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Monogenic autoinflammatory diseases: new insights into clinical aspects and pathogenesis

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Abstract

Purpose of review—The genetic and clinical characterizations of monogenic autoinflammatory syndromes have led to ground breaking insights into the regulation of inflammatory responses to endogenous and exogenous inducers or triggers of inflammation and continue to uncover key inflammatory pathways of the innate immune system. This article summarizes recent progress in the clinical aspects and understanding of the pathogenesis of this growing spectrum of diseases.

Recent findings—The understanding of the spectrum of organ manifestations in autoinflammation was expanded by the discovery of two novel monogenic diseases both caused by the absence of an anti-inflammatory signal and added evidence that increased IL-1 signaling can cause aseptic osteolytic bone lesions and that the absence of IL-10 signaling causes inflammatory enterocolitis in neonates. New knock in animal models for TNF-receptor-associated periodic syndrome, and familial Mediterranean fever and cryopyrin-associated periodic syndromes allow insights into the complexity of the dysregulated immune pathways. Exploring 'triggers' of the NLRP3 inflammasome spurred studies of tissue inflammation in diseases including gout and those that previously have not been considered inflammatory in nature such as diabetes, fibrosing lung disease and possibly coronary artery disease.

Summary—The genetic characterization of a growing number of monogenic autoinflammatory diseases has provided important insights into the phenotypic expression of single gene disorders and the complexity of the dysregulated inflammatory pathways leading to clinical disease. Knowledge obtained from these disorders is pertinent to a number of common disorders and provides new targets for drug development.

Introduction

Inflammation has evolved as a physiologic mechanism necessary to defend our bodies from external and internal 'danger' triggers such as infections and waste from dying cells [1]. Low-grade inflammation can also be a response found in 'stressed tissues' such as through fat deposits in obesity and the shearing stress of high blood pressure on vessel walls in hypertension [2]. The inflammatory response has several components that include a trigger or inducer of the response such as infection, tissue damage, and tissue stress; a sensor recognizing the trigger such as Toll-like receptors and the recently discovered intracellular receptors (NOD-like receptors, NLRs); the mediators that coordinate and execute a response (such as cytokines, chemokines, and signaling pathways); and the target tissues that are affected by the inflammatory mediators [1]. The discovery of monogenic and genetically complex auto-inflammatory diseases has led to a growing understanding of how mutations that affect the different components of an inflammatory response can lead to human diseases [3•].

More than 10 years ago the discovery of mutations in *MEFV* and *TNFRSF1A* causing familial Mediterranean fever (FMF) and TNF-receptor-associated periodic syndrome (TRAPS), respectively, spurred the concept of auto-inflammation. This laid the foundation for a new class of disorders that are characterized by excessive innate immune responses to

known and yet unknown triggers leading to episodic systemic and organ-specific inflammation. Mutations in the then novel gene, *NLRP3*, cause the cryopyrin-associated periodic syndromes (CAPSs), and *NLRP3* was the first member of a large group of intracellular sensors of danger recognition implicated in human disease. The formation of an NLRP3-containing multimolecular complex termed the 'inflammasome' leads to the activation of IL-1 and provides a molecular link between the recognition of danger and the activation of the pro-inflammatory cytokine IL-1 as an early 'alarm or response' cytokine [4]. With the progression of the genome project, the identification of additional intracellular sensor molecules that could be activated by 'danger signals' such as pathogen-associated molecular patterns (PAMPs) derived from bacterial and viral pathogens and damage-associated molecular patterns (DAMPs) such as exogenous environmental noxious triggers (i.e. silica and asbestos) and endogenous signals from stressed and dying cells (i.e. ATP, uric acid and cholesterol crystals) was accomplished. The NLRP3 inflammasome is by far the best studied, and its activation has been implied in the inflammatory response in a number of genetically complex disorders *in vivo* and *in vitro* [5]. The rediscovery of IL-1 as a central cytokine in human disease was spurred by the striking clinical responses of CAPS patients to IL-1 blockade with anakinra, a daily administered recombinant IL-1 receptor antagonist.

Several advances have occurred in the study of monogenic auto-inflammatory syndromes including the recent discovery that the deficiency of the IL-1 receptor antagonist in humans leads to a severe neonatal inflammatory disease with osteolytic bone lesions and pustular skin lesions and the discovery that loss of function mutations in the IL-10 receptor leads to early-onset enterocolitis. These discoveries have expanded the clinical spectrum of IL-1-mediated disease and have demonstrated the critical role of IL-10 in the regulation of gut inflammation. The molecular targets revealed from disease-based gene discovery have stimulated research aimed at understanding the function of dysregulated inflammatory pathways that lead to end organ damage. The development of mouse models, in which a mutated TNF receptor (*TNFRSF1A*, the gene causing TRAPS), mutated cryopyrin (*NLRP3*, the gene causing CAPS) and pyrin (*MEFV*, the gene causing FMF) were knocked in, allows further dissection of the inflammatory mediator pathways that lead to the systemic and organ-specific disease manifestations seen in patients with these conditions.

In summary, the study of autoinflammatory disorders poses new questions regarding the molecular mechanisms that lead to organ-specific inflammation and provides us with molecular targets for rational drug design focused on the correction of the abnormal protein function on inflammatory pathways. This review describes the currently known monogenic auto-inflammatory disorders (Table 1) and will focus on summarizing advances over the last 18 months in the understanding of these disorders and the implications for some polygenic diseases.

Cryopyrin-associated periodic syndromes

Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID) comprise the spectrum of CAPS ranging from FCAS at the mild end and NOMID, also called CINCA, at the most severe end of the spectrum. CAPS are caused by autosomal dominant gain of function mutations in *NLRP3* (also known as *NALP3* or *CIAS*), the gene encoding cryopyrin. Most cases of FCAS and MWS are familial but nearly all cases of NOMID occur as a result of sporadic mutations. Disease manifestations include fever, an urticaria-like rash, arthralgia, conjunctivitis, and progressive hearing loss. In addition, severe headache, meningitis, mental retardation, and bony overgrowth occur in NOMID. Cryopyrin mutations lead to increased activity of the caspase-1 activating inflammasome, with increased conversion of pro-

IL-1[beta] into its active form, IL-1[beta]. IL-1[beta] is central to the pathogenesis of CAPS, and these diseases are universally responsive to IL-1 blocking medications (Fig. 1).

Clinical updates

Anakinra demonstrated sustained efficacy in the control of serum inflammatory markers up to 26–42 months in a cohort of 10 patients with NOMID [6•]. Improvements in growth parameters and neurologic outcomes were seen; however, persistence of central nervous inflammation and ongoing hearing loss were observed in some patients. Anakinra doses ranged from 1 to 10 mg/kg/day with good tolerability of the treatment.

Two longer acting IL-1-blocking medications have been FDA approved for the treatment of FCAS and MWS: rilonacept (Arcalyst, IL-1 Trap) in February 2008 and canakinumab (Ilaris) in June 2009 under the orphan drug program. Weekly subcutaneous injections of rilonacept were efficacious in the treatment of FCAS and MWS in 44 patients in a placebo-controlled study [7•]. In an open label dose finding study [8], five patients showed long-term efficacy at 2 years' follow-up. Four patients, three with MWS, required higher doses of medication for optimal disease control. Subcutaneous injections of canakinumab every 8 weeks were given to 35 patients in a randomized withdrawal study [9•]. Complete remission was seen in 97% of the patients on treatment and randomization to placebo led to disease flares in 81% of patients whereas all patients on treatment remained in remission.

As unbound IL-1[beta] is difficult to measure in serum and plasma, the administration of canakinumab allowed investigators to quantify IL-1[beta]-canakinumab complexes and approximate basal levels of IL-1[beta] to be 6 ng/dl in normal subjects and 31 ng/dl in patients with CAPS [10]. In contrast to rilonacept which binds IL-1[alpha] and IL-1[beta], canakinumab is specific for IL-1[beta] and the clinical and laboratory responses to canakinumab indicate that IL-1[beta] is the pivotal cytokine responsible for clinical disease manifestations in CAPS.

About 40–60% of patients with classical clinical manifestations of NOMID and a complete response to IL-1-blocking agents are negative for *CIAS1* mutations using routine analysis from peripheral blood. Previous reports have suggested that somatic mosaicism may account for some of the cases of ‘mutation negative’ patients [11,12]. Low-level mosaicism causing disease was reported in a patient with clinical NOMID who had a de novo somatic genetic mutation (D303H) in *CIAS1* in 30–38% of circulating leukocytes and epithelial cells [13]. As the procedures to assess somatic mutations involve time consuming subcloning techniques, somatic mutations are currently only evaluated in a research context.

Pathogenesis updates

Two research groups developed *NLRP3* (human MWS) mutation knock in mouse models to characterize inflammatory mediators and adaptive immune responses [14•,15•]. Systemic inflammation and infiltration of innate immune cells was seen; however, mice had massive infiltrates of granulocytes in dermis and epidermis which contrasts to human disease in which epidermal disease is absent. Although one group reported high levels of IL-17, increased TH17 differentiation and the development of anti-DNA antibodies [15•], the disease also developed in Rag1 deficient, Nlrp3 double mutant mice, which lack mature T and B cells, demonstrating that the disease can develop in the absence of Th17 cells [14•]. In addition, autoimmunity with the development of ANA antibodies in human disease is extremely rare. Further studies exploring the role of IL-17 may be needed to further clarify the role of IL-17 in this disease.

The number and diversity of NLRP3 inflammasome activating triggers that have been identified in in-vitro assays suggest a convergent common molecular pathway that directly

interacts with the NLRP3 inflammasome such as the ROS system [16]. A recent report [17] shows that the altered kinetics of early IL-1 release in CAPS patients may be due to alterations in the redox state at the basal level in untreated patients followed by early exhaustion of the cells in response to TLR triggering. The increased IL-1[beta] secretion was decreased by pharmacologic inhibition of the redox response suggesting that a reducing environment may be critical for inflammasome activity.

Pediatric granulomatous arthritis

Pediatric granulomatous arthritis (PGA; familial cases also known as Blau syndrome and sporadic cases also known as neonatal-onset sarcoidosis) is an autosomal dominant inflammatory disorder due to mutations in *NOD2* [3•]. Patients classically present with the 'triad' of noncaseating granulomatous uveitis, arthritis, and rashes.

Clinical update

Clinical manifestations of 45 patients with PGA followed in a large cohort study were reported [18]. The majority of patients presented with the classic triad; however, atypical systemic manifestations including vasculitis, nephritis, interstitial lung disease, pulmonary emboli, cardiomyopathy, and hepatosplenic granulomas were observed.

Genotype-phenotype analyses in PGA suggest a more variable penetrence of the disease than previously reported as asymptomatic heterozygous carriers have been identified in a family with E383K mutation positive PGA [19]. So far all disease-associated mutations in PGA are in the regulatory (NOD) domain and have been associated with constitutive NF-[kappa]B activation [20]. There was no clear relationship between the severity of the clinical manifestations and basal NF-[kappa]B activity. Visual impairment tended to occur more frequently in patients with the R334W compared with the R334Q mutation [20].

Pathogenesis updates

Case reports suggest effective treatment with IL-1 [21] and TNF-blocking agents [22]. However, recent clinical and in-vitro data suggested that the pathogenesis of PGA cannot be attributed to IL-1 defects alone and may be more complex. In one study [23], unstimulated and LPS-stimulated peripheral blood cells cultured from patients with PGA did not differ in IL-1[beta] production when compared to controls and both patients with PGA who were assessed in that study did not respond to IL-1-blocking therapy with anakinra.

Mutated NOD2 signaling is associated with increased NF-[kappa]B activation [24] (Fig. 1). Thalidomide is a drug that suppresses NF-[kappa]B induction in response to a number of inflammatory stimuli [25]. Two patients with severe PGA had a clinical response and in-vitro studies showed a reduced ability for monocytes to form giant cells and osteoclasts in the presence of thalidomide [26].

Familial Mediterranean fever

FMF is an autosomal recessive disease, caused by mutations in *MEFV*, the gene encoding the protein pyrin [27,28]. FMF typically presents with 1–3 day episodes of fever with sterile peritonitis, pleuritis, arthritis, and rash which may be complicated by the development of amyloidosis [3•]. Colchicine is a first line treatment and is very effective in the treatment of most patients and in preventing amyloidosis [29].

Clinical update

New criteria for pediatric FMF have been developed as the traditional classification criteria have lower sensitivity and specificity in children than in adults. FMF in children may

initially present with fever alone but typically progresses to more classic features within 3 years [30]. Fever alone is particularly common in children under the age of 2 [30]. The new pediatric criteria include the presence of fever, abdominal pain, chest pain, arthritis, and a family history of FMF. The presence of two or more of these criteria diagnosed FMF in children with a sensitivity of 86.5% and a specificity of 93.6% in the Turkish population. The criteria have not been validated in populations with a lower incidence of FMF [31].

Most of the disease-causing mutations in FMF are located on exon 10 of the *MEFV* gene which encodes the B30.2 domain of the pyrin protein [3•]. However, genetic variants found in exons 2 and 3 are often associated with nonspecific inflammatory manifestations and are of uncertain clinical significance. Two of these variants on exon 3, P369S/R408Q, occur in cis and have a high allele frequency (1.3% in Caucasians and higher than 5% in Asians). One group found the variant in 40 symptomatic and four asymptomatic family members [32•]. The 20% of patients who fulfilled FMF criteria had somewhat atypical attacks and a partial response to colchicine and two patients had vague symptoms which responded to anakinra. Modeling suggested that these variants do not affect the secondary structure of pyrin nor binding of the protein to wild-type and mutated PSTPIP1 [32•]. Another variant, E148Q on exon 2, has an allele frequency of 0.5–5% in Caucasians and up to 23% in Japanese. Asymptomatic individuals homozygous for this mutation [33,34] have been reported in some populations but in Greek and Turkish patients E148Q seems to confer susceptibility to a nonspecific inflammatory phenotype [35,36]. Interestingly, two groups report that a single heterozygous mutation in *MEFV* is enough to develop FMF and that the majority of patients present with typical clinical features of FMF [37•,38•]. In another study, the clinical presentation of patients with recurrent fevers and only one mutant *MEFV* allele appeared to be similar to homozygous patients and most patients required colchicine therapy [39].

Finally, the small studies of *MEFV* mutations in diseases other than FMF found *MEFV* mutations at a higher frequency in fibromyalgia with elevated IL-1[beta] levels [40] as well as with systemic onset juvenile idiopathic arthritis (SoJIA) [41]. The common *MEFV* mutations were not found to have an association with Crohn's disease or ulcerative colitis [42].

Pathogenesis update

S100A12 levels are very high in systemic onset juvenile idiopathic arthritis and are being evaluated as a biomarker in FMF. S100A12, a neutrophil derived damage-associated molecular pattern (DAMP) protein, is a member of the S100 calcium-binding proteins that are expressed at sites of inflammation. S100A12 levels were 290 times higher in children with active FMF when compared with normal controls [43•]. These levels decreased after the initiation of colchicine therapy but remained higher in patients with persistent and even inactive disease, suggesting that S100 proteins may be sensitive biomarkers of ongoing inflammation.

Pyrin can act as a pro-inflammatory or anti-inflammatory mediator of inflammation depending on the functional models examined. Wild-type pyrin seems to mediate anti-inflammatory properties [44], whereas mutated protein may mediate increased IL-1 processing and secretion through the formation of an inflammasome-like complex [45]. A previous report [46] also suggests that pyrin can serve a pro-inflammatory role in a transfection model.

The structure of the C-terminal B30.2 domain of pyrin was recently crystallized. This is the domain that encodes exon 10 and is the most frequent site of FMF mutations. The majority of mutations were found to cluster in a shallow cavity covered with hydrophobic amino

acids, the predicted peptide-binding site, suggesting that they may impact ligand binding [47•]. The B30.2 domain is also the domain that interacts directly with caspase-1 to convert pro-IL-1[beta] to active IL-1[beta] [44].

Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome manifests with sterile purulent arthritis and pustular skin disease including cystic, scarring acne, and pyoderma gangrenosum [48,49]. It is due to mutations in *PSTPIP1*, also known as CD2-binding protein 1 (CD2BP1) [48]. Treatment with IL-1-blocking agents is based largely on expert opinion and the rationale of targeting the known aberrant pathways.

Clinical update

Case reports of successful treatment of pyogenic arthritis with anakinra [50,51] exist in addition to reports of responses to high doses of anti-TNF therapy [52].

Pathogenesis update

PSTPIP1 has been shown to bind pyrin [53] resulting in the unmasking of its pyrin domain and recruitment of ASC. Mutations in *PSTPIP1* in PAPA syndrome prevent phosphorylation of the molecule and lead to prolonged binding to pyrin. This causes more efficient oligomerization with adaptor proteins including ASC and prolonged activation of caspase-1 and the inflammasome, resulting in the formation of active IL-1[beta] and inflammation [46] (Fig. 1). Interestingly, a polymorphism of the *PSTPIP1* promoter was reported to be associated with Crohn's disease and aseptic abscesses [54]. PSTPIP1 can form tubulin-dependent homodimers which generated membrane-associated filaments that impacted in-vivo trafficking of PSTPIP1 [55].

TNF-receptor-associated periodic syndrome

TRAPS is characterized by prolonged episodes of fevers accompanied by abdominal pain, pleuritis, migratory skin rashes, fasciitis, and periorbital edema. It is a dominantly inherited disorder due to mutations in *TNFRSF1A*, encoding the TNF receptor type 1. The first-line treatment is generally with TNF-inhibiting medications; however the treatment response is often incomplete [56].

Clinical update

Anakinra has been reported to be successful in some resistant cases [57,58]. TRAPS is a rare disease; the incidence of TRAPS in Germany was determined in a prospective study at 5.6 per 10 000 000 person-years [59].

Pathogenesis update

Despite the known genetic defect, the mechanism of disease pathogenesis remains incompletely understood. An initial report showed delayed TNF receptor cleavage from cells in a patient with TRAPS implicating increased signaling through the TNF receptor; however, the majority of patients do not have receptor shedding defects. Most mutations in the TNF receptor occur in the extracellular domain and affect receptor folding and trafficking, resulting in the retention of misfolded TNF receptor complexes in the endoplasmic reticulum [60,61].

A mouse knock-in model of mutant *TNFR1* indicated that mutated TNF receptor has a high affinity for TNF but does not function as a cell surface receptor. Mutant receptors rather accumulate intracellularly in the endoplasmic reticulum resulting in enhanced activation of

MAPKs and secretion of pro-inflammatory cytokines upon stimulation with LPS [62••]. In fact, mutant receptors no longer oligomerized with wild-type receptors but rather formed disulfide-linked homo-oligomers. The enhanced inflammatory phenotype depended on intact TNF receptor on the cell surface leading to the hypothesis that an autocrine loop forms between mutated TNFR1 signaling in the endoplasmic reticulum with wild-type TNF receptor signaling necessary to respond to inflammatory cytokine release [62••]. These findings provide a rationale as to why the disease is inherited in an autosomal dominant manner and also offer an explanation regarding the partial response to TNF blockade [56] (Fig. 1).

Additional evidence is building to suggest that cytokines other than TNF may be important in disease pathogenesis. Previous reports have shown that patients with TRAPS have increased NF-[kappa]B activation, the major signaling molecule involved in the secretion of pro-inflammatory cytokines. Peripheral blood mononuclear cells mutation positive TRAPS patients had significantly increased activation of NF-[kappa]B as well as higher than expected levels of functional TNFR1 at the cell surface [63]. Interestingly, TRAPS patients may have an exaggerated inflammatory response to treatment with infliximab. In one study [64], significant increases in the secretion of the inflammatory cytokines IL-1[beta], IL-1R1, IL-6, IL-8, and IL-12 in peripheral blood mononuclear cells from TRAPS patients compared with normal controls after incubation with infliximab were seen. An additional report [65] indicates that NF-[kappa]B activation may in fact be decreased in response to TNF stimulation of leucocytes from patients with TRAPS. This was not seen in response to LPS or IFN-[gamma] suggesting that there may be an alternative stimulus other than TNF that is responsible for the previously observed activation of NF-[kappa]B in these patients.

Hyperimmunoglobulinemia D with periodic fever syndrome

Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) presents with fever, lymphadenopathy, rash, arthralgia, and abdominal pain. Episodes last several days and recur every 4–8 weeks. Febrile episodes are often triggered following vaccinations, trauma, or stress. Although serum immunoglobulin D levels may be elevated, they may also be normal and there is little diagnostic utility in measuring their levels [66]. The disease is caused by autosomal recessive mutations in mevalonate kinase (*MVK*) [67,68], a gene known to cause mevalonic aciduria, and patients may have elevated urine mevalonic acid. The recognition of the same genetic defect suggested that HIDS is on the milder end and mevalonate aciduria on the severe end of a clinical spectrum. As the enzyme mutated is part of the isoprenoid and cholesterol synthesis pathway, its relevance to causing inflammation has been puzzling.

Clinical update

The long-term outcomes of patients with HIDS were described [69]. Clinical symptoms began at a median age of 6 months; however, it took on average 9.9 years to make the diagnosis. Disease attack frequency decreased with age. Amyloidosis occurred infrequently in 2.9% of patients. Most patients were treated with prednisone, anakinra, and/or etanercept. An attempt has been made to define criteria to assist in excluding patients from genetic testing that are unlikely to have disease. Patients with HIDS had either an onset age less than 5 years or painful attacks with a length less than 14 days [70] with a sensitivity of 100% and specificity of 28%, suggesting that mutations are unlikely in patients that do not meet either of these two criteria.

Pathogenesis update

Evidence exists for a pathologic role of IL-1[beta] activation through caspase-1 [71] and for successful treatment with anakinra in acute crises [72]. Treatment of monocytes with

simvastatin, an inhibitor of isoprenoid biosynthesis mimicking mevalonate kinase deficiency, resulted in increased activation of capase-1-mediated IL-1[beta] activation [73]. Inhibition of enzymes involved in the synthesis of geranylgeranyl pyrophosphates (GGPPs), members of the isoprenyls, resulted in increased IL-1[beta] production from normal peripheral blood cells in response to LPS which was similar to that observed in patients with HIDS [74]. The phenotype in LPS-stimulated blood from HIDS patients could be reversed with the addition of GGPPs or mevalonic acid. TNF-[alpha] may also be important in disease pathogenesis [75] and TNF inhibitors have been effective in the treatment of this syndrome in some cases [76–78].

Auto-inflammatory bone diseases and chronic recurrent multifocal osteomyelitis

Chronic recurrent multifocal osteomyelitis (CRMO) are a number of noninfectious, auto-inflammatory disorders resulting in sterile osteomyelitis. Of particular concern are vertebral lesions that may lead to collapse. The spectrum of CRMO consists of monogenic and likely polygenic conditions. Subsets of patients with a perinatal onset of osteolytic lesions were found to have monogenic conditions: Majeed syndrome caused by autosomal recessive mutations in *LPIN2* [79] and deficiency of the IL-1 receptor antagonist (DIRA), discussed in this chapter below. There is evidence for missense mutations in *PSTPIP2* in the cmo murine model of CRMO [80]; however, mutations in the genes associated with the monogenic forms of aseptic osteomyelitis have not been found in most children with genetically undefined CRMO. Children typically present at school age with distinct bony lesions and pustular skin lesions. Clinical similarities with the known monogenic disorders suggest shared inflammatory pathways and investigations are ongoing.

Clinical update

First-line therapy in patients with the clinical, genetically undefined form of CRMO is NSAIDs with steroids, methotrexate, sulfasalazine, and TNF inhibitors in resistant cases. The disease is usually self-limiting but a sizeable proportion of patients experience a prolonged disease course [81]. Bisphosphonate therapy with pamidronate is emerging as a treatment modality for bony lesions and pain, particularly in patients with vertebral lesions [82]. One study [83] showed that 26% of patients had spinal involvement and 52% of those patients had vertebral deformities. The majority but not all patients with spinal involvement had pain. The pain resolved in all patients within 3 months after treatment with pamidronate with no adverse events. Whole-body MRI detecting CRMO-related lesions not observed on plain radiography may make MRI a more sensitive modality in assessing and following bone lesions [84].

Deficiency of the IL-1 receptor antagonist

A new autosomal recessive disorder of IL-1 regulation was described in 2009 due to mutations in the IL-1 receptor antagonist (IL-1Ra) [85••,86••]. Eight patients, from Newfoundland (one), Holland (five from three families) and Lebanon (two brothers), were homozygous for a frame shift or missense mutation leading to a truncated nonfunctional protein [85••]. Two patients from Puerto Rico were homozygous for a 175-kb genomic deletion including *IL1RN* and five adjacent genes [85••,86••]. The allele frequency of these founder mutations was 0.2% in Newfoundland and 1.3% in the Northern part of Puerto Rico suggesting that unrecognized clinical cases likely exist. Patients present in the perinatal period with systemic inflammation, multifocal osteolytic lesions, periosteitis, and a pustular rash. Other clinical features include heterotopic bone formation around the proximal femur, thrombosis, and rarely vasculitis. Interestingly, organ manifestations seen in NOMID

including meningitis, cochlear inflammation, hearing loss, and conjunctivitis or uveitis were not present in DIRA patients. However, two children died in the neonatal period due to a severe inflammatory response syndrome. The absence of the negative regulator, IL-1 receptor antagonist, leads to unopposed signaling of IL-1[alpha] and IL-1[beta] through the IL-1 receptor Type I with increased production of pro-inflammatory cytokines. Like CAPS patients, DIRA patients have a dramatic respon

Early-onset enterocolitis (IBD) due to lack of a functional IL-10 receptor

Also in 2009, a new autosomal recessive disorder was described due to mutations in the IL10 receptor. In four patients, three distinct homozygous mutations in the genes *IL10RA* and *IL10RB*, encoding the IL10R1 and IL10R2 proteins which form a heterotetramer to make up the interleukin-10 receptor have been reported to cause a neonatal disease presenting with severe inflammatory bowel disease and folliculitis [87••]. These ‘lack of function’ mutations result in the loss of IL-10 signaling as manifested by deficient STAT3 phosphorylation after stimulation with IL-10. Levels of TNF[alpha] and other inflammatory cytokines including IL-1[alpha], IL-1[beta], and IL-6 were increased. One of the patients underwent an allogeneic stem cell transplant with sustained resolution of symptoms at 1 year following transplant. This disorder proves that loss of signaling of the anti-inflammatory cytokine IL-10 is sufficient to cause a pro-inflammatory syndrome with enterocolitis as a main clinical feature.

Table 2 lists the monogenic disorders resulting from primary defects in either inflammatory sensors or subsequent mediator pathways.

Implications of disease-based gene discoveries on the understanding of common inflammatory disorders

Monogenic auto-inflammatory disorders have provided insights into key inflammatory pathways that regulate inflammation in particular the understanding of the role of inflammasomes in human disease. In a number of more common disorders, several of which less classically associated with an inflammatory disorder, inflammasome activation has been recognized as an important factor in causing an ongoing inflammatory response. These disorders include the activation of the inflammasome by uric acid causing gout [88] and stimulation of the inflammasome by asbestos and silica causing asbestosis [89] and silicosis [89]. Newer evidence implicates convergence of triggers to activate the NLRP3 inflammasome in an even wider spectrum of diseases. The expanding list of diverse processes with emerging evidence for a pathogenic role for inflammasome activation include type 2 diabetes [90], atherosclerosis [91,92], Alzheimer's dementia [93], stem cell transplant outcomes [92], and tumorigenesis [94–96]. Less well understood are the mechanisms by which the inflammasome is triggered and the roles of targeted anti-inflammatory treatment with IL-1 or caspase inhibition in these disorders. These remain topics of active investigation.

Conclusion

The number of monogenic auto-inflammatory disorders is rapidly expanding. These disorders provide unique insights into the mechanisms of key inflammatory pathways that evolved to protect the integrity of organisms. The identification of mutations in patients with auto-inflammatory diseases in sensors of danger or in the mediator pathways that coordinate a response to danger signals allows us to understand the impact of a single molecule or protein disruption on the multiple organs that are affected in patients. As the pathogenic mechanisms of many diseases are increasingly understood, the complexity of the

inflammatory response is appreciated. Further understanding of the molecular pathways and their key regulators has uncovered IL-1 as a pivotal target in diseases associated with inflammasome activation and will continue to provide molecular targets for the treatment of inflammatory conditions. Therapeutic strategies that allow the manipulation of danger recognition and the associated signaling pathways will lead not only to the development of new treatments for a number of rare genetic conditions, but also to the exploration of these pathways in more common, genetically complex disorders in which regulation of inflammation is of importance.

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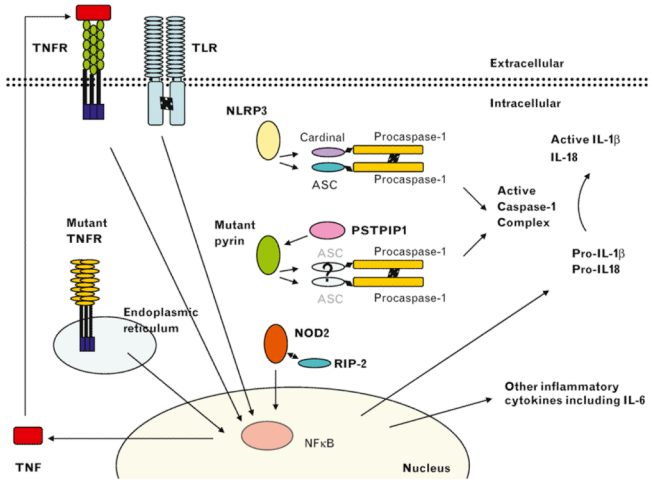

Figure 1.

CAPS, FMF, and PAPA result in activation of the caspase-1 complex. In CAPS, mutations in *NLRP3* result in increased assembly of the NLRP3 inflammasome and active caspase-1 through interactions with cardinal, ASC, and procaspase-1. In PAPA, mutations in *PSTPIP1* result in its increased binding to pyrin and activation of active caspase-1. In FMF, mutant pyrin is pro-inflammatory in some conditions and results in caspase-1 activation. Active caspase-1 then cleaves pro-IL-1β to form active IL-1β and IL-18 in CAPS, FMF, and PAPA. In PGA, mutant NOD2 binds RIP-2 leading to increased NF-κB production and the transcription of pro-IL-1β and other inflammatory cytokines. In TRAPS, the mutant TNF receptor (TNFR) is sequestered in the endoplasmic reticulum leading to NF-κB production and transcription of a number of pro-inflammatory cytokines. An inflammatory feedback loop is generated through the production of TNF-α that can bind and signal through the wild-type TNFR on the cell surface. Toll-like receptor (TLR) stimulation *in vitro* induces pro-IL-1β and other cytokine production and models an essential first step in initiating an inflammatory response.

Table 1

Disease	Gene	Protein	Inheritance pattern	Disease onset	Flare/fever pattern	Specific organ inflammation	Treatment
CAPS:							
FCAS	*NLRP3*, *NALP3*, *CIAS1* (1q44)	Cryopyrin, NLRP 3	Autosomal dominant	First 6 months of life, cold induced	<24 h	Urticarial-like rash, conjunctivitis, arthralalgia	IL-1 blockade
MWS	*NLRP3*, *NALP3*, *CIAS1* (1q44)	Cryopyrin, NLRP 3	Autosomal dominant	Infancy to adolescence	24–48 h or continuous with flares	Urticarial-like rash, conjunctivitis, arthralalgia, hearing loss, meningitis (mild)	IL-1 blockade
NOMID	*NLRP3*, *NALP3*, *CIAS1* (1q44)	Cryopyrin, NLRP 3	Autosomal dominant/ de novo	Neonatal or early infancy	Continuous with flares	Urticarial-like rash, conjunctivitis, arthralalgia, hearing loss, meningitis, bony epiphyseal hyperplasia	IL-1 blockade
DIRA	*IL1RN* (2q14)	IL-1 receptor antagonist	Autosomal recessive	Neonatal or early infancy	Continuous with flares	Pustular rash, bony osteolytic lesions, periostitis, pneumonilis (rare), vasculitis (rare)	IL-1 receptor antagonist (anakinra)
FCAS2	*NLRP12*	Monarch-1	Autosomal/dominant	Childhood, cold induced	2–10 days, 1–3 3 per episodes per month	Urticarial-like rash, hearing loss, arthralgia, aphthous ulcers	IL-1 blockade?
FMF	*MEFV* (16p13)	Pyrin, marenostrin	Autosomal recessive	80% of the cases occur before the age of 20	1–3 days	Rash, peritonitis, pleuritis, arthritis	Colchicine, rarely IL-1 and TNF blockade or thalidomide if colchicines resistant
HIDS	*MVK* (12q24)	Mevalonate kinase	Autosomal recessive	Median age at onset 6 months	3–7 days	Rash, arthralgia, abdominal pain, lymphadenopathy, retinal dystrophy	NSAIDS, corticosteroids, TNF and IL-1 blockade
PAPA	*CD2BP1* (15q24)	PSTPIP1	Autosomal dominant	Early childhood	Common	Pustular acne, pyoderma gangrenosum, pyogenic arthritis	Local and systemic corticosteroids, TNF or IL-1 blockade
TRAPS	*TNFRSF1A* (12p13)	TNF receptor 1	Autosomal dominant	Median age at onset 3 years	1–4 weeks	Migratory rash, abdominal pain, pleuritis, fasciitis, periorbital edema	TNF blockade, steroids, IL-1 blockade, colchicine is ineffective

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Disease	Gene	Protein	Inheritance pattern	Disease onset	Flare/fever pattern	Specific organ inflammation	Treatment
PGA	*NOD2* (16q12)	Nod2	Autosomal dominant/ de novo	Early childhood	Uncommon	Rash, uveitis, arthritis	NSAIDS, corticosteroids, methotrexate, cyclosporine, TNF or IL-1 blockade
Majeed's syndrome	*LPIN2* (18p11)	Lipin2	Autosomal recessive	Early infancy (1–19 months)	Weeks–months	Sterile osteomyelitis, anemia	NSAIDS, corticosteroids, interferon-α
IL-10 receptor deficiency	*IL10RA* (11q23) *IL10RB* (21q22)	IL-10 receptor, *IL10RB* also forms IL-22, -26, -28, -29 receptors	Autosomal recessive	Neonatal or early infancy	Continuous with flares	Colitis with fistula formation, folliculitis	Bone marrow transplantation

Table 2

Disease	Known inducers	Sensor or modifier	Mediator(s)/mediator pathways	Target organ
CAPS:				
FCAS	Cold	**Cryopyrin, NLRP 3**	Activated caspase-1 causing oversecretion of IL-1β	Skin, eyes, joints
MWS	Unknown, cold in some, infections, stress	**Cryopyrin, NLRP 3**	Activated caspase-1 causing oversecretion of IL-1β	Skin, eyes, joints, inner ear, meninges (mild)
NOMID	Unknown, infections, stress	**Cryopyrin, NLRP 3**	Activated caspase-1 causing oversecretion of IL-1β	Skin, eyes, joints, inner ear, meninges, epiphyses of long bone
FMF	Unknown	**Pyrin**	Partially activating caspase-1 causing IL-1β secretion, altered apoptosis	Skin, joints, peritoneum, pleura
PAPA	Unknown, skin trauma	**PSTPIP1**	Increased binding of pyrin to ASC activating caspase-1 causing IL-1β secretion	Skin, joints
PGA	Unknown	**NOD2**	Increased NF-κB production	Skin, eyes, joints/synovium
HIDS	Childhood immunizations	Mevalonate kinase	Lack of **mevalonate kinase** leading to isoprencid deficiency activating caspase-1 causing IL-1β secretion, altered apoptosis	Skin, eyes, joints, lymph nodes
DIRA	Mechanical skin trauma, infections	n/a	Lack of **IL-1Ra** leading to unopposed IL-1α and IL-1β signaling	Skin, bones, lungs (rare), blood vessels (rare)
TRAPS	Unknown, stress, trauma	n/a	Altered **TNFR1** signal increasing IL-1β, IL-6, TNF-α	Skin, eyes, joints, peritoneum, pleura
IL-10 receptor deficiency	Commensal gut flora	n/a	Lack of anti-inflammatory **IL-10R** signaling	Colon, skin

Mutant protein is marked in bold.