

# Periodic fever syndrome and autoinflammatory diseases

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## Abstract

The concept of autoinflammatory disease as a new disease classification has resulted in a paradigm shift in our understanding of the the broad spectrum of immunological diseases. The effectiveness of interleukin-1 blockade in a variety of disorders has resulted in a marked reduction in suffering for many of these patients.

## Introduction and context

Over the past 10 years a group of monogenic diseases, termed the hereditary periodic fever syndromes (HPFS), which present with recurrent inflammation and unexplained fevers as part of their phenotype, have been classified as autoinflammatory in nature, residing at the extreme of the immunological disease continuum proposed in 2006 [1]. The HPFS typically manifest in the paediatric population. There has been remarkable progress in delineation of the genetic pathways involved and successful management of these syndromes. These conditions are linked at the functional level, as the reported mutations are manifested in cells and proteins of the innate immune system. There are at least five HPFS, which include two autosomal recessive conditions, familial Mediterranean fever (FMF) and hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), in addition to a group of autosomal dominant diseases, including tumor necrosis factor receptor-associated periodic syndrome (TRAPS), pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, as well as three related conditions, collectively termed the cryopyrin-associated periodic syndromes (CAPS). Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, and neonatal onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, and articular syndrome (NOMID/CINCA) are all included in the

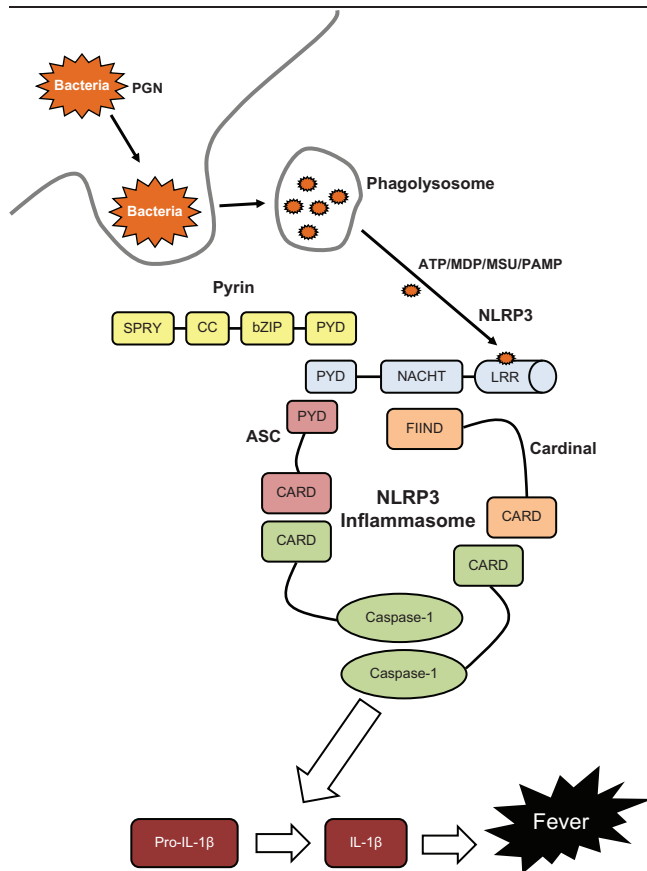
CAPS group. The genes responsible for all these autoinflammatory HPFS have been identified, and include *MEFV* (encoding pyrin) responsible for FMF, *TNFRSF1A* for TRAPS, mevalonate kinase for HIDS, *CIAS1/NLRP3* for CAPS, and the *PSTPIP1* gene responsible for PAPA syndrome. These are relatively rare diseases but are associated with increased mortality and morbidity due to an increased potential for development of amyloidosis and other complications [2].

The wider spectrum of autoinflammatory disease includes polygenic conditions with a predominantly innate immune component, such as Crohn's disease [2], as well as those major histocompatibility complex class I-associated conditions, including psoriasis, ankylosing spondylitis, reactive arthritis, and Behçet's disease, that are considered as intermediate diseases in the immunological disease continuum [1]. These conditions all show strong clinical overlap.

## Recent advances

The *NLRP3* mutations cause spontaneous activation of the inflammasome complex, leading to excessive interleukin (IL)-1 $\beta$  secretion (Figure 1). This excessive secretion is responsible for the clinical manifestations of CAPS, as well as playing a role in a number of other autoinflammatory diseases, including FMF and TRAPS.

**Figure 1. Activation of the NLRP3 inflammasome leads to cleavage of pro-IL-1 $\beta$ , by caspase-1, into the mature IL-1 $\beta$**



Activation usually occurs through stimulation with microbial peptides, such as peptidoglycan (PGN), monosodium urate (MSU), and other pathogen-associated molecular patterns (PAMP). These PAMP are recognised by the leucine-rich repeat domain (LRR) of NLRP3. Mutations in the NACHT domain of NLRP3 cause spontaneous activation of the this multimeric protein complex, which leads to over-production of IL-1 $\beta$ . This excessive secretion of IL-1 $\beta$  is mainly responsible for the clinical manifestations of the cryopyrinopathies (CAPS) and plays a role in all periodic fevers. Screening for mutations in the NACHT domain of NLRP3 is routinely carried out for diagnosis of CAPS; however mutations are only found in around 50% of cases. ASC, apoptosis-associated speck-like protein containing a CARD; bZIP, basic leucine zipper; CARD, caspase recruitment domain; CC, coiled coil; FIIND, function to find domain; MDP, muramyl dipeptide; PYD, pyrin domain; SPRY, sPLA/ryanodine receptor domain.

*In vitro* and murine studies have shown that the B30.2 domain of pyrin interacts directly with caspase-1 to modulate IL-1 $\beta$  production, resulting in high levels of IL-1 $\beta$  [3].

Until recently the mainstay of treatment for CAPS has been anakinra, a recombinant non-glycosylated human IL-1R antagonist, which blocks IL-1 $\beta$  from binding to its receptor with remarkable efficacy [4]. Two alternative

IL-1 antagonists are now available. Studies have shown that rilonacept, which acts as a soluble decoy receptor for both IL-1 $\beta$  and IL-1 $\alpha$ , can produce rapid symptomatic improvement [5]. A fully humanised monoclonal antibody against IL-1 $\beta$ , canakinumab, has also been approved for use in FCAS and Muckle-Wells syndrome. A published phase III clinical study demonstrated that canakinumab was effective in CAPS patients, with 34 of 35 patients achieving a complete clinical response within 15 days [6].

A pilot study has shown that IL-1 $\beta$  inhibition by anakinra is also effective in both acute gout [7] and resistant pseudogout [8]. Following on from this success, a proof-of-concept study of rilonacept was conducted in 10 patients with chronic gout; this was the first controlled and blinded study of an IL-1 blocking agent in this condition [9]. Rilonacept has the advantage of a long plasma half-life and the ability to bind to IL-1 $\beta$  with high affinity [10]; it also binds to both IL-1 $\alpha$  and the IL-1 receptor antagonist (IL-1ra) but with less affinity [11].

Treatment of the autoinflammatory disorder TRAPS is also moving towards targeted IL-1 $\beta$ . Therapy had traditionally involved corticosteroids, to which the fever is particularly responsive [12], and then progressed onto anti-tumour necrosis factor (anti-TNF) agents, which have been used with varying degrees of success. Etanercept, a recombinant human TNFR2-Fc fusion protein, has demonstrated good efficacy [13] whereas the monoclonal anti-TNF antibody infliximab may induce a paradoxical inflammatory reaction and should be avoided in suspected cases of TRAPS [14,15]. More recently, anakinra has been used to treat TRAPS patients [16], with one study demonstrating a prompt response in all patients, with normalisation of acute phase reactant levels [17].

A novel neonatal autoinflammatory disease, deficiency of IL-1ra (DIRA), has recently been described, caused by recessive mutations in the IL-1 receptor gene (*IL1RN*) with heterozygous carriers being asymptomatic [18,19]. These mutations, identified by two separate groups, result in a truncated protein that is not secreted, causing cells to be hyper-responsive to IL-1 $\beta$  stimulation. Disease manifestations include multifocal osteomyelitis, periostitis, and pustulosis; the condition can be fatal but surviving children have been treated successfully with anakinra, resulting in a rapid reduction of the skin eruptions and inflammation, along with regression of the bone abnormalities. These studies suggest that treating DIRA patients promptly with IL-1ra may prevent development of painful and debilitating bone abnormalities [18].

A subset of systemic onset juvenile idiopathic arthritis (SoJIA) has been classified as an autoinflammatory disease in recent years. A leukocyte gene expression study of SoJIA patients identified a unique IL-1 $\beta$  signature when compared to controls, and this signature changed significantly in patients undergoing IL-1 $\beta$  blockade [20]. However, subsequent studies have failed to replicate the IL-1 $\beta$  signature [21] and excessive IL-1 $\beta$  secretion was not found in SoJIA patients at any stage of therapy in one report [22]. Other potential markers of SoJIA have also been reported; serum levels of the myeloid-related proteins 8 and 14 (MRP-8 and MRP-14) were significantly higher in SoJIA patients than in healthy or other disease controls [23]. Apart from IL-1 blockade, treatment with the anti-IL-6 receptor monoclonal antibody tocilizumab has also proved to be effective in SoJIA patients [24], providing another promising therapeutic avenue in this previously difficult to manage disorder.

In the wider disease spectrum, genes with functions in the innate immune system have also been identified as conferring risk to Crohn's disease, thereby supporting an autoinflammatory component in the pathogenesis. The susceptibility genes include two autophagy genes, *ATG16L1* [25] and *IRGM* [26], and a regulatory region downstream of *NLRP3* [27]. Autophagy is linked to innate immunity by delivery of microbial degradation products to intracellular pathogen recognition receptors [28]. TNF blockade is the treatment of choice in Crohn's disease, but IL-1 $\beta$  blockade is ineffective and may aggravate the condition [29].

### Implications for clinical practice

The increased clinical awareness of autoinflammatory disease and the remarkable effectiveness of IL-1 blockade have raised a number of questions about which compound (short, intermediate, or long acting) to use in a variety of these disorders, and how early to intervene in the course of disease in order to prevent the development of skeletal and central nervous system defects in conditions such as CAPS and DIRA. It is possible that prophylactic IL-1 inhibition will be employed in the future to avoid long-term sequelae after positive screening for these conditions.

Sustained IL-1 suppression may have potentially serious long-term effects, which are currently unknown. Furthermore, biologics-based therapies are expensive and not readily available for all patients who might benefit; for example, IL-1 $\beta$  inhibition is not in routine use for gout but may have a therapeutic advantage over hypouricaemic therapies in more severe cases. Encouraging results have been obtained from the use of small molecules, such as caspase-1 inhibitors, as an alternative approach to

biologics-based therapies. The orally available pro-drug VX-765, a potent, selective inhibitor of caspase-1, blocked IL-1 $\beta$  secretion in peripheral blood mononuclear cells from FCAS patients and this may represent a future therapeutic option [30].

### Abbreviations

CAPS, cryopyrin-associated periodic syndrome; DIRA, deficiency of IL-1ra; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D with periodic fever syndrome; HPFS, hereditary periodic fever syndromes; IL, interleukin; IL-1ra, IL-1 receptor antagonist; NOMID/CINCA, neonatal onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, and articular syndrome; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; SoJIA, systemic onset juvenile idiopathic arthritis; TNF, tumour necrosis factor; TRAPS, tumor necrosis factor receptor-associated periodic syndrome.

### Competing interests

The authors declare that they have no competing interests.

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