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Hereditary auto-inflammatory disorders and biologics

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Abstract The term *auto-inflammatory disorders* has been coined to describe a group of conditions characterized by spontaneously relapsing and remitting bouts of systemic inflammation without apparent involvement of antigen-specific T cells or significant production of auto-antibodies. The hereditary periodic fever syndromes are considered as the prototypic auto-inflammatory diseases, and genetic studies have yielded important new insights into innate immunity. DNA analysis has greatly enhanced the clinical characterization of these conditions, and elucidation of their molecular aetiopathogenesis has suggested that therapies may be aimed at specific targets within the immune cascade. The availability of biologic response modifiers such as inhibitors of tumour necrosis factor (TNF) and interleukin-1 β has greatly improved the outlook for some of these disorders, although effective therapies remain elusive in patients with certain conditions, including hyperimmunoglobulinaemia-D with periodic fever syndrome (HIDS) and a proportion of those with TNF-receptor associated periodic syndrome (TRAPS). Indeed, outstanding challenges and the unique potential to further elucidate molecular mechanisms in innate immunity are illustrated by the dashed early hope that TNF blockade would be a panacea for TRAPS: not only is etanercept (Enbrel) ineffective in some cases, but there are anecdotal reports of this condition being greatly exacerbated by infliximab (Remicade).

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Introduction

The auto-inflammatory disorders encompass disease categories such as hereditary periodic fever (HPF) syndromes, granulomatous inflammation, complement disorders and vasculitis syndromes [5, 82], examples of which can be found in Table 1 together with their associated genes, proteins and clinical features. Many of the auto-inflammatory disorders can be attributed to mutations in the pyrin family of genes, including pyrin itself, the NODs (nucleotide-binding oligomerization domains) and NALPs [NACHT, leucine-rich repeat (LRR), and pyrin domain (PYD)] [77]. For example, Crohn's disease and Blau syndrome are associated with NOD2 mutations; however, for the purpose of this review, we will

Table 1 Some auto-inflammatory disorders with associated genes and proteins together with their associated disease characteristics

Inflammatory disorder	Gene (chromosome)	Protein	Distinguishing characteristics
Hereditary periodic fever			
FMF	<i>MEFV</i> (16p13)	Pyrin	Lower-limb rashes, amyloidosis, Mediterranean epidemiology
HIDS	<i>MVK</i> (12q24)	Mevalonate kinase	Lymphadenopathy, vomiting and diarrhoea
TRAPS	<i>TNFRSF1A</i> (12p13)	TNF receptor 1	Periorbital oedema, abdominal pain, myalgia, arthralgia, chest pain, headache
FCAS	<i>CIAS1</i> (1q44)—also called NALP3	Cryopyrin/NALP3	Rash, fever and joint pain following generalized exposure to cold
MWS	<i>CIAS1</i> (1q44)	Cryopyrin/NALP3	Urticaria, periodic arthralgia, sensorineural deafness, general inflammation and amyloidosis
CINCA	<i>CIAS1</i> (1q44)	Cryopyrin/NALP3	Fever, chronic meningitis, uveitis, sensorineural deafness, urticaria and deforming arthritis
PAPA	<i>CD2BP1</i> (15q24)	PSTPIP1	Pyoderma gangrenosum, severe cystic acne and adult-onset insulin-dependent diabetes mellitus
Granulomatous inflammation			
Crohn's disease	<i>NOD2</i> (16q12)	NOD2	Recurrent abdominal pains, chronic diarrhoea, weight loss
Blau syndrome	<i>NOD2</i> (16q12)	NOD2	Arthritis, uveitis, skin rash and granulomatous inflammation
Vascular syndrome			
Behçet's disease	<i>HLA-B51</i> ^a (6p21)		Genital and oral ulceration, vasculitis, uveitis, arthralgias
Complement disorder			
Systemic lupus erythematosus			Arthralgias, fatigue, rash, photosensitivity, chest pain

FMF Familial Mediterranean fever; *HIDS* Hyper-IgD syndrome; *TRAPS* TNF-receptor associated periodic syndrome; *FCAS* familial cold auto-inflammatory syndrome; *MWS* Muckle–Wells syndrome; *CINCA* chronic infantile neurologic, cutaneous and articular syndrome; *PAPA* pyogenic sterile arthritis, pyoderma gangrenosum and acne; *MEFV* Mediterranean fever; *CIAS* cold-induced auto-inflammatory syndrome 1; *TNF* tumour necrosis factor; *TNFRSF* TNF super family receptor; *NALP* NACHT, LRR, and PYD domains; *NOD* nucleotide-binding oligomerization domain [56, 88, 90]

^a Predisposition association

concentrate on the HPFs and the role of biological response modifiers, more commonly known as 'biologics,' in their treatment. These agents are designed to inhibit the effects of pro-inflammatory cytokines, including tumour necrosis factor (TNF) and interleukin (IL)-1 β , which contribute to the disease process.

HPFs and their treatment

The HPFs can be divided into autosomal-recessive and autosomal-dominant disorders (Table 1). Familial Mediterranean fever (FMF, MIM 249100) and hyperimmunoglobulinaemia-D (hyper-IgD) with periodic fever syndrome (HIDS, MIM 260920) are recessive disorders. The dominant HPFs include the TNF-receptor associated periodic syndrome (TRAPS, MIM 142680), the NALP3-associated disorders [familial cold auto-inflammatory syndrome (FCAS, MIM 120100), Muckle–Wells syndrome (MWS, MIM 191100), chronic infantile, neurologic, cutaneous and articular syndrome/neonatal-onset multi-system inflammatory disease (CINCA/NOMID, MIM 607115)], and pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA, MIM 606347). The associated genes and the chromosomes on which they are found are listed in Table 1.

The availability of screening for the mutations involved has significantly increased our ability to identify these conditions, and an increased understanding of the underlying biology has enabled vastly improved therapies to be implemented [40, 63]. The specific biologic response modifiers such as anti-TNF (etanercept/Enbrel, infliximab/Remicade and adalimumab/Humira) and the IL-1 receptor antagonist anakinra (Kineret) have much improved the outlook for some of these disorders. We will briefly describe the pathogenesis of all known HPFs and current therapeutic options for these disorders, with particular emphasis on the use of biological response modifiers.

Familial Mediterranean fever

FMF is the most well known and best characterized of the HPFs. The mutated gene, *MEFV*, encoding pyrin/marenostrin protein, was identified in 1997 and found to be predominantly expressed in neutrophils, monocytes and eosinophils but not in lymphocytes [4, 9], suggesting a potential functional role in the regulation of inflammation. The vast majority of FMF-associated mutations are located in the B30.2 (SPRY) domain, at the carboxy terminus of the protein [34]. This domain is thought to function as a ligand binding or signal transduction domain, and therefore, B30.2 mutations may cause delayed apoptosis and inflammation by the reduced ability of pyrin to moderate IL-1 β activation [34, 82]. There are over 100 variants in the *MEFV* gene recorded to date [14], and the majority are disease-associated mutations. The three most commonly reported mutations are M694V, M680I and V726A [28].

FMF can be differentiated clinically from dominant periodic fevers by the very characteristic predominant inflammation of the pleural, pericardial and peritoneal linings [18]. Rash confined to the legs is another discriminatory feature, as is a family history consistent with autosomal-recessive inheritance (i.e., affected siblings rather than parents).

Substantial subclinical inflammation occurs between attacks in many FMF patients [52], underlying a high incidence of AA amyloidosis in patients who do not receive effective colchicine therapy. AA amyloid fibrils are derived from the circulating acute phase reactant serum amyloid A protein (SAA), which is the most sensitive and objective lab marker of inflammatory activity in the HPFs. AA amyloidosis may eventually occur in any individual with sustained acute phase overproduction of SAA, with a median latency of about 20 years. It usually presents with proteinuria, and the clinical picture is dominated by renal dysfunction; clinically significant involvement of the gastro-intestinal tract may also occur, as may substantial deposits in the spleen and adrenal glands. AA amyloidosis also occurs relatively frequently in patients with MWS, CINCA/NOMID and TRAPS, but is rare in HIDS.

The remarkable therapeutic response of FMF to colchicine was identified by Goldfing in 1972 [32]. It greatly reduces the frequency and intensity of clinical attacks, and by effectively suppressing inflammation generally in this particular disease, very largely prevents the development of amyloidosis [94]. However, despite the efficacy of colchicine, amyloidosis remains an important cause of morbidity and mortality in FMF, most likely relating to lack of such treatment, insufficient dosing, poor compliance and, in a small proportion of cases, perhaps approximately 5%, a genuine lack of response [8]. No other therapy is of proven long-term efficacy in FMF, but experience is now gradually being obtained with biologics, with encouraging reports filtering through (Table 2).

Studies of the efficacy of thalidomide, interferon (IFN) α [12, 13, 86, 87] and bone marrow transplantation (one case) have been reported [67, 84]. Therapeutic administration of IFN α , an antiviral cytokine with immunomodulatory properties, has yielded mixed results in patients with FMF; a double-blind placebo-controlled trial of 34 FMF patients failed to demonstrate significant symptomatic benefit but did show objective amelioration of associated acute phase activity [86]. In a smaller pilot study eight patients resistant to

Table 2 Current clinical evidence for treatment of HPFs with biologics

	Etanercept (soluble TNFR II-human Fc fusion protein)	Infliximab (chimeric humanized IgG1 anti-TNF antibody)	Anakinra (recombinant human interleukin-1 receptor antagonist)	Other
FMF				IFN (15+/-) (13+)(16+) thalidomide (22+)
HIDS	33++, 34+, 35-, 28+		28+	Thalidomide (23-) simvastatin (32+)
TRAPS	34+, 60+, 47-	56-	59+	
FCAS			79+, 80+	IL-converting enzyme/caspase-1 inhibitor VX-765 ^b [81]
MWS			78+	
CINCA			81+, 82+, 83+	
PAPA				

Numbers refer to citation of published report. These reports have been categorised as demonstrating either a therapeutic benefit (+), no observed benefit (+/-) or (-) if the condition worsened with therapy

^b The IL-converting enzyme/caspase-1 inhibitor VX-765 has not yet been tested in clinical trials but has shown promise in *in vitro* studies

colchicine were additionally treated with IFN α , and all but one reported reduction in abdominal pain [13]. Calguneri et al. also reported a case study of a 17-year-old Turkish boy with FMF who developed polyarteritis nodosa (PAN) 2 weeks after hepatitis A infection. The condition of this patient improved after therapy with intravenous and oral corticosteroids and intravenous cyclophosphamide, but FMF attacks and vasculitic skin lesions recurred a few months later while he continued to receive colchicine and immunosuppressive agents. IFN α therapy was added, and the attacks resolved within 3 months; no other symptoms were experienced during follow-up of 28 months [12]. These various findings suggest that IFN α has a modest disease-modifying effect in FMF.

Thalidomide, which has TNF-inhibiting properties, can be beneficial in a proportion of patients with chronic inflammatory diseases such as rheumatoid arthritis (RA) [54], Behçet's [35] and Crohn's disease [27]. Seyahi et al. reported an FMF patient resistant to colchicine who responded well to thalidomide. The patient received 100 mg/day for the first 7 months, associated with approximately one attack per month, but had only three further attacks during the subsequent 8 months when the dose was increased to 200 mg/day [76]. Thalidomide has also been reported to have limited efficacy in controlling febrile attacks in HIDS [23]. Although the possible beneficial effect of thalidomide in FMF supports investigation of specific TNF inhibitors in some HPFs, few individuals can tolerate thalidomide itself in the long term due to somnolence, constipation, thromboembolism or development of irreversible neuropathy.

As yet, there is little published experience of specific TNF blockade in FMF, although a single case report does describe complete remission of febrile abdominal episodes during the 72-week follow-up of a patient with colchicine-resistant disease [73].

TNF blockade with etanercept, as discussed below, has benefited the course of AA amyloidosis in a patient with TRAPS [24], although the benefit of any agent in amyloidosis depends entirely on its ability to suppress acute phase SAA production. It has been proposed that IL-1 β may have a role in the pathogenesis of FMF, but no study of IL-1 β blockade has so far been reported. However, we have received a cautionary personal communication that a patient with colchicine-resistant FMF did not benefit from 4 weeks' treatment with anakinra.

The hyperimmunoglobulinaemia-D with periodic fever syndrome

HIDS is recessively inherited and was recognised as a separate entity in 1984 [89]. It is caused by mutations in the mevalonate kinase (MK) gene, *MVK*, resulting in a deficient activity of the MK enzyme [22, 43]. This periodic fever syndrome is characterized by attacks of arthralgia, lymphadenopathy, headache, skin lesions and abdominal pain with diarrhoea, lasting up to 1 week. MK is responsible for phosphorylation of mevalonic acid to yield 5-phosphomevalonic acid in the isoprenoid pathway [10]. This leads to production of cholesterol, a precursor of steroid hormones and bile acids, and also nonsterol isoprenoids required for the prenylation of target proteins. Studies suggest that isoprenoid compounds affect the stability and/or maturation of MK [29, 42].

Ninety per cent of patients diagnosed with HIDS have the MK V377I variant due to the 1129G>A mutation in the *MVK* gene, along with the same or a different mutation in the second allele. It is known that insufficiency of isoprenoid pathway end products leads to increased IL-1 β secretion in MK-deficient cells.

Despite its name, not all patients with HIDS have an elevated plasma concentration of IgD, even during febrile attacks. The mechanisms by which abnormalities in MK activity cause inflammation remain unclear. MK is involved in cholesterol biosynthesis, but decreased cholesterol production is unlikely to drive the disease because cholesterol levels in HIDS patients can be in the low–normal range, and there are more severe disorders of cholesterol biosynthesis that do not have an auto-inflammatory phenotype [50]. The hypothesis regarding lack of isoprenoid production resulting in increased IL-1 β has been discussed above [29]. In contrast to other hereditary auto-inflammatory disorders, HIDS is rarely complicated by AA amyloidosis. The first such case was reported recently in Italy [72]; since then, we have diagnosed two further cases, one each from Britain and Germany. The management of HIDS is unsatisfactory. Treatment with various anti-inflammatory agents, ranging from colchicine to non-steroidal anti-inflammatory drugs (NSAIDs), steroids and thalidomide is not generally effective. However, two more promising approaches that have shown some success are the use of simvastatin and etanercept.

Simvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme preceding MK in the cholesterol biosynthetic pathway, and a study showed a reduction in the number of days of illness in five of six HIDS patients when it was taken continuously [79]. Treatment with etanercept has yielded mixed results, ranging from favourable in two children [83] to a partial response [6] and no response [59] in two other case studies. A recent well-executed study by Bodar et al. further indicated that response in HIDS to etanercept is variable, but the study also provided anecdotal evidence that anakinra may be more effective than etanercept in reducing the duration of HIDS symptoms [10]; these authors suggest that treatment on demand during symptomatic attacks might be a reasonable approach in light of current evidence. The nature of HIDS as a rare disease in which attacks can vary substantially in character, frequency and severity, as well as ameliorating with age in many cases, highlights the difficulties in conducting rigorous controlled trials in the HPFs generally. Given a lifetime incidence of AA amyloidosis in HIDS of less than 1–2%, and rarity of other serious complications, and the unknown potential for long-term adverse effects with all biologic agents, many patients are likely to prefer on-demand treatment rather than continuous treatment.

TNF-receptor associated periodic syndrome

Previously called familial hibernian fever (FHF) [92], TRAPS is characterized by recurrent attacks of fever, abdominal pain, synovial inflammation, rash, conjunctivitis and periorbital oedema typically lasting 1–4 weeks (Table 1). It is associated with mutations in the TNF receptor 1 (TNFR1) gene, *TNFRSF1A* [64], and is the second most common inherited periodic fever after FMF [2]. In health, TNFR1 is shed from receptors on cell surfaces, producing a pool of potentially TNF-neutralizing soluble TNFR1 in the plasma. Some TNFR1 variants implicated in TRAPS result in a defect of this shedding process (C52F, T50K, T50M etc.), leading to increased cell surface expression and reduction in circulating TNFR1, and offering a plausible mechanism for TNF-mediated inflammation in this disorder [65]. However, many mutations do not cause a shedding disorder, and other disease mechanisms have now been identified, some of which may be mutation-specific [24]. The heterogeneity of TRAPS is further supported by the absence of mutations in the coding

region of *TNFRSF1A* in some patients and families with clinically indistinguishable phenotypes [2, 5, 21].

To date there are at least 46 recorded mutations in *TNFRSF1A* [85], a large proportion of which are missense mutations resulting in substitution of cysteine residues in the extracellular region and, therefore, loss of structurally important disulphide bridges [65]. There is some evidence that cysteine mutations are associated with a higher risk of developing AA amyloidosis [5], presumably by causing more severe inflammatory disease, but susceptibility to amyloid is also governed by other unknown factors, some of which may be inherited themselves. The risk of amyloidosis appears to be substantial in some families with TRAPS, even those in whom TRAPS is relatively mild, and all patients with TRAPS must be regarded to remain at risk for so long as they continue to have acute phase activity.

The TNF cytokine, which also acts as an endogenous pyrogen, acts as a homotrimer that binds to the trimeric form of TNFR1 on cell surfaces. This can signal apoptosis via death domain proteins TRADD (TNF-receptor-associated death domain) and FADD (Fas-associated death domain) or activate transcription factors such as NF- κ B (nuclear factor-kappaB) and JNK (*c*-Jun NH₂-terminal kinase) via TRADD, TRAF (TNF-receptor associated factors) and RIP (receptor interacting protein), leading to inflammation [64]. Corticosteroids are generally effective in TRAPS, but unacceptable and increasing doses are often required. Great hope was placed on a role for anti-TNF therapy when the genetic basis of TRAPS was identified, and etanercept (Enbrel) has been the most widely used anti-TNF agent in TRAPS. It is a recombinant human TNFR (p75)-Fc fusion protein comprising two TNFRSF1B receptors linked by an IgG1 Fc fragment, and is administered subcutaneously either once (50 mg) or twice weekly (25 mg).

There is published information on the effect of etanercept in more than 30 TRAPS patients to date [6, 7, 11, 25, 31, 44, 45, 47, 49, 53, 68, 71, 78, 80, 91], and results are mixed. Whilst regression of amyloidosis in some patients receiving etanercept [24, 26] provides compelling evidence for remission of inflammatory disease, the development of amyloidosis in a patient whose symptoms of TRAPS were controlled by etanercept is extremely disappointing [45]. Present consensus is that etanercept appears to be of use in replacing or reducing steroid requirements in the treatment of TRAPS, but response is partial or even absent in some cases. A formal trial of etanercept to evaluate its efficacy in TRAPS is in progress, with generally encouraging preliminary results [46].

Interestingly, anecdotal experience suggests that other anti-TNF agents, including a TNFR1 (p55) fusion protein and infliximab, a mouse–human chimeric monoclonal IgG1 antibody to TNF, is not effective in patients with TRAPS [25], and indeed, may severely worsen the disease. Therapy comprising two infliximab infusions (3 mg/kg at 14-day intervals) led to severe exacerbation of a 27-year-old patient's TRAPS symptoms within 2 days of the infusions, beginning with abdominal cramps followed by very painful arthritis. After the first infusion it was necessary to increase his prednisone dose to 60 mg daily, which was gradually tapered 1 week after the second infusion (Paul Hasler, personal communication). Exacerbation of TRAPS associated with the R92Q variant has occurred in two patients that we have treated, one of whom subsequently received etanercept with excellent effect for 2 years to date. Similarly, exacerbation of TRAPS has been reported in a patient with the C33Y variant who received a recombinant humanised fusion protein of two TNFR1 molecules and IgG1 (p55TNFr-Ig) [91]. The mechanism responsible for these pro-inflammatory effects is unknown but of considerable interest because it may shed light on the functional effects of TRAPS causing mutations. The efficacy of adalimumab, a fully

humanised anti-TNF monoclonal antibody, has not yet been tested in TRAPS, but the above observations suggest caution.

The long-term benefit and potential adverse effects of etanercept in TRAPS is unknown, although anecdotal observations have suggested relapse within 1 or 2 years of commencing treatment. Indeed, it has even been suggested that the benefit of etanercept in TRAPS could be entirely non-specific and simply reflect ‘general’ anti-inflammatory properties of this agent. Certainly, no long-term studies have been reported. Since TNF plays a key role in the response to infection, and the TNF pathway is disrupted in TRAPS, increased susceptibility to infection, including reactivation of tuberculosis (TB), are real concerns [16, 58]. Screening for TB with purified protein derivative (PPD) tests are recommended to exclude quiescent TB before initiation of any kind of anti-TNF therapy.

Anakinra, a recombinant IL-1 receptor antagonist (IL-1ra), has shown modest efficacy in the treatment of RA [48] but astonishing benefit in MWS, FCAS and CINCA/NOMID, supporting a pivotal role for IL-1 β in these hereditary auto-inflammatory disorders (discussed below). Although an important role for IL-1 β in TRAPS has not necessarily been suggested by pathogenetic studies, the excellent clinical response to anakinra of a patient with TRAPS who was unresponsive to etanercept [78], and our own similar dramatic observations in another case with amyloidosis, suggests otherwise. It is clear that there is still much to learn about the effect of TRAPS-causing mutations on TNF signalling pathways, with the hope that this will enable more targeted medical intervention.

Pyogenic sterile arthritis, pyoderma gangrenosum and acne

Pyogenic sterile arthritis, pyoderma gangrenosum and acne is a dominantly inherited condition due to mutations in *PSTPIP1* on chromosome 15. Thus far, the only PAPA-associated mutations to have been reported in *PSTPIP1* are A230T and E250Q [85], which are located at the PTP-PEST binding site. As the name PAPA suggests there are at least three distinct clinical features associated with this incredibly destructive inflammatory disorder, and recurring episodes of joint, skin and muscle inflammation are common. Some patients are affected by pyoderma gangrenosum-like ulcerative skin lesions, and others are affected by severe cystic acne [93].

Shoham et al. have demonstrated that the pathophysiology of PAPA is due to a marked increase in the interaction of proline serine threonine phosphatase-interacting protein 1 (*PSTPIP1*) [62] with pyrin due to tyrosine hyperphosphorylation. Pyrin is thought to modulate inflammation through down-regulation of IL-1 β , which in turn leads to acceleration of apoptosis. Along with NALP3, pyrin interacts with ASC by means of their homologous pyrin domains [74]. PAPA causing mutations in *PSTPIP1* are thought to reduce pyrin’s regulatory effect on IL-1 β in the inflammasome.

Familial cold auto-inflammatory syndrome, Muckle–Wells syndrome and chronic infantile neurologic, cutaneous and articular syndrome/neonatal-onset multi-system inflammatory disease

FCAS, MWS and CINCA/NOMID are caused by mutations in the *CIAS1/NALP3* gene encoding cryopyrin/NALP3 and form a group of disorders with overlapping characteristics. Symptoms of FCAS occur intermittently, whereas those of MWS and CINCA/NOMID tend to be more frequent or constant [66]. MWS and CINCA/NOMID are usually symptomatic from birth, although FCAS (previously called familial cold urticaria or FCU) may not be evident for some years. FCAS typically presents as episodes of fever, rash, arthralgia and conjunctivitis following exposure to cold, lasting a day or two. Amyloidosis is sometimes observed in FCAS but is more commonly associated with MWS, as is progressive sensorineural deafness [1]. Some rash and fever occur daily in many patients with MWS. CINCA/NOMID is the most severe of the three conditions, with neonatal-onset, recurrent arthralgias and chronic sterile meningitis, which is associated with neurological impairment in a significant percentage of cases. As with MWS progressive deafness may also develop with age, and CINCA/NOMID can be fatal in childhood even without amyloidosis [70].

The NALP3 protein consists of three domains: a pyrin domain, an NBS/NACHT (nucleic acid binding site/neuronal apoptosis inhibitor protein, CIITA, HET-E and TP1) domain and an LRR (leucine-rich repeat) domain [51]. Mutations in the *CIAS1/NALP3* gene are mostly found within the NACHT domain, and those that are not are located in its flanking regions, or rarely in the LRR domain. These mutations have potent effects on function of the inflammasome, the platform through which NALP3 acts. The NALP3 inflammasome, similar to that originally described for NALP1 [60], is a multimeric protein complex that mediates the processing of IL-1 β . Its components include NALP3 (cryopyrin/PYPAF1), an adaptor protein; ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain), Cardinal and caspase-1 (also known as ICE, interleukin-1 converting enzyme) [3]. Caspase-1 cleaves a 116-amino acid region from the 5' end of the cytosolic pro-IL-1 β (p35) to convert it into active IL-1 β (p17) [20]. IL-1 β is a potent pro-inflammatory cytokine, originally characterized as and called an endogenous pyrogen, which is normally activated in response to infection, injury and immunological challenge. Increased secretion of IL-1 β has a multitude of effects, including fever mediated through induction of prostaglandins [69].

The disease-causing *CIAS1/NALP3* mutations link MWS, FCAS and CINCA/NOMID into one family of disorders, referred to by some as 'pyrinopathies' or CAPS (cryopyrin-associated periodic syndromes). What were for many years considered three distinct diseases turn out to merely represent a spectrum of clinical symptoms, with FCAS being the mildest, MWS being of intermediate severity, and CINCA/NOMID being the most severe. The majority of mutations clustered within the highly conserved NACHT domain of *CIAS1/NALP3* appear to result in spontaneous caspase-1 activation and excessive IL-1 β production [3], which suggested IL-1 β antagonism as a strategy for therapy. Indeed, treatment with anakinra in all three conditions has produced the most striking and dramatic improvements in any of the hereditary auto-inflammatory disorders.

Therapy of MWS complicated by AA amyloidosis with anakinra has proven to be life-saving. Hawkins et al. reported two patients whose intense refractory multi-system inflammatory disease remitted within hours of administration of IL-1ra. The acute phase response abated completely within days, and both patients have experienced sustained

complete remission of MWS-related inflammation, resolution of amyloid-related nephrotic syndrome and no adverse effects during over 3 years of daily anakinra therapy [38]. Three further MWS patients with median SAA concentration of over 140 mg/l have also remained in complete clinical and serological remission for nearly 3 years [36].

Management of FCAS has also been revolutionized by anakinra therapy. In a study by Hoffman et al. pretreatment of patients with anakinra was found to block clinical symptoms and serological abnormalities following an experimental cold challenge [41]. Anakinra has also produced remarkable improvement in CINCA/NOMID, the most severe disease in this spectrum, enabling major reductions in or cessation of corticosteroid therapy. Several studies have emerged demonstrating a dramatic clinical change with a disappearance of fatigue, rash, conjunctivitis and arthralgia in most reports [30, 33, 57]. As the life expectancy of patients with CINCA/NOMID is reduced, the effect of anakinra on mental and physical development of these children is eagerly awaited. It is hoped that early and prolonged treatment with anakinra may prevent the deafness and abnormal neurological and skeletal development [37, 75]. Anakinra has also been reported to be an effective therapy in treating disease flares in PAPA syndrome, although only in one case so far [19].

The rapid amelioration of symptoms upon treatment of MWS, FCAS and CINCA/NOMID disorders with anakinra not only identified IL-1 β as the pivotal mediator of disease in these disorders and its antagonism as an effective strategy for therapy but also provided a rationale for the development of specific inhibitors of caspase-1 activation. One such inhibitor, VX-765 (Vertex Pharmaceuticals), is the orally bioavailable prodrug of a potent and selective inhibitor of ICE/caspase-1. VX-765 is currently under development, and preliminary studies have shown promise for this drug as a novel therapy for NALP3-related disorders. Using peripheral blood mononuclear cells (PBMCs) from healthy controls and FCAS patients with three different *CIAS1/NALP3* mutations, VX-765, via its active metabolite VRT-043198, inhibited lipopolysaccharide (LPS)-induced IL-1 β and IL-18 production with very similar efficacy and potency. The effectiveness of this inhibitor in an *ex vivo* model supports its testing in patients with MWS, FCAS and CINCA/NOMID [81].

Conclusions

Genetic, molecular and clinical studies of rare hereditary auto-inflammatory disorders form compelling examples of translating basic research into advances in clinical practice, which may be applicable to numerous more common inflammatory diseases such as gout [61]. Indeed, not only can highly specific biologic agents continue to help dissect out molecular pathways in inflammation, but clinical trials in patients with specific disease entities such as MWS, FCAS and CINCA/NOMID can also provide unique information on efficacy of new drugs designed to inhibit specific cytokine pathways. A number of novel inhibitors of IL-1 β are under development at the present time, and some have already entered clinical testing in patients with these various diseases, as proof of principle.

Although recent advances in treatment of hereditary auto-inflammatory diseases have given much to be optimistic about, the long-term risks and benefits of TNF and IL-1 inhibitors are not yet known. Development of neutralizing anti-chimeric antibodies (HACAs) has been a particular problem in some patients treated with infliximab, albeit much reduced by co-administration of methotrexate. All forms of TNF blockade are associated with

increased risk of infection and potential reactivation of TB, and possibly lymphoma, problems that have not come to light with anakinra. Indeed, it is worth bearing in mind that anakinra underwent early testing in extremely high doses among patients with severe sepsis without detriment.

It remains clear that further development of alternative, effective and affordable therapies is required. One avenue under current investigation is the development of small-molecule inhibitors of TNF that mediate their effects by inhibiting specific intracellular signalling pathways either by antagonising activation of transcription factors [55] or through inhibition of the processing enzyme TACE. Recently, a compound that inhibits TNF receptor binding by interfering with TNF trimer assembly and stability has been developed [39]. Deng et al. have also recently reported the successful amelioration of inflammatory arthritis in mice by the use of soluble versions of pre-ligand assembly domain (PLAD) [15]. The PLAD is a portion of the extracellular region of TNFRs that mediates receptor chain association essential for signalling. This study provides proof of concept that the use of PLAD proteins to disrupt TNF signalling is effective and a possible future therapy for not only RA but also TRAPS and other TNF-centric disorders [15]. A further alternative and novel therapy involves specific targeting of the NF- κ B transcription factor. Cytokines such as IL-1 β and TNF that are stimulated by NF- κ B can also directly induce NF- κ B activation and thus promote further inflammation through this positive auto-regulatory loop. A short cell-permeable peptide (nemo binding domain peptide; NBD) which binds to I κ B kinase alpha (IKK α) and IKK β , thus disrupting their association with IKK γ (NEMO), has been found to block TNF-induced NF- κ B activation in vivo. NEMO is absolutely critical for the function of the IKK complex and subsequent NF- κ B activation. Animal models of inflammation have shown that continuous administration of the NBD peptide effectively ameliorates inflammatory responses. This peptide may represent a viable therapeutic treatment for the recurrent flares associated with several of the auto-inflammatory disorders with particular relevance for TRAPS, MWS, FCAS and CINCA/NOMID [17].

In conclusion, the relatively recent concept of auto-inflammatory disease is exemplified by the HPFs because their pathogenesis is directly related to innate immune responses with little evidence of disordered acquired immunity. Therapy directed at blocking the effects of key cytokines has been remarkably effective in treating some cases of HPF, but much work remains to be done to find effective therapies for the majority of these patients.

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