

The autoinflammatory syndromes

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Purpose of review

To review the remarkable recent progress in our understanding of a range of inflammatory conditions in humans that until recently appeared unrelated. The term autoinflammatory disease has been proposed to describe a group of disorders characterized by attacks of seemingly unprovoked inflammation without significant levels of autoantibodies and autoreactive T cells.

Recent findings

As the link between the innate immune response and disease susceptibility has become more apparent, some remarkable associations have emerged. The majority of hereditary periodic fevers are due to mutations in the pyrin and tumour necrosis factor receptor superfamilies of molecules, both of which are intimately involved in innate immunity. Pyrin/marenostrin protein is mutated in familial Mediterranean fever, while mutations in a related protein, cryopyrin, are associated with Muckle-Wells/familial cold urticaria and chronic infantile neurologic cutaneous and articular syndrome. Both of these proteins interact with the apoptotic speck-like protein involved in caspase-1 activation and regulation of nuclear factor kappa B transcription; furthermore cryopyrin contains regions of homology with the nucleotide-binding oligomerization domain 2 protein, which is associated with susceptibility to Crohn's disease. Variants in the leucine-rich repeat domain of nucleotide-binding oligomerization domain are found in approximately 20% of patients with Crohn's disease, depending on ethnic background, while mutations in the NACHT domain are associated with a rare dominant granulomatous disease called Blau syndrome.

Summary

The study of autoinflammatory disease has progressed from genetics to definition of the functional defects in these patients. Although a direct association between defective innate immune responses to bacterial components and these diseases has not been formally established, much ongoing research is aimed towards confirmation of that hypothesis.

Keywords

autoinflammatory, apoptosis, chronic infantile neurologic cutaneous and articular syndrome/neonatal-onset multisystem inflammatory disease, cryopyrin/NACHT, leucine-rich repeat and pyrin domain-containing protein 3/pyrin-containing Apaf1-like protein 1, Crohn's disease, interleukin-1, nuclear factor- κ B, NACHT, pyrin/marenostrin

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Abbreviation

APAF1	apoptotic protease activating factor 1
ASC	apoptosis-associated speck-like protein with a CARD
CARD	caspase recruitment domain
CIAS1	cold-induced autoinflammatory syndrome 1 gene
CINCA	chronic infantile neurologic cutaneous and articular syndrome
FCU	familial cold urticaria
IBD	inflammatory bowel disease
LRR	leucine-rich repeat
MWS	Muckle-Wells syndrome
NACHT	NAIP, CIITA, HET-E and TP1 domain
NALP3	NACHT, LRR and PYD-containing protein 3
NBS	nucleotide binding site
NF κ B	nuclear factor- κ B
NOD	nucleotide-binding oligomerization domain
NOMID	neonatal-onset multisystem inflammatory disease
OCT1	octamer-binding protein 1
PAPA	pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome
PYD	pyrin domain
PYPAF1	pyrin-containing Apaf1-like protein 1
TNF	tumour necrosis factor

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Introduction

The term 'autoinflammatory' has been attributed to the distinct pathogenesis of a group of disorders characterized by unexplained recurrent attacks of inflammation without any evidence that this process is related to auto-antigen exposure. A partial list of these disorders has been proposed [1] and the hereditary periodic fever syndromes take pride of place as the prototype autoinflammatory diseases (Table 1). Significant conceptual breakthroughs in our understanding of the molecular basis of inflammatory mechanisms in general have occurred in the past 5 years, with successive identification of the genetic basis of all the known hereditary periodic fever syndromes and their association with the innate immune response. During the past year the susceptibility gene for Muckle-Wells syndrome (MWS)/familial cold urticaria (FCU) and chronic infantile neurologic cutaneous and articular syndrome (CINCA)/neonatal-onset multisystem inflammatory disease (NOMID) syndrome have been identified. Mutations in cytokine recognition and signalling molecules have been implicated in the disease mechanisms of all except one of these disorders, that is hyperimmunoglobulinaemia D with periodic fever syndrome (HIDS; MIM 260920). Disordered interleukin-1 processing, regulation of nuclear factor- κ B (NF κ B) transcription factor, as well as possible defective cellular apoptosis, have emerged as unifying themes in the pathogenesis. Mutations in genes encoding the tumour necrosis factor (TNF) receptor and pyrin superfamilies of molecules may lead to persistence of leukocytes that would ordinarily undergo apoptosis,

Table 1. A partial list of autoinflammatory disorders, discussed in this paper, and for which the susceptibility genes have been identified

Hereditary periodic fever syndromes and related conditions		Gene/chromosome	Protein
FMF	MIM 294100	<i>MEFV</i> (16p13)	Pyrin/marenostrin
HIDS	MIM 260920	<i>MVK</i> (12q24)	Mevalonate kinase
TRAPS (FHF)	MIM 142680	<i>TNFRSF1A</i> (12p13)	TNF receptor 1
FCU/FCAS	MIM 120100	<i>CIAS1/NALP3/PYPAF1</i> (1q44)	Cryopyrin/NALP3/PYPAF1
MWS	MIM 191900	<i>CIAS1/NALP3/PYPAF1</i> (1q44)	Cryopyrin/NALP3/PYPAF1
CINCA/NOMID	MIM 607115	<i>CIAS1/NALP3/PYPAF1</i> (1q44)	Cryopyrin/NALP3/PYPAF1
PAPA	MIM 604416	<i>CD2BP1</i> (15q24)	CD2-binding protein 1
Granulomatous disorders			
Crohn's disease (IBD)	MIM 266600	<i>NOD2</i> (16q12)	Nucleotide-binding oligomerization domain 2
Blau syndrome	MIM 186580	<i>NOD2</i> (16q12)	Nucleotide-binding oligomerization domain 2

FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinaemia D with periodic fever syndrome; TRAPS, tumour necrosis factor receptor-associated periodic syndrome; FHF, familial Hibernian fever; FCU, familial cold urticaria; FCAS, familial cold autoinflammatory syndrome; *CIAS1*, cold-induced autoinflammatory syndrome 1 gene; *NALP3*, NACHT, LRR and PYD-containing protein 3; *PYPAF1*, pyrin-containing Apaf1-like protein 1; MWS, Muckle-Wells syndrome; CINCA, chronic infantile neurologic cutaneous and articular syndrome; NOMID, neonatal-onset multisystem inflammatory disease; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, and acne; *CD2BP1*, CD2-binding protein 1; IBD, inflammatory bowel disease; Blau syndrome, chronic granulomatous synovitis with uveitis and cranial neuropathy; *NOD2*, nucleotide-binding oligomerization domain 2; TNF, tumour necrosis factor.

thus permitting the amplification of relatively mild inflammatory stimuli. Although a direct connection between microbial triggering of inflammatory events has not been established, circumstantial evidence does indeed suggest that whilst the foot soldiers of the innate immune system (e.g. proinflammatory cytokines such as TNF and interleukin-1) have been deployed for active field duty, the joint chiefs-of-staff (T and B cells) perform mainly observatory roles from their citadel of adaptive immunity.

The hereditary periodic fevers

The blanket term 'hereditary periodic fevers' has been applied to a group of distinct heritable disorders characterized by unexplained episodes of fever and severe localized inflammation. The membranous synovial and serosal linings are particular targets leading to articular and abdominal pain; in addition these patients may suffer from rashes, and varying degrees of neurological involvement. Familial Mediterranean fever (FMF; MIM 294100), inherited as an autosomal-recessive trait, is the most prevalent hereditary periodic fever worldwide and the FMF gene (designated *MEFV*) is expressed predominantly in granulocytes [2], activated monocytes and in early leukocyte development [3]. The biological function of pyrin/marenostrin (FMF protein) is the subject of intensive research, and a consensus regarding its function is gradually being achieved.

Pyrin/marenostrin contains at least four different conserved domains composed of an N-terminal 92 amino acid residue pyrin domain, B-box zinc-finger, coiled coil and B30.2 domains (Fig. 1). The pyrin domain (PYD) has been predicted by circular dichroism spectra comparison [4••] as well as computational techniques [5•] to be a member of the six-helix bundle death domain-fold superfamily that includes death domains,

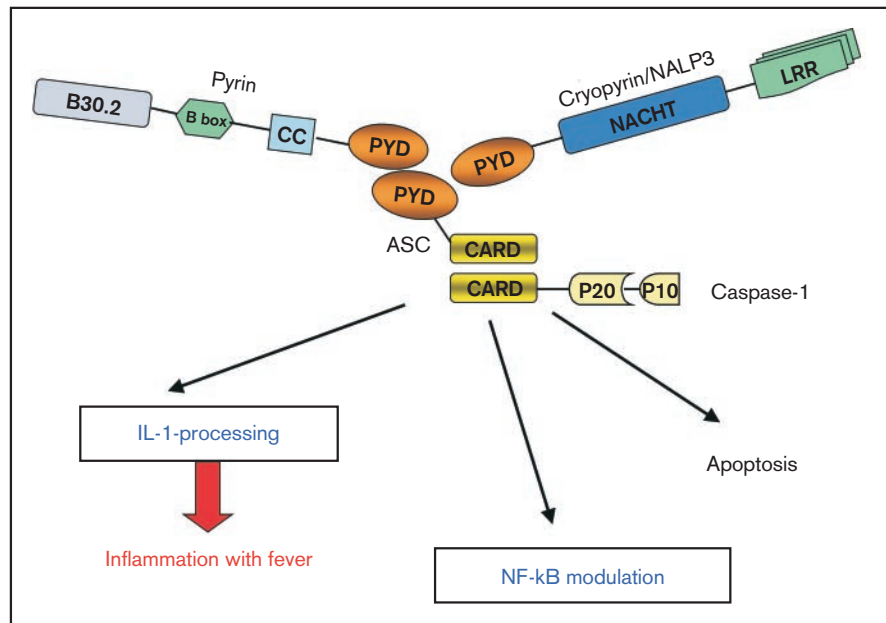
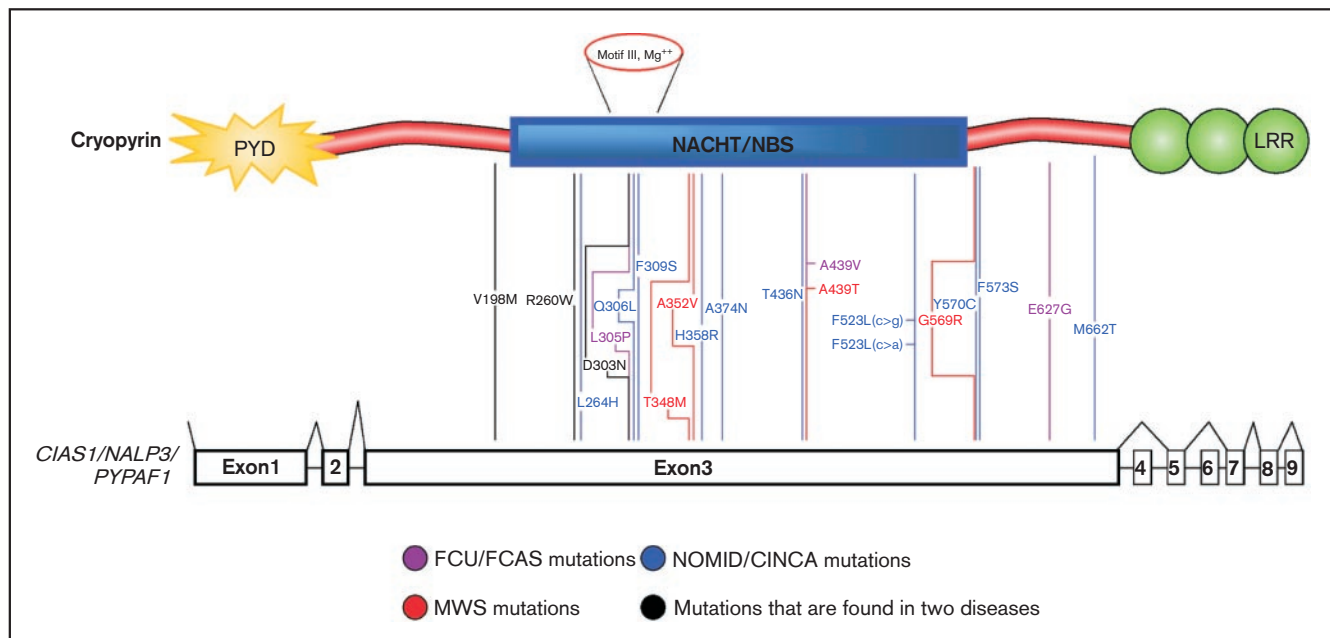
death effector domains, and caspase recruitment domains (CARDs) [6•]. These domains, found in a range of proteins, are thought to function in apoptotic and inflammatory signaling pathways through homotypic protein-protein interactions. Pyrin/marenostrin binds apoptosis-associated speck-like protein (ASC) with a caspase recruitment domain (Pycard/ASC) [5•], which is an adaptor protein involved in the activation of caspase-1 (interleukin-1 β converting enzyme) [7•,8•]. Caspase-1 recruitment may then progress to any of the disparate processes of interleukin-1 production, NF κ B regulation [9•], or involvement in apoptosis pathways [5•] (Fig. 1).

Evidence that pyrin/marenostrin has an antiinflammatory role comes from targeted disruption of pyrin in the mouse, which shows an increase in interleukin-1 processing, and defective lipopolysaccharide and interleukin-4-induced apoptosis in peritoneal monocytes [10]. Most human mutations are localized in the B30.2 domain at the C-terminal end of pyrin/marenostrin, and for the moment the functional role of this domain is unknown.

Further information about the function of pyrin/marenostrin may come from identification of the gene for pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome (PAPA; MIM 604416), which is a rare autosomal dominant disorder characterized by recurrent inflammatory episodes with accumulation of sterile, pyogenic, neutrophil-rich material in the joints. Mutations of the CD2-binding protein 1 (*CD2BP1*) give rise to PAPA syndrome [11••]; recent data from our collaborators have shown that *CD2BP1* may interact with pyrin (N. Shoham, manuscript in preparation). The effect of PAPA-associated mutations on the pyrin/marenostrin binding and downstream pathways is under investigation, but it is tempting to

Figure 1. Proteins containing the N terminal PYD domain regulate inflammation via their interaction with ASC

The assembly of cryopyrin and ASC is thought to induce interleukin-1 processing through caspase-1, whereas pyrin/marenostrin may act as an inhibitor of this recently defined inflammation pathway. Loss of function mutations in the pyrin/marenostrin protein, as found in familial Mediterranean fever patients, could potentially lead to autoinflammation by reducing the pyrin inhibitory role. Alternatively, gain of the function mutations in cryopyrin, as found in MWS/FCU/NOMID patients, could activate this pathway.

**Figure 2. The spectrum of diseases associated with *CIAS1/NALP3/PYPAF1* mutations**

All mutations have been identified in exon 3 of this gene, with 14/2 mutations located within the NACHT/NBS domain, while six mutations are found in the region of cryopyrin flanking the NACHT domain. Three of these mutations (*D303N*, *Q306L*, and *D309S*) are clustered near the Mg⁺⁺ binding site of Motif III of the NACHT domain, and there are four other mutation clusters (a.a. 260–264; a.a. 348–358; a.a. 436–439; a.a. 569–573) that indicate the presence of other important but unknown functional sites.

Some mutations, *V198M*, *R260W* and *D303N*, are associated with more than one phenotype.

speculate that the disease mutations may somehow affect the interaction between pyrin/marenostrin and CD2BP1.

MWS (MIM 191900) and FCU (MIM 120100), also called familial cold autoinflammatory syndrome, are two related autosomal dominant conditions that result from mutations in a protein with homology to pyrin/marenostrin, variously termed cryopyrin, NALP3 (for NACHT, leucine-rich repeat (LRR) and PYD-containing proteins), or PYPAF1 (for pyrin-containing Apaf1-like protein 1) [12•,13•,14•] (Fig. 2). All disease mutations, however, are located within exon 3 of this gene (alternatively referred to as *CIAS1*, *NALP3*, or *PYPAF1*), and are mostly confined to the NACHT domain (also called the nucleotide binding site (NBS) domain). The assembly of cryopyrin/NALP3/PYPAF1 and Pycard/ASC is thought to induce interleukin-1 processing through caspase-1 activation (Fig. 1). Cryopyrin/NALP3/PYPAF1 function may be controlled by specific inhibitors (as yet unidentified but pyrin/marenostrin may perform that role) and it is proposed that the mutations of the NACHT (for NAIP, CIITA, HET-E and TP1) domain would affect the binding of such an inhibitor resulting in spontaneous caspase-1 activation with interleukin-1 production and fever (Fig. 1). Alternatively, this protein may be proinflammatory and these mutations might induce increased functional activity with unprovoked attacks of inflammation.

A striking example of the way molecular genetics is radically altering our perception of autoinflammation, and indeed inflammation in general, has resulted from the discovery of a range of phenotypes associated with *CIAS1/NALP3/PYPAF1* mutations. Feldmann *et al.* [15•] described distinct mutations in the NACHT domain of cold-induced autoinflammatory syndrome 1 (*CIAS1*) in unrelated patients with CINCA syndrome, alternatively known as NOMID. Aksentijevich *et al.* expanded the panel of CINCA/NOMID-causing mutations, and further supported the preliminary observation that the majority of mutations in these patients have arisen *de novo* [16]; it is likely that this phenotype is sufficiently severe as to impair reproductive fitness. Consistent with the recently reported role of PYD-containing proteins (including pyrin/marenostrin and *CIAS1/NALP3/PYPAF1*) in interleukin-1 regulation, an increase in interleukin-1 β processing was found in the one CINCA/NOMID patient studied. Although CINCA/NOMID-related mutations are also located in the same NACHT/NBS region, these are distinct mutations, with the exception of *D303N*, which has also been found in MWS (Fig. 2). These mutations tend to cluster into specific areas within the NACHT/NBS region, including the Mg²⁺-coordinating aspartate around residue 300, which suggests that they may disrupt the function of this domain.

Granulomatous disease

During the last couple of years a significant breakthrough in the genetics of complex diseases has resulted from the discovery, made by two independent groups, that the *CARD15/NOD2* gene (more usually denoted as *NOD2*, nucleotide-binding oligomerization domain 2) is one of the major susceptibility genes for Crohn's disease [17•,18•].

Numerous clinical, epidemiological and molecular genetics studies have already indicated that inflammatory bowel disease (IBD) is a complex disease in which both genetic and environmental factors are important in disease pathogenesis, and that this interaction is likely to determine disease phenotype and progression. Multiple genome screens have identified several IBD candidate intervals, but only the pericentromeric region of chromosome 16 has been universally replicated, and in Crohn's disease rather than ulcerative colitis patients [19•]. It therefore became clear that one of the major Crohn's disease susceptibility genes (*IBD1*) was likely to reside in this interval, and *NOD2* was identified as the first Crohn's disease susceptibility gene by the application of both positional cloning methods [17•], and positional candidate gene screening [1]. The *NOD2* protein and its homologue, *NOD1*, are members of a growing family of cytosolic proteins implicated in inflammation and innate immunity. At the structural level, NODs are related to the apoptosis regulator Apaf-1 protein through homology at their N-terminal CARD domains, and their centrally located NBS/NACHT domains [6•]. *NOD* proteins are also related to the NBS-LRR class of plant R protein at their C-terminal LRR regulatory domains, as well as to mammalian Toll-like receptors; both plant R proteins and Toll-like receptors regulate the host response to pathogens [20•]. Previous in-vitro overexpression studies in mammalian tissues had already shown that NODs induce NF κ B activation through the NOD/RICK (RIP-like interacting CLARP kinase) signaling pathway, which requires the CARD domain, and that NOD-LRRs act as intracellular receptors for components of microbial pathogens, and are essential for lipopolysaccharide-mediated NF κ B activation. These studies also indicate that both of these functions appear to be independent of Toll-like receptors, and that NODs might act as cytosolic counterparts of Toll-like receptors.

Despite the fact that over 60 *NOD2* sequence variations have been reported, during the last year it has become apparent that the three main *NOD2* mutations (*R702W*, *G908R*, and *1007fs*, which is due to *3020insC*, resulting in a truncated protein) in the LRR domain principally predispose to Crohn's disease (not to ulcerative colitis), and only *1007fs* has been unequivocally associated with susceptibility to Crohn's disease [21•,22•,23,24]. In a

recent report, Lasage *et al.* [22•] found that 50% of their Crohn's disease patients had at least one of 30 disease-associated *NOD2* variants in the NOD2-LRR domain, while 17% of patients who presented with earlier onset and a more frequent stricturing phenotype were found to have double mutations, supporting a gene-dosage effect in Crohn's disease, and suggesting recessive inheritance of *NOD2* susceptibility gene.

Furthermore, Ogura *et al.* [18••] have shown deficient lipopolysaccharide-mediated NF κ B activation in human embryonic kidney 293T cells transfected with the 1007fs truncated protein and thus proposed a failure of the mutant protein to control bacterial invasion through NF κ B activation. This defect could potentially lead to abnormal T-cell-mediated responses, inflammation, and aberrant cytokine production, all of which are hallmarks of Crohn's disease.

The identification of *NOD2* as a major Crohn's disease susceptibility gene has also provided a key insight which has led to the elucidation of the genetic basis of a rare inflammatory disorder, Blau syndrome, which is characterized by granulomatous synovitis, with uveitis and cranial neuropathies. Since Crohn's disease and Blau syndrome both shared overlapping phenotypes of granulomatous pathology and overlapping linkage interval on chromosome 16, this led to the discovery of disease-associated mutations in the NBS domain of *NOD2* in patients with Blau syndrome [25•] (Table 1).

In those IBD patients who do not carry the common *NOD2* mutations, a novel association of a single nucleotide polymorphism (−857C) in the promoter of the TNF gene has been reported in both Caucasian and Japanese cohorts [26•,27]; IBD is not linked to *NOD2* in Japanese patients. Preliminary functional analysis has shown that binding of the octamer-binding protein 1 (OCT1) transcription factor to the TNF promoter is abrogated by the presence of this single nucleotide polymorphism, and that the inhibitory effects of OCT1 on the NF κ B activation pathway are diminished as a result [26•].

Finally, a specific haplotype of the cytokine gene cluster on chromosome 5q31 has also been shown by linkage disequilibrium (LD) mapping to confer susceptibility to Crohn's disease [28•]. Although no single causal mutation has been identified, it was suggested that multiple single nucleotide polymorphisms (SNPs) within the whole block might affect regulation of one or more genes within the cluster and thus predispose to the disease.

Conclusion

The study of autoinflammatory syndromes in the postcloning era involves trying to define clinically

relevant functional defects in the hope of developing improved therapies for patients suffering from these chronic and debilitating diseases. Knowledge obtained from such studies may also provide insights into the complexities of more common inflammatory diseases like rheumatoid arthritis, psoriasis and human systemic lupus erythematosus.

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