapping clinical features such as urticaria-like skin rash, and varying degrees of systemic inflammation, indicate that these conditions lie along a clinical continuum [8•]. NOMID has the most severe clinical phenotype and worst prognosis; FCAS is relatively mild with a good prognosis, and MWS lies in between. Only half of all patients with clinical NOMID have a

demonstrable mutation in *CIAS*, which led to the exploration of the role of somatic mosaicism in causing NOMID [9]. In one NOMID patient with CNS disease, a somatic mutation resulted in the presence of Y570C change in only 16.7% of cells in whole blood. This mutation was previously described as a germline mutation in patients with NOMID [10]. In patients who are negative for mutations in *CIAS1*, screening for other candidate genes, including *ASC*, has proven negative to date [8•,11•].

Tumor necrosis factor receptor-associated periodic syndrome—In patients with TRAPS, the interpretation of substitutions in *TNFRSF1A* can prove challenging. For example, the P46L substitution occurs in up to 20% of clinically asymptomatic individuals in a West African population, which suggests that in this population, it represents a polymorphism rather than a disease-causing mutation. As in-vitro studies suggest a pro-inflammatory role, this polymorphism may confer a biologic advantage; however, its impact may differ according to varying genetic backgrounds. The clinical significance of another *TNFRSF1A* substitution, R92Q, was determined in family studies of patients with recurrent fevers. The R92Q genotype did not correlate with the TRAPS phenotype although it was associated with heterogeneous clinical symptoms. The authors therefore suggest that R92Q is a reduced penetrance variant, and that it may play a role in a wider spectrum of inflammatory disorders [12].

Hyperimmunoglobulinemia-D with periodic fever syndrome—HIDS was initially identified in the Netherlands, and is most prevalent in patients of Northwest European origin albeit with isolated cases in more diverse ethnic groups, with a recent report describing HIDS in two siblings from India [13].

Advances in our understanding of the pathophysiology of monogenic autoinflammatory diseases

Several in-vitro models have been developed to better characterize the pathophysiologic pathways in these conditions.

Familial Mediterranean fever—The FMF-associated gene, *MEFV*, encodes the protein pyrin. The role of pyrin in the regulation of inflammation in healthy individuals and in the diseased state remains unclear but recent studies have provided insights into pyrin's complex interactions with numerous regulatory proteins. Pyrin is composed of four domains, which include the pyrin domain (PYD), B-box, coiled-coil, and B30.2 (also called SPRY) domains (Fig. 1). Although mutations are found throughout *MEFV*, the most severe are found in exon 10, which encodes the B30.2 domain. Three groups have modeled the structure of the B30.2 domain, and have computed its interactions with caspase-1, an enzyme that can activate the pro-inflammatory cytokine IL-1 β [14•–16•]. The B30.2 domain of wildtype pyrin binds directly to caspase-1 and inhibits the production of IL-1 β [17•,18•]; one study demonstrated that disease-causing mutations in *MEFV*, such as M694V and M680I, encode amino-acid changes proximal to these binding sites, which prevent the binding of B30.2 to caspase-1 and thus lead to elevations in IL-1 β levels and inflammation [18•]. In an in-vitro transfection model, wildtype pyrin acts as a proinflammatory molecule via the formation of a pyrin inflammasome complex [19]. A recent publication [20] is in keeping with this postulated

pro-inflammatory role of pyrin, as it demonstrates that as monocytes differentiate into macrophages, pyrin protein expression diminishes with a parallel reduction in levels of IL-1 β . All the above studies have been generated using in-vitro or murine models of disease, and the results may be explained by the changing role of pyrin depending on its cellular context. The relevance of these findings to human disease remains to be determined, however.

Cryopyrin-associated periodic syndrome—The disease manifestations of CAPS have been more clearly linked to the overexpression of the pro-inflammatory cytokine IL-1 β . Although cryopyrin has not yet been crystallized, computer modeling of the structure suggests that wildtype cryopyrin forms an inactive closed-ring structure. This model predicts that the rings open following stimulation and autoaggregate to form a multiprotein complex called the inflammasome. Inflammasome formation results in the release of active IL-1 β . In the disease state, mutant cryopyrin spontaneously adopts the open form, which results in inflammasome assembly with subsequent activation of caspase-1 and its enzymatic activation of IL-1 β [8•].

The cold-induced inflammation seen in patients with FCAS was simulated *ex vivo*. Patient cells spontaneously released IL-1 β in response to incubation at 32°C, a result that was blocked by anakinra, and that confirmed that modest cold exposure can trigger IL-1 β release in these patients [21]. The role of mutant *CIAS1*-induced necrosis described in an in-vitro model needs further evaluation [22].

Tumor necrosis factor receptor-associated periodic syndrome—‘Defective shedding’ of the mutant TNF receptors (TNFR1) from the cell surface was found in a subset of patients with TRAPS. The decrease in receptor cleavage from the cell surface was thought to cause persistent pro-inflammatory cellular signaling and a relative lack of the anti-inflammatory soluble TNF receptor in serum [1]. Additional data suggest that mutant TNFR1 becomes misfolded and fails to travel to the cell surface but remains in the endoplasmic reticulum. This intracellular aggregation of mutant TNFR1 may lead to ligand-independent activation through the ‘endoplasmic reticulum stress’ response; alternatively, intracellular signaling complexes may form [23••]. Neutrophils from patients with TRAPS fail to apoptose appropriately, thereby suggesting another mechanism by which the inflammatory response may be perpetuated [24•].

Hyperimmunoglobulinemia-D with periodic fever syndrome—HIDS results from mutations in *MVK*, which encodes the protein mevalonate kinase, an enzyme in the cholesterol synthesis pathway. This pathway produces a diverse group of compounds including isoprenoids, which have anti-inflammatory properties. It remains unclear whether the inflammatory phenotype of HIDS is mediated by an excess of upstream mevalonate or a relative deficiency of isoprenoid compounds. Recent ex-vivo experiments support the latter hypothesis [25]. Another mechanism to prolong generalized inflammation may be due to defective lymphocyte apoptosis in cells from HIDS patients following stimulation [26•]. Severe mevalonate kinase deficiency results in mevalonic aciduria, which is at the severe end of the spectrum of *MVK*-associated clinical diseases. In addition to the features seen in HIDS, patients with mevalonic aciduria develop mental retardation and have a poor

prognosis. A sibling allogeneic stem-cell transplant was performed in a young patient with mevalonic aciduria, who also had CNS disease. Transplantation led to resolution of febrile episodes and subsequent withdrawal of immunosuppression. Longer term follow-up is needed to determine if neurologic features are due to CNS inflammation or other mechanisms of CNS damage [27•].

Clinical aspects and treatment of the autoinflammatory diseases

Amyloidosis is an insidious complication of many auto-inflammatory syndromes.

AA amyloidosis in autoinflammatory syndromes—The natural history of amyloidosis was recently summarized in a retrospective analysis of a national center's cohort of 374 patients of whom 32 (9%) had an autoinflammatory syndrome [28•]. Other diagnoses included inflammatory arthritis, chronic infection, Crohn's disease and miscellaneous causes. Lower median serum amyloid A (SAA) levels and the regression in amyloid burden significantly correlated with decreased mortality and improved renal prognosis. Median SAA levels below 10 mg/l were associated with a decrease in amyloid deposits and superior survival, and a median SAA level of less than 4 mg/l had the lowest relative risk of death. These data suggest the value of serial SAA measurements in monitoring and guiding clinical care. SAA assays will require further certification to facilitate their use in the US.

In FMF, the *MEFV* genotype M694V has been most strongly associated with amyloidosis; an additional risk factor is the serum amyloid A 1 α / α genotype. A physician survey in 14 countries collected data on 2482 genetically confirmed cases of FMF, which is estimated to represent over 50% of all genetically confirmed cases worldwide. The prevalence of renal amyloidosis was 11.4% [29•]. In a multivariate analysis, the country of recruitment was the strongest predictor for amyloidosis, with a three-fold increased risk of amyloidosis for patients in Arabian countries, Turkey and Armenia compared with the US and West European countries. The association of amyloidosis and infant mortality rates by country suggests that a common environmental factor may underlie this phenomenon. Therefore the country should be considered for prophylactic colchicine therapy. Interestingly, one patient with the T50M mutation in *TNFRSF1A* who denied ever having had symptoms suggestive of TRAPS, including fever, developed AA amyloidosis [30].

The first three reports of amyloidosis in HIDS occurred almost simultaneously. One patient with HIDS and the SAA 1 α / α genotype developed a rapidly progressive pauci-immune glomerulonephritis and end-stage renal disease (ESRD). Although the renal biopsy was without evidence of amyloidosis, biopsies of the gastrointestinal and respiratory tracts confirmed AA amyloid deposits [31]. Two more patients with HIDS who developed AA amyloidosis resulting in ESRD were described [32].

Current therapy in patients with amyloidosis focuses on controlling the underlying inflammation but the continued renal deterioration and death in a significant number of patients illustrate the unmet needs of this devastating condition. A new compound, eprodisate, which inhibits the formation and deposition of amyloid fibrils in tissue was evaluated in a 24-month-long, randomized, controlled trial involving 183 patients (20% with autoinflammatory syndromes). Those patients who received eprodisate had a slower decline

in renal function. Eprodisate had no impact on the development of end-stage renal disease or death, the primary end-points for the trial [33•]. The ability to slow the decline in renal function constitutes an advance. The lack of control for underlying anti-inflammatory treatment, however, an unequal distribution of patients with chronic infections and lower baseline serum C-reactive protein in the eprodisate group all suggest that further evaluation of this drug is required.

Cryopyrin-associated periodic syndrome and therapy—Evidence that overproduction of active IL-1 β is the pivotal disease-causing mechanism in patients with CAPS comes from a number of recent publications. A prospective study [34•] reported a dramatic response to the inhibition of IL-1 with anakinra in 18 patients with *CIAS1* mutation-positive and negative NOMID. Not only did rash and acute-phase reactants improve, but the treatment also improved the neurologic disease manifestations, including headaches. Intracranial pressure, white-cell counts and protein levels decreased significantly in the patients in whom cerebrospinal fluid (CSF) was obtained, and hearing improved or remained stable in all evaluable patients. Withdrawal of therapy resulted in a rapid relapse of symptoms, suggesting that continuous inhibition of IL-1 β is required. MRI sequences visualized leptomeningeal and cochlear inflammation and may assist in diagnosis and guide therapy. Data from an Italian registry [11•] describe the clinical features and encouraging response to anakinra therapy in patients with NOMID. Seven of the 12 patients had significant perinatal events that contributed to the development of mental retardation. In common with other reports [8•,35,36], poor correlation in genotype–phenotype between mutations and disease severity in patients with CAPS was found. The use of anakinra in other forms of CAPS is increasing, including its use in children with FCAS [37].

IL-6, a mediator of inflammation downstream of IL-1 β in patients with NOMID, is elevated in the serum and CSF of NOMID patients. This led to the use of the humanized anti-IL6 receptor antibody, tocilizumab, to treat an infant with severe NOMID and interstitial lung disease who had a partial response to TNF inhibition and IL-1 β inhibition with anakinra [38]. Although the acute-phase response markers improved, skin, eye and joint disease persisted on IL-6 inhibition and the child died from cardiac failure after 2 months of therapy. This patient had an earlier partial response to a maximal dose of 1.6 mg/kg day of anakinra, but higher doses of anakinra are often necessary to control disease and can be administered safely [34•,39].

The characteristic bony overgrowth seen in NOMID is the result of deranged endochondral bone formation, as evidenced by lack of palisading cartilaginous columns in the bone biopsy of the growth plate in one patient [40]. Once established, this feature may not be controlled with anakinra therapy. An erosive arthritis affecting both small and large joints [41] was described in four generations of a French family with mutation-positive CAPS (T348M). Although the affected family members were HLA DR4 positive, they were anti-CCP and rheumatoid factor negative. A further feature in this family was the presence of demyelination on imaging; however, neurophysiologic testing and CSF analyses were normal.

Hyperimmunoglobulinemia-D with periodic fever syndrome: clinical aspects—

HIDS has traditionally been considered a benign disease, and typically symptoms resolve or greatly improve by the third decade. This has been challenged, not only by reports of AA amyloidosis in these patients, but also the description [42] of a 7-year-old female who developed macrophage activation syndrome (MAS) following a flare of HIDS. Differentiating MAS, a potentially deadly condition, from acute HIDS may be difficult; however, a drop in sedimentation rate despite ongoing clinical evidence of inflammation should trigger the consideration of MAS. One patient with a novel mutation in *MVK* resulting in severe mevalonate kinase deficiency developed glomerulonephritis that was unresponsive to steroid therapy whereas anakinra therapy resulted in resolution of proteinuria and fewer febrile episodes [43].

Pediatric granulomatous arthritis: clinical aspects—

An international registry [44•] has provided further insights into Blau syndrome and early-onset sarcoidosis. Their data suggest that these conditions are equivalent clinically and the authors propose the use of the single term ‘pediatric granulomatous arthritis’ (PGA) to include both conditions. Patients with ‘classic’ features, namely arthritis, dermatitis and uveitis, bore specific mutations in *NOD2/CARD15* whereas genetic testing in patients with atypical clinical features alone demonstrated no mutations. The authors suggest that genotyping in patients with ‘classic’ features may reduce the need for invasive procedures to confirm the diagnosis. In contrast to adult-onset sarcoidosis, lung disease is not a classical feature of PGA. In a patient diagnosed with Blau syndrome as an infant, however, lymphadenopathy with interstitial pneumonitis developed during his teenage years [45]. It is notable that there is no increase in *NOD2/CARD15* mutations in patients with adult-onset sarcoidosis compared with controls [46]. TNF inhibition using infliximab but not etanercept was described as beneficial in a recent report of twins with PGA [47].

Synovial biopsies from patients with Blau syndrome characteristically contain noncaseating granulomata [44•]; this is in contrast to the nonspecific inflammatory changes described in other autoinflammatory conditions. A lymphocyte-predominant chronic inflammatory infiltrate has been described in NOMID [48], and sterile granulocytic infiltrate in FMF [49].

Autoinflammatory diseases become more complex: new features and new members

Reports of the occurrence of autoinflammatory syndromes with common autoimmune diseases have emerged. One series found a 4 times increased prevalence of multiple sclerosis among FMF patients compared with expected rates in the Turkish population [50]. One patient with CAPS had concomitant biopsy-proven celiac disease [51], which was also seen in two of the 12 patients in an Italian series of NOMID [11•]. Determining whether a proinflammatory milieu due to excessive inflammasome activity contributes to the development of autoreactive T-cells and autoimmunity, will require further investigation.

The spectrum of autoinflammatory diseases continues to expand, with the recent inclusion of Schnitzler syndrome, the syndrome of urticaria-like skin rash and monoclonal gammopathy. Although *CIAS1* mutations have not been detected in Schnitzler syndrome, anakinra therapy has been associated with a dramatic clinical response [52]. The disease spectrum of systemic

onset juvenile inflammatory arthritis (SOJIA) and adult onset Still's disease (AOSD) has been suspected to belong to the group of autoinflammatory diseases, with response to anakinra notable in a subset of these patients [53]. Marked elevations of the proinflammatory cytokine IL-18 in patients with SOJIA, AOSD and, in particular, in MAS may provide early clues to their pathogenesis [53–55]. Behçet's disease has been considered an autoinflammatory disease [56], but with no confirmed causative non-HLA genes identified. One study examined the frequency of mutations in genes associated with FMF, CAPS or PAPA (*MEFV*, *CIAS1* and *PSTPIP1*), and found no increase in these mutations in Behçet's patients compared with controls [57]. False hopes were raised when murine models of chronic recurrent multifocal osteomyelitis (CRMO), another suspected autoinflammatory disease, were found to have mutations in *PSTPIP2* [58]. A closely related gene, *PSTPIP1*, was previously found to result in PAPA [59]. Disappointingly, to date, no mutations in *PSTPIP1* or *PSTPIP2* have been found in humans with CRMO [60].

The role of 'danger recognition gone awry' in autoinflammatory diseases and beyond

While toll-like receptors (TLRs) have been recognized as innate immune sensors of extracellular 'danger' for some time [61,62•], the recent discovery of new families of intracellular 'danger' sensors was pioneered by the discovery of pyrin. This protein, mutated in FMF, belongs to a larger family of TRIM proteins of which some members have been shown to sense intracellular 'danger' [63,64•]. The discovery that cryopyrin, the protein mutated in CAPS, carried a motif predicted to sense microbial 'danger' signals, added this protein to yet another family of intracellular 'danger' sensors, the NOD-like receptors, and spurred attempts to find their triggers [65]. The exciting data suggesting that cryopyrin is required for the detection of numerous 'danger' signals including bacteria, toxins, monosodium urate crystals that are released by necrotic cells, and calcium pyrophosphate dehydrate crystals [66•,67•,68•,69•] confirmed initial suspicions that cryopyrin played a crucial role in innate immunity. These findings have revolutionized not only our understanding of the physiology of danger recognition but also provided us with a model to test how flares in rheumatic conditions may be triggered. The discovery of the pathogenesis of both gout and pseudogout is an example of this revolution, as evidenced by the discovery that monosodium urate crystals activate the cryopyrin inflammasome to release IL-1 β [70•]. Although the inflammatory response in gout may be amplified via MyD88-mediated cytokine production [71•,72], the clinical response of nine of 10 gout patients to IL-1 blockade in an open-label proof of concept study clinically confirms the role of IL-1 β oversecretion in gout [73].

Initial observations regarding the role of the innate immune system in other common rheumatic diseases including rheumatoid arthritis, dermatomyositis and systemic lupus erythematosus (SLE) [74,75,76•,77] will require further investigation. Interestingly, in SLE, abnormal TLR signaling is, in part, responsible for the interferon signature seen in this disease, which strongly suggests that a dysregulation in the innate immune system may contribute to the pathogenesis of SLE [78•,79]. The clinical efficacy of hydroxychloroquine in SLE has been partially attributed to the inhibition of certain TLRs [80•]. The finding that anti-Ro52/SSA, an antibody commonly found in SLE and Sjögren's targets TRIM 21, a molecule similar to pyrin [81], may provide further clues of the involvement of the innate

immune system in SLE. Future studies need to explore the concept that in polygenic conditions such as SLE, minor alterations in both the innate and adaptive immune system may be required to result in clinical disease.

Conclusion

The discovery of genes underlying the monogenic auto-inflammatory syndromes has not only led to a better understanding of the pathogenesis of these conditions but also provided rational targets for anticytokine therapy. The evolving description of the molecular pathways that lead to danger recognition and signaling may provide new targets for drug development. While great strides have been made in our understanding of autoinflammation in monogenic diseases and, consequently, the innate immunity, much work remains to be done, especially regarding the involvement of the innate immune system in the more common rheumatic diseases.

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References and recommended reading

- Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 117–118).

1. McDermott MF, Aksentijevich I, Galon J, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell*. 1999; 97:133–144. [PubMed: 10199409]
2. Hull KM, Shoham N, Chae JJ, et al. The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations. *Curr Opin Rheumatol*. 2003; 15:61–69. [PubMed: 12496512]
3. Martinon F, Glimcher LH. Gout: new insights into an old disease. *J Clin Invest*. 2006; 116:2073–2075. [PubMed: 16886051]
- 4•. Simon A, van der Meer JW, Vesely R, et al. Approach to genetic analysis in the diagnosis of hereditary autoinflammatory syndromes. *Rheumatology (Oxford)*. 2006; 45:269–273. [PubMed: 16234278] [A good paper that introduces a clinical decision model to guide the use of genetic testing.]
5. Federici L, Rittore-Domingo C, Kone-Paut I, et al. A decision tree for genetic diagnosis of hereditary periodic fever in unselected patients. *Ann Rheum Dis*. 2006; 65:1427–1432. [PubMed: 16707534]
6. Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum*. 1997; 40:1879–1885. [PubMed: 9336425]
7. Tchernitchko DO, Gerard-Blanluet M, Legendre M, et al. Intrafamilial segregation analysis of the p.E148Q MEFV allele in familial Mediterranean fever. *Ann Rheum Dis*. 2006; 65:1154–1157. [PubMed: 16439437]

- 8•. Aksentijevich ID, Putnam C, Remmers EF, et al. The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model. *Arthritis Rheum.* 2007; 56:1273–1285. [PubMed: 17393462] [A clinical description of patients with a spectrum of CAPS and introduction of a new model of cryopyrin function.]
9. Saito M, Fujisawa A, Nishikomori R, et al. Somatic mosaicism of CIAS1 in a patient with chronic infantile neurologic, cutaneous, articular syndrome. *Arthritis Rheum.* 2005; 52:3579–3585. [PubMed: 16255047]
10. Aksentijevich I, Nowak M, Mallah M, et al. De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. *Arthritis Rheum.* 2002; 46:3340–3348. [PubMed: 12483741]
- 11•. Caroli F, Pontillo A, D'Osualdo A, et al. Clinical and genetic characterization of Italian patients affected by CINCA syndrome. *Rheumatology (Oxford).* 2007; 46:473–478. [PubMed: 16920754] [A good paper on the clinical spectrum of NOMID patients in Italy.]
12. Ravet N, Rouaghe S, Dode C, et al. Clinical significance of P46L and R92Q substitutions in the tumour necrosis factor superfamily 1A gene. *Ann Rheum Dis.* 2006; 65:1158–1162. [PubMed: 16569687]
13. Lawrence A, Hol F, Aggarwal A, Drenth JP. Hyperimmunoglobulinaemia D syndrome in India: report of two siblings with a novel mutation. *Ann Rheum Dis.* 2006; 65:1674–1676. [PubMed: 17105862]
- 14•. Woo JS, Imm JH, Min CK, et al. Structural and functional insights into the B30.2/SPRY domain. *EMBO J.* 2006; 25:1353–1363. [PubMed: 16498413] [Paper presents models of the B30.2 domain found in the TRIM family of intra-cellular molecules that include pyrin, the protein mutated in FMF.]
- 15•. Masters SL, Yao S, Willson TA, et al. The SPRY domain of SSB-2 adopts a novel fold that presents conserved Par-4-binding residues. *Nat Struct Mol Biol.* 2006; 13:77–84. [PubMed: 16369487] [Paper presents models of the B30.2 domain found in the TRIM family of intra-cellular molecules that include pyrin, the protein mutated in FMF.]
- 16•. Grutter C, Briand C, Capitani G, et al. Structure of the PRYSPRY-domain: implications for autoinflammatory diseases. *FEBS Lett.* 2006; 580:99–106. [PubMed: 16364311] [Paper presents models of the B30.2 domain found in the TRIM family of intra-cellular molecules that include pyrin, the protein mutated in FMF.]
- 17•. Papin S, Cuenin S, Agostini L, et al. The SPRY domain of pyrin, mutated in familial Mediterranean fever patients, interacts with inflammasome components and inhibits proIL-1 β processing. *Cell Death Differ.* 2007; 14:1457–1466. [PubMed: 17431422] [This paper demonstrates the interaction of pyrin with caspase-1, thus inhibiting IL-1 β production.]
- 18•. Chae JJ, Wood G, Masters SL, et al. The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1 β production. *Proc Natl Acad Sci U S A.* 2006; 103:9982–9987. [PubMed: 16785446] [This paper shows that the binding of pyrin and caspase-1, the enzyme that activates IL-1 β and the authors show that IL-1 β production is reduced in mutated versus wildtype pyrin.]
19. Yu JW, Wu J, Zhang Z, et al. Cryopyrin and pyrin activate caspase-1, but not NF- κ B, via ASC oligomerization. *Cell Death Differ.* 2006; 13:236–249. [PubMed: 16037825]
20. Seshadri S, Duncan MD, Hart JM, et al. Pyrin levels in human monocytes and monocyte-derived macrophages regulate IL-1 β processing and release. *J Immunol.* 2007; 179:1274–1281. [PubMed: 17617620]
21. Rosengren S, Mueller JL, Anderson JP, et al. Monocytes from familial cold autoinflammatory syndrome patients are activated by mild hypothermia. *J Allergy Clin Immunol.* 2007; 119:991–996. [PubMed: 17320940]
22. Fujisawa A, Kambe N, Saito M, et al. Disease-associated mutations in CIAS1 induce cathepsin B-dependent rapid cell death of human THP-1 monocytic cells. *Blood.* 2007; 109:2903–2911. [PubMed: 17164343]
- 23•. Lobito AA, Kimberley FC, Muppidi JR, et al. Abnormal disulfide-linked oligomer-ization results in ER retention and altered signaling by TNFR1 mutants in TNFR1-associated periodic fever syndrome (TRAPS). *Blood.* 2006; 108:1320–1327. [PubMed: 16684962] [This paper presents

evidence that mutated TNF receptor molecules are misfolded and remain in the ER, and it introduces a new concept of how mutations in the TNF receptor can lead to inflammation in TRAPS patients.]

- 24•. D'Ossualdo A, Ferlito F, Prigione I, et al. Neutrophils from patients with TNFRSF1A mutations display resistance to tumor necrosis factor-induced apoptosis: pathogenetic and clinical implications. *Arthritis Rheum.* 2006; 54:998–1008. [PubMed: 16508982] [The authors imply that abnormal apoptosis of neutrophils in patients with TRAPS may be another mechanism that leads to ongoing inflammation.]
25. Mandey SH, Kuijk LM, Frenkel J, Waterham HR. A role for geranylgeranylation in interleukin-1beta secretion. *Arthritis Rheum.* 2006; 54:3690–3695. [PubMed: 17075828]
- 26•. Bodar EJ, van der Hilst JC, van Heerde W, et al. Defective apoptosis of peripheral-blood lymphocytes in hyper-IgD and periodic fever syndrome. *Blood.* 2007; 109:2416–2418. [PubMed: 17138829] [The authors imply that abnormal apoptosis of lymphocytes in patients with HIDS may be another mechanism that leads to ongoing inflammation.]
- 27•. Neven B, Valayannopoulos V, Quartier P, et al. Allogeneic bone marrow transplantation in mevalonic aciduria. *N Engl J Med.* 2007; 356:2700–2703. [PubMed: 17596604] [This is an interesting case report on the short term outcome of therapy with allogeneic bone marrow transplantation in a patient with mevalonic aciduria who went into inflammatory remission.]
- 28•. Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med.* 2007; 356:2361–2371. [PubMed: 17554117] [This is an excellent review of a single center's experience with patients with AA amyloidosis with description of risk factors leading to renal failure and death.]
- 29•. Touitou I, Sarkisian T, Medlej-Hashim M, et al. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. *Arthritis Rheum.* 2007; 56:1706–1712. [PubMed: 17469185] [This cross sectional review of patients with FMF entered into a registry shows that country rather than genotype is the major risk factor for development of amyloidosis.]
30. Kallinich T, Haffner D, Rudolph B, et al. "Periodic fever" without fever: two cases of nonfebrile TRAPS with mutations in the TNFRSF1A gene presenting with episodes of inflammation or monosymptomatic amyloidosis. *Ann Rheum Dis.* 2006; 65:958–960. [PubMed: 16308343]
31. Siewert R, Ferber J, Horstmann RD, et al. Hereditary periodic fever with systemic amyloidosis: is hyper-IgD syndrome really a benign disease? *Am J Kidney Dis.* 2006; 48:e41–e45. [PubMed: 16931207]
32. Lachmann HJ, Goodman HJ, Andrews PA, et al. AA amyloidosis complicating hyperimmunoglobulinemia D with periodic fever syndrome: a report of two cases. *Arthritis Rheum.* 2006; 54:2010–2014. [PubMed: 16732551]
- 33•. Dember LM, Hawkins PN, Hazenberg BP, et al. Eprodisate for the treatment of renal disease in AA amyloidosis. *N Engl J Med.* 2007; 356:2349–2360. [PubMed: 17554116] [This is the first randomized controlled trial in patients with systemic AA amyloidosis which reports a modest impact on the decline of renal function.]
- 34•. Goldbach-Mansky R, Dailey NJ, Canna SW, et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. *N Engl J Med.* 2006; 355:581–592. [PubMed: 16899778] [This the largest trial with the IL-1 receptor antagonist, anakinra, in patients with NOMID/CINCA that demonstrates the pivotal role of IL-1b in the pathogenesis of not only systemic inflammation but also the specific organ disease including the CNS and inner ear, and establishes therapy with anakinra as the standard of care for this condition. MRI sequences visualize CNS and inner ear inflammation and may be of diagnostic value and guide therapy.]
35. Arostegui JI, Aldea A, Modesto C, et al. 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]
36. Hentgen V, Despert V, Lepretre AC, et al. Intrafamilial variable phenotypic expression of a CIAS1 mutation: from Muckle-Wells to chronic infantile neurological cutaneous and articular syndrome. *J Rheumatol.* 2005; 32:747–751. [PubMed: 15801036]
37. O'Connell SM, O'Regan GM, Bolger T, et al. Response to IL-1-receptor antagonist in a child with familial cold autoinflammatory syndrome. *Pediatr Dermatol.* 2007; 24:85–89. [PubMed: 17300660]

38. Matsubara T, Hasegawa M, Shiraishi M, et al. A severe case of chronic infantile neurologic, cutaneous, articular syndrome treated with biologic agents. *Arthritis Rheum.* 2006; 54:2314–2320. [PubMed: 16802372]
39. Goldbach-Mansky R, Pucino F, Kastner DL. Treatment of patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, articular syndrome: comment on the article by Matsubara et al. *Arthritis Rheum.* 2007; 56:2099–2101. author reply 2101–2102. [PubMed: 17530657]
40. Hill SC, Namde M, Dwyer A, et al. Arthropathy of neonatal onset multisystem inflammatory disease (NOMID/CINCA). *Pediatr Radiol.* 2007; 37:145–152. [PubMed: 17136361]
41. Lequerre T, Vittecoq O, Saugier-Verber P, et al. A cryopyrin-associated periodic syndrome with joint destruction. *Rheumatology (Oxford).* 2007; 46:709–714. [PubMed: 17178739]
42. Rigante D, Capoluongo E, Bertoni B, et al. First report of macrophage activation syndrome in hyperimmunoglobulinemia D with periodic fever syndrome. *Arthritis Rheum.* 2007; 56:658–661. [PubMed: 17265501]
43. Nevyjel M, Pontillo A, Calligaris L, et al. Diagnostics and therapeutic insights in a severe case of mevalonate kinase deficiency. *Pediatrics.* 2007; 119:e523–e527. [PubMed: 17261617]
44. Rose CD, Wouters CH, Meiorin S, et al. Pediatric granulomatous arthritis: an international registry. *Arthritis Rheum.* 2006; 54:3337–3344. [PubMed: 17009307] [This report provides evidence for Blau syndrome and early onset sarcoidosis to be considered as synonymous.]
45. Becker ML, Martin TM, Doyle TM, Rose CD. Interstitial pneumonitis in Blau syndrome with documented mutation in CARD15. *Arthritis Rheum.* 2007; 56:1292–1294. [PubMed: 17393391]
46. Milman N, Nielsen OH, Hviid TV, Fenger K. CARD15 single nucleotide polymorphisms 8, 12 and 13 are not increased in ethnic Danes with sarcoidosis. *Respiration.* 2007; 74:76–79. [PubMed: 16397396]
47. Milman N, Andersen CB, Hansen A, et al. Favourable effect of TNF-alpha inhibitor (infliximab) on Blau syndrome in monozygotic twins with a de novo CARD15 mutation. *Apmis.* 2006; 114:912–919. [PubMed: 17207093]
48. Yarom A, Rennebohm RM, Levinson JE. Infantile multisystem inflammatory disease: a specific syndrome? *J Pediatr.* 1985; 106:390–396. [PubMed: 3973776]
49. Langer HE, Huth F, Behfar S, Zeidler H. Synovitis in familial Mediterranean fever. *Dtsch Med Wochenschr.* 1985; 110:1695–1700. [PubMed: 3876924]
50. Akman-Demir G, Gul A, Gurol E, et al. Inflammatory/demyelinating central nervous system involvement in familial Mediterranean fever (FMF): coincidence or association? *J Neurol.* 2006; 253:928–934. [PubMed: 16511642]
51. Shaker M, Edwards S, Chionuma H, et al. Association between celiac sprue and cryopyrin associated autoinflammatory disorders: a case report. *Pediatr Rheumatol Online J.* 2007; 5:12. [PubMed: 17550587]
52. de Koning HD, Bodar EJ, Simon A, et al. Beneficial response to anakinra and thalidomide in Schnitzler's syndrome. *Ann Rheum Dis.* 2006; 65:542–544. [PubMed: 16096327]
53. Fitzgerald AA, Leclercq SA, Yan A, et al. Rapid responses to anakinra in patients with refractory adult-onset Still's disease. *Arthritis Rheum.* 2005; 52:1794–1803. [PubMed: 15934079]
54. Maeno N, Takei S, Imanaka H, et al. Increased interleukin-18 expression in bone marrow of a patient with systemic juvenile idiopathic arthritis and unrecognized macrophage-activation syndrome. *Arthritis Rheum.* 2004; 50:1935–1938. [PubMed: 15188370]
55. Sugiura T, Maeno N, Kawaguchi Y, et al. A promoter haplotype of the interleukin-18 gene is associated with juvenile idiopathic arthritis in the Japanese population. *Arthritis Res Ther.* 2006; 8:R60. [PubMed: 16563174]
56. Yazici H, Fresko I. Behcet's disease and other autoinflammatory conditions: what's in a name? *Clin Exp Rheumatol.* 2005; 23:S1–S2. [PubMed: 16273757]
57. Kone-Paut I, Sanchez E, Le Quellec A, et al. Autoinflammatory gene mutations in Behcet's disease. *Ann Rheum Dis.* 2007; 66:832–834. [PubMed: 17213252]
58. Ferguson PJ, Bing X, Vasef MA, et al. A missense mutation in pstpip2 is associated with the murine autoinflammatory disorder chronic multifocal osteomyelitis. *Bone.* 2006; 38:41–47. [PubMed: 16122996]

59. Shoham NG, Centola M, Mansfield E, et al. Pyrin binds the PSTPIP1/ CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc Natl Acad Sci USA*. 2003; 100:13501–13506. [PubMed: 14595024]
60. Jansson A, Renner ED, Ramser J, et al. Classification of nonbacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. *Rheumatology (Oxford)*. 2007; 46:154–160. [PubMed: 16782988]
61. Medzhitov R, Preston-Hurlburt P, Janeway CA Jr. A human homologue of the *Drosophila* Toll protein signals activation of adaptive immunity. *Nature*. 1997; 388:394–397. [PubMed: 9237759]
- 62•. O'Neill LA, Bowie AG. The family of five: TIR-domain-containing adaptors in Toll-like receptor signalling. *Nat Rev Immunol*. 2007; 7:353–364. [PubMed: 17457343] [This expert review summarizes the rapidly evolving area of TLR signaling.]
63. James LC, Keeble AH, Khan Z, et al. Structural basis for PRYSPRY-mediated tripartite motif (TRIM) protein function. *Proc Natl Acad Sci USA*. 2007; 104:6200–6205. [PubMed: 17400754]
- 64•. Ting JP, Kastner DL, Hoffman HM. CATERPILLERS, pyrin and hereditary immunological disorders. *Nat Rev Immunol*. 2006; 6:183–195. [PubMed: 16498449] [This review of the extended NOD family of proteins and their interacting proteins including pyrin, shows the involvement of these proteins in autoinflammatory syndromes (FCAS, MWS and NOMID) and the immunodeficiency syndrome, Bare lymphocyte syndrome.]
65. Delbridge LM, O'Riordan MX. Innate recognition of intracellular bacteria. *Curr Opin Immunol*. 2007; 19:10–16. [PubMed: 17126540]
- 66•. Kanneganti TD, Ozoren N, Body-Malapel M, et al. Bacterial RNA and small antiviral compounds activate caspase-1 through cryopyrin/Nalp3. *Nature*. 2006; 440:233–236. [PubMed: 16407888] [This is a groundbreaking paper that demonstrates the role of cryopyrin in sensing intracellular bacterial and viral triggers.]
- 67•. Mariathasan S, Weiss DS, Newton K, et al. Cryopyrin activates the inflammasome in response to toxins and ATP. *Nature*. 2006; 440:228–232. [PubMed: 16407890] [This is another paper that demonstrates the role of cryopyrin in responding to pathogen-induced cellular stress signals.]
- 68•. Ogura Y, Sutterwala FS, Flavell RA. The inflammasome: first line of the immune response to cell stress. *Cell*. 2006; 126:659–662. [PubMed: 16923387] [Review summarizing recent evidence regarding the role of NOD-like proteins in triggering innate immune responses.]
- 69•. Meylan E, Tschopp J, Karin M. Intracellular pattern recognition receptors in the host response. *Nature*. 2006; 442:39–44. [PubMed: 16823444] [Review summarizing recent evidence regarding the role of NOD-like proteins in triggering innate immune responses.]
- 70•. Martinon F, Petrilli V, Mayor A, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*. 2006; 440:237–241. [PubMed: 16407889] [This paper represents a major advance in our understanding of how urate crystals result in inflammation.]
- 71•. Chen CJ, Shi Y, Hearn A, et al. MyD88-dependent IL-1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. *J Clin Invest*. 2006; 116:2262–2271. [PubMed: 16886064] [This paper highlights how urate crystals utilize another innate immune pathway to result in inflammation.]
72. Akahoshi T, Murakami Y, Kitasato H. Recent advances in crystal-induced acute inflammation. *Curr Opin Rheumatol*. 2007; 19:146–150. [PubMed: 17278929]
73. So A, De Smedt T, Revaz S, Tschopp J. A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res Ther*. 2007; 9:R28. [PubMed: 17352828]
74. Roelofs MF, Boelens WC, Joosten LA, et al. Identification of small heat shock protein B8 (HSP22) as a novel TLR4 ligand and potential involvement in the pathogenesis of rheumatoid arthritis. *J Immunol*. 2006; 176:7021–7027. [PubMed: 16709864]
75. Greenberg SA, Pinkus JL, Pinkus GS, et al. Interferon-alpha/beta-mediated innate immune mechanisms in dermatomyositis. *Ann Neurol*. 2005; 57:664–678. [PubMed: 15852401]
- 76•. Baccala R, Hoebe K, Kono DH, et al. TLR-dependent and TLR-independent pathways of type I interferon induction in systemic autoimmunity. *Nat Med*. 2007; 13:543–551. [PubMed: 17479100] [This paper encapsulates advances of recent years in respect of the role of TLRs in the interferon signature of many autoimmune diseases.]

77. McGonagle D, McDermott MF. A Proposed Classification of the Immunological Diseases. *PLoS Med.* 2006; 3:e297. [PubMed: 16942393]
- 78•. Marshak-Rothstein A. Toll-like receptors in systemic autoimmune disease. *Nat Rev Immunol.* 2006; 6:823–835. [PubMed: 17063184] [This article reviews the emerging evidence for the involvement of TLRs in auto-immunity.]
79. Berghofer B, Frommer T, Haley G, et al. TLR7 ligands induce higher IFN- α production in females. *J Immunol.* 2006; 177:2088–2096. [PubMed: 16887967]
- 80•. Lafyatis R, York M, Marshak-Rothstein A. Antimalarial agents: closing the gate on Toll-like receptors? *Arthritis Rheum.* 2006; 54:3068–3070. [PubMed: 17009223] [This editorial draws on the emerging evidence that TLRs are involved in the pathogenesis of SLE and suggests that hydroxychloroquine efficacy in SLE may in part be due to its interactions with TLRs.]
81. Ottosson L, Hennig J, Espinosa A, et al. Structural, functional and immuno-logic characterization of folded subdomains in the Ro52 protein targeted in Sjogren's syndrome. *Mol Immunol.* 2006; 43:588–598. [PubMed: 15916807]

Figure 1. Schematic representation of pyrin, cryopyrin and NOD2/CARD15

Pyrin (left) is composed of four domains including the pyrin domain (PYD), B-box, coiled-coil, and B30.2 (also called SPRY) domains. The B30.2 domain is postulated to interact with intracellular pathogens. Mutated pyrin results in familial Mediterranean fever. Although the role of wild-type pyrin remains unclear, one of its roles may be to inhibit the cryopyrin inflammasome. Cryopyrin (center) acts as an intracellular sensor of danger, and is composed of three domains: a pyrin domain, a central NACHT domain and a terminal domain consisting of leucine-rich repeats (LRR). The LRR domain is involved in the recognition of certain intracellular bacteria, bacterial and viral RNA, toxins and intracellular crystals. Once activated, cryopyrin forms a macromolecular complex termed the inflammasome that results in the release of the active form of the pro-inflammatory cytokine IL-1 β . Cryopyrin-associated periodic syndromes are associated with mutant cryopyrin, which results in spontaneous inflammasome assembly and release of IL-1 β . In patients with Blau syndrome/early-onset sarcoidosis, the NACHT domain of NOD2/CARD15 (right) is

mutated. Variants of the gene encoding the LRR domain of this protein have been described in patients with Crohn's disease. The LRR domain of NOD2/CARD15 plays a role in the detection of muramyl dipeptide, a component of the cell wall of both gram-negative and gram-positive bacteria.

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Table 1

Monogenic autoinflammatory conditions

	Inheritance	Underlying gene	Duration of attacks	Clinical features (major)	Treatment
Familial Mediterranean fever	Autosomal recessive	<i>MEFV</i> - encoding pyrin	1-3 days	Fever with peritonitis, erysipeloid erythema, and monoarthritis	Daily colchicine, anti-TNF or IL-1 receptor antagonist (investigational)
Hyper IgD syndrome	Autosomal recessive	<i>MVK</i> -encoding mevalonate kinase	3-7 days	Fever, maculopapular rash, diarrhea, abdominal pain	Investigational use of montelukast, anti-TNF or IL-1 therapy
TNF receptor-associated periodic syndrome	Autosomal dominant	<i>TNFRSF1A</i> - encoding p55 TNF receptor	Days to weeks	Fever, peritonitis, large joint arthritis, periorbital edema	Corticosteroid, anti-TNF therapy
Cryopyrin-associated periodic syndromes					
Familial cold autoinflammatory syndrome	Autosomal dominant	<i>CIAS1/NLRP3</i> encoding cryopyrin	Up to 1 day	Cold-induced urticarial rash, arthralgia and conjunctivitis	IL-1 receptor antagonist
Muckle-Wells syndrome	Autosomal dominant	<i>CIAS1/NLRP3</i> encoding cryopyrin	Several days or continuous	Urticarial rash, deafness, conjunctivitis, and arthritis	IL-1 receptor antagonist
Neonatal-onset multisystem inflammatory disease	Majority are <i>de novo</i>	<i>CIAS1/NLRP3</i> encoding cryopyrin	Continuous	Urticarial rash, epiphyseal overgrowth, meningitis, mental retardation, deafness	IL-1 receptor antagonist
Pyogenic arthritis with pyoderma gangrenosum and acne	Autosomal dominant	<i>PSTPIP1</i>	Episodic lasting weeks to months	Severe cystic acne, pyoderma gangrenosum, arthritis	Corticosteroids, IL-1 receptor antagonist or anti-TNF therapy
Pediatric granulomatous arthritis including Blau syndrome and early onset sarcoidosis	Autosomal dominant/ <i>de novo</i>	<i>NOD2/CARD15</i> encoding NOD2	Chronic inflammation	Granulomatous inflammation of joints, eyes and skin, rarely affects lung	Corticosteroids, anti-TNF therapy (investigational)

Table 2

Complex genetic diseases in which autoinflammation has been shown to play a role

	Autoinflammatory protein implicated in disease	Duration of attacks	Clinical features (major)	Treatment
Acute gout/pseudogout	Wild-type cryopyrin senses crystals triggering attacks	1-3 days	Acute arthritis – erythema, great toe, ankle and knee in gout. Pseudogout upper limb joints	Nonsteroidal anti-inflammatory drugs, corticosteroids or colchicine in acute setting. IL-1 receptor antagonist (investigational)
Crohn's disease, ileal variant	<i>NOD2/CARD15</i> variants encoding NOD2	Chronic inflammation	Granulomatous inflammation of the gastrointestinal tract	Numerous immunosuppressants, anti-TNF therapy, antibody therapies targeting $\alpha 4$ integrin (Natalizumab)