Review

Inherited autoinflammatory diseases: a critical digest of the recent literature

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ABSTRACT

In this paper we provide a critical digest of the recent literature on inherited autoinflammatory diseases. We reviewed all the articles published during the last 24 months on monogenic autoinflammatory diseases and selected the most relevant studies regarding the pathogenesis, clinical aspects and management of these conditions. In particular, we focused the attention on the more frequent conditions, familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS) and TNF-receptor associated periodic syndrome (TRAPS).

Introduction

The autoinflammatory syndromes are a group of multisystem disorders characterised by recurrent episodes of fever and systemic inflammation affecting the eyes, joints, skin, and serosal surfaces. These syndromes differ from autoimmune diseases by several features, including the periodicity whereas autoimmune diseases are progressive and the lack of signs of involvement of adaptive immunity such as association with HLA aplotypes, high-titer autoantibodies or antigen-specific T cells. Thus, autoinflammatory syndromes are recognised as disorders of innate immunity (1). Since 1997 a growing number of diseases have been identified (2). For reasons of space we decided to prevalently focus the present review on the three more frequent diseases (FMF, CAPS and TRAPS) with a final paragraph devoted to the less frequent and the newly identified diseases.

Familial Mediterranean fever (FMF)

Novel insights in the pathogenesis

FMF is the most frequent among hereditary recurrent inflammatory disorders. It presents with an autosomal recessive pattern of inheritance and is due to mutations in the *MEFV* (*Me*diterranean *Fe*ver) gene, coding for the pyrin protein.

One of the most significant advance in the attempt to understand mechanisms underlying FMF pathogenesis is represented by the recent work by Chae *et al*. (3). In contrast to previous works, the paper highlighs the possibility that FMF is sustained by Pyrin gain-of-function rather than loss-of-function mutations. By inserting the B30.2 domain of human origin into murine pyrin (which lacks a B30.2 orthologous domain), with three among the most frequent mutations in FMF (*i.e*. M680I, M694V and V726A), the Authors generated different mouse models displaying severe spontaneous inflammatory phenotype recapitulating FMF. Because the disease was induced in the homozygous mice with insertion (KI) of FMF-associated mutant B30.2 domain rather than disruption of WT pyrin, the hypothesis postulated was that pyrin mutations causing FMF may lead to a gain of function. However, the absence of diseased phenotype in heterozygous mice was consistent with recessive trait of inheritance in FMF and with an actual loss-of-function model. Null mice (*Mefv*$^{-/-}$) were then crossed with *Mefv* $^{V726A/+}$ mice in order to produce hemizygotes expressing only mutant pyrin from a single allele. Both null and hemizygotes weren't featured by a diseased phenotype, indicating that missense mutations on both alleles are necessary, thus implying the importance of the amount of mutant pyrin in causing the disease. The Authors then crossed *Mefv* $^{V726A/V726A}$ mice with IL-1 receptor-deficient animals, and demonstrated that the blockage of IL-1 signalling ameliorated the inflammatory

phenotype in these mice (3). *Mefv* $^{V726A/V726A}$ mice were then crossed with Asc-deficient murine model, resulting in complete ablation of caspase-1- driven IL-1β secretion in CD11b^{+} bone marrow derived machophages. Conversely, CD11b^{+} cells purified from *Mefv* $^{V726A/V726A}$ /*Nlrp3*$^{-/-}$ animals displayed conserved IL-1β secretion and systemic inflammation, suggesting that in this model, gain-of-function pyrin mutations induce IL-1β pathway activation and severe autoinflammation in *NLRP3*-independent manner (3).

A recent work from our group sought to define the role of IL-1β pathway activation in FMF patients, by assessing the degree of IL-1β production and its modulation in *Mefv*-mutated monocytes freshly purified from peripheral blood mononuclear cells (PBMC) of FMF patients (4). By analysing a cohort of 21 patients together with 14 healthy carriers and 30 genetically negative healthy donors (HD), enhanced IL-1β secretion was demonstrated in FMF monocytes following LPS-induced activation. The degree of IL-1β release correlated with number of high penetrance mutations, consistent with the gene-dosage effect of mutant pyrin also supported by Chae *et al*. (3) and by the clinical evidences suggested by the paper by Federici *et al*. (see below) (5). Contrary to what was demonstrated in the FMF KI animal model, silencing of *NLRP3* consistently inhibited the LPS-induced IL-1β secretion in both mutated and genetically negative subjects. Thus, activity of NLRP3 was shown to be necessary in the presence of either mutated and wild-type pyrin, suggesting that increased secretion of IL-1β in FMF patients is NLRP3-dependent (4).

Clinical and therapeutic novelties

The actual impact of *MEFV* mutations on the FMF phenotype is still matter of debate. Indeed up to 30% of FMF patients are carriers of a mono allelic mutation of *MEFV* gene. On the other hand, an even more consistent group of healthy individuals are heterozygous for *MEFV* mutations (6, 7). To address the actual impact of *MEFV* mutations on the clinical phenotype, 113 children carrying *MEFV* mutations (44 with mutations in two alleles, 69 heterozygous) and 205 children negative for mutations in genes associated with periodic fevers were recently analysed in a large national collaborative multicentre study (5). FMF patients were divided in different subgroups according with their genotype, namely penetrance of *MEFV* variants (high penetrance *vs* low penetrance) and number of mutated alleles involved. Interestingly, the frequency of 'familial Mediterranean fever (FMF)-like symptoms' decreases from patients carrying two high penetrance mutations towards patients with a single low penetrance mutation with an opposite trend for the clinical manifestations prevalently associated to a PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis)-like phenotype (5). These results support in humans the hypothesis of a dose-effect of *MEFV* mutations in the determination of the inflammatory phenotype demonstrated in knock-in mouse models (3).

The possible impact of ethnic, environmental and genetic factors on the severity of clinical presentation was recently investigated in a large cohort of 346 paediatric FMF patients collected by the Eurofever Registry, a large international Registry (8, 9). The patients were divided into three groups:

i) patients living in the eastern Mediterranean;

ii) patients with an eastern Mediterranean ancestry but who were living in central-western Europe;

iii) patients without a Jewish, Turkish, Armenian or Arabic ethnic background and living in western European countries (such as Italy, Greece, Spain, France, the UK).

Interestingly a multivariate analysis showed that the variables independently associated with severity of disease presentation were country of residence, presence of M694V mutation (either bi-allelic or mono-allelic) and positive family history, confirming in a paediatric population the actual impact of the environment on the severity of the disease (10).

The use of colchicine had a tremendous impact on the management of the disease with a clear amelioration of the quality of life of the patients and a dramatic reduction of the incidence of amyloidosis (11). Recently a Turkish group reported a study aimed to evaluate the survival rate, the causes of death and the prognostic factor in FMF patients followed by a single tertiary centre in the "colchicine era" (12). They retrospectively collected clinical information in 587 FMF patients. 94% of patients were on colchicine treatment but only 61% of them used colchicine regularly. Despite the use of colchicine, 28% of patients still presented fever attacks with a severe disease activity in 43% of them. Fortyfour patients (7.5%) displayed a renal disease, and 37 had a biopsy proven amyloidosis. In the follow-up period 14 patients died and amyloidosis was recognised as the main cause in 7 cases (12). Thus, it is now clear that even if colchicine dramatically changes the natural history of the disease, a relevant number of patients still present an incomplete response to the drug, as also recently pointed out by the analysis of the FMF patients enrolled in the Eurofever registry, in which 37% of the patients were classified as incomplete responders to colchicine (13).

The use of IL-1 targeting drugs was recently proposed as a valid therapeutic strategy in colchicine resistant FMF (14, 15). Anakinra and canakinumab, have been reported to be generally effective in case reports and non-controlled series in more than 30 patients with colchicine-resistant or intolerant FMF (16-18). Blocking IL-1 has been used with good results even in a small cohort of patients with AA amyloidosis and chronic renal failure (18). In the majority of cases colchicine was maintained after the introduction of anakinra even if at a lower dose. Recently, Hashkes *et al*. reported the results of a randomised, double-blind, study for rilonacept (IL-1 TRAP) in 14 colchicine-resistant or intolerant FMF patients (19). Participants were aged 4 years or older and were required to have an estimated mean of 1 or more FMF attacks per month for 3 months before screening and 1 or more attacks per month during screening despite receiving adequate colchicine treatment. Patients were treated with rilona-

cept 2.2 mg/kg (maximum, 160mg) or equal volume of placebo, both given once weekly by subcutaneous injection. Rilonacept significantly reduced the frequency of FMF attacks versus placebo and ameliorated the physical health-related quality of life (19).

Cryopyrin-Associated Periodic Syndromes (CAPS)

Novel insights in the pathogenesis

The *NLRP3*-mutated cells display a constitutively turned-on inflammasome, causing caspase-1-driven IL-1β over-production (20). A recent paper by Balow *et al*. further confirmed the role of IL-1β in this context, and defined a CAPS-related signature together with IL1-responsive downstream transcripts spectrum (21). Namely, by performing a microarray-based gene expression profiling in PBMC purified from patients affected by different autoinflammatory diseases (*i.e*. MCW/CINCA, TRAPS, HIDS, PAPA) and healthy donors (HD), the Authors pooled out a set of differentially expressed genes (DEG) in CAPS cells including transcripts driving innate and adaptive immune responses and other cellular processes such as reactive oxygen species (ROS)-associated genes and apoptosis. The analysis revealed the nuclear factor kappa B (NF-κB) signalling pathway as the most significant network differently expressed in severe CAPS. This was in agreement with previous studies defining IL-1β as an inducer of NF-κB and identifying the latter as one of the key-players capable of priming *NLRP3*. Beside NF-κB, this CAPS profiling also unveiled the role of several other genes linked to innate immunity but, intriguingly, also to adaptive immune response, probably activated as result of downstream perturbation in cytokine networking (21). This is also in line with the recent observation of a significantly increased IL-17 serum levels as well as a higher frequency of TH17 in CAPS patients compared to control subjects, supporting the central role of IL-1β in the differentiation of TH17 in human inflammatory conditions (22).

In the paper by Balow *et al*. the network analysis identified in CAPS also a cluster of genes regulated by JUN (AP1), which is downstream of IL1β and whose dysregulation has been involved in bone homeostasis and which is of particular interest because of the bony overgrowth occurring in CINCA patients (21). This aspect has been recently explored by generating a knock-in (KI) mouse model globally expressing the D301N *NLRP3* mutation corresponding to the D303N in human *NLRP3* (23). These mice recapitulated the severe skeletal deformations featuring CINCA patients (growth retardation, disorganised growth plate and reduced bone mass). Interestingly, evaluation of key pathways of osteoclastogenesis in bone marrow-derived macrophages (BMDM) such as M-CSF-induced Akt or the RANKL-mediated ERK and JNK, revealed level of activation comparable to wild-type (WT) cells, suggesting that the D301N mutation caused increased osteoclastogenesis that was independent of MAPK, NFκB and Akt pathways (23).

Thus, IL-1β signalling disruption occurring in crypyrinopathies triggers a cascade of complex cellular events leading to aberrant homeostatic tissue responses. One of the main downstream target of IL-1β is the proinflammatory IL-6 (22). Patients with *NLRP3* inflammasome-mediated conditions, were reported to display increased IL-6 serum level (22, 24), raising the possibility that this cytokine may actually represent an additional therapeutic target. However, the recent work from McGeough *et al*. identified IL-6 more as a marker of inflammation rather than a key-player in inflammasome-related diseases. Using 2 different animal models the Authors highlighted the possibility that IL-1β and IL-6 may not be actually coupled in pathogenesis, and suggested that IL-6 could be a simple marker of inflammation without a causative role in CAPS (25). Indeed, CAPS patients with active diseases display higher serum levels of IL-6 in respect to healthy controls, but not comparable to the levels observed in patients with systemic onset juvenile idiopathic arthritis (22), a disease that, in contrast with CAPS, display an optimal response to IL-6 blockade (26, 27). Carta *et al*. also highlighted the ancillary role of IL-6 in human primary monocytes from CAPS patients (28). In particular, analysis of LPS-primed monocytes revealed that IL-6 production was severely impaired in CAPS compared to HD. Resting CAPS monocytes exhibited signs of stress, including elevated levels of reactive oxygen species (ROS) and fragmented mitochondria, and that stress marks were dramatically worsened by TLR stimulation (28). Carta *et al*. provided evidence for a link between redox homeostasis perturbation and consequent protein synthesis inhibition. The latter, in turn, resulted in severe impairment of production of cytokines downstream IL-1, such as IL-1Ra and IL-6 (28). Thus, this paper further underlined the central role of oxidative stress in *NLRP3* mutated monocytes, suggesting that redox unbalance and the consequent inhibition of translation are likely responsible for the impaired production of IL-1Ra and IL-6. The latter, coupled to increased IL-1β release, may give reason of the severity of the IL-1-related clinical manifestations and the predominant implication of innate immunity in CAPS.

The role of ROS in *NLRP3* activation was highlighted also in the work by Menu *et al*. (29). In this study, the Authors demonstrated that ER stress inducers cause *NLRP3* inflammasome activation in human and murine macrophages, with mechanisms requiring ROS generation and potassium efflux. Interestingly, a role for the well known ER stress effectors such as pERK, IREα or ATF6 was not demonstrated, ruling out the involvement of the classical UPR signalling and suggesting that ER stress regulates *NLRP3* through an UPR-independent manner. The finding that ER stress activated *NLRP3* inflammasome in a ROS-dependent fashion, led the Authors to suggest that ER may also be sensed by mitochondria (29). In an earlier work from the same group, in fact, the Authors provided evidence that *NLRP3* inflammasome senses mitochondrial dysfunction. In particular, by blocking mitophagy/autophagy, which have been recently recognised as negative modulators of inflammasome activity, accumulation of ROS-generating damaged mitochondria occurred, resulting in *NLRP3* activity induction

(30). Actually, beside UPR response, other pathways have been reported to radiate from the ER or mitochondria, but the precise alternative signalling remains unclear. Interestingly, MAMs modulate the efflux of several factors between the ER and mitochondria, including exchange of Ca2+. One of the more recent and novel finding in exploring pathogenic players in CAPS concerns, indeed, Ca2+ and cyclic AMP (cAMP). These molecules have been recently recognised as pivotal regulators of the *NLRP3* inflammasome, and they have been pointed out as potential molecular targets in CAPS pathogenesis. Namely, Lee *et al*. demonstrated in mice that the calcium sensing receptor (CASR) activates the *NLRP3* inflammasome through intracellular Ca2+ increase and cAMP decrease. Moreover, cAMP was shown to inhibit inflammasome activation by directly binding to *NLRP3* in human PBMC. Interestingly, this work was able to demonstrate that the binding affinity of cAMP for CAPS associated mutants was lower than for WT *NLRP3*, resulting in uncontrolled IL-1β release featuring CAPS PBMC (31).

Clinical and therapeutic novelties

As emphasised by the name itself (*i.e*. cryopyrin-associated), the three syndromes Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS) and Neonatal-onset multisystem inflammatory disease (NOMID/CINCA) are closely related on genetic basis, as they share their pathophysiological foundation on the presence of dominantly inherited or *de novo* missense mutations in *NLRP3* gene encoding NLRP3/cryopyrin.

Almost 30–40% of CAPS patients presenting with indistinguishable clinical features and response to treatment in respect to *NLRP3*-mutated patients, is negative for mutation of *NLRP3* gene.

In 2005 Saito *et al*. reported the case of a 15 years old boy with typical CINCA phenotype who was found to have somatic mosaicism of *NLRP3* gene (32). The same group recently coordinated an international case-control study in order to detect somatic *NLRP3* mosaicism in NOMID/CINCA syndrome patients who had shown no mutation during conventional sequencing. Subcloning and sequencing of *NLRP3* was performed in these mutation-negative NOMID/CINCA syndrome patients and their healthy relatives (33). Somatic *NLRP3* mosaicism was identified in 18 of the 26 patients (69.2%). Estimates of the level of mosaicism ranged from 4.2% to 35.8%. Mosaicism was not detected in any of the 19 healthy relatives. *In vitro* functional assays indicated that the detected somatic *NLRP3* mutations had disease-causing functional effects (33).

From a clinical point of view particular attention has been focused on the significance of specific mutations whose role is not still clear and particularly on E311K, V198M and Q703K variants. Kuemmerle *et al*. (34) studied 42 living members of an index patient's family carring the E311K mutation to evaluate the phenotype associated with this specific mutation. Among the 42 family members only 13 clinically affected patients were heterozygous carriers of the E311K mutation. The clinical spectrum of the subjects carrying the same mutation varied widely. Interestingly, 7 patients described an erythematous, non-urticarial rash while febrile episodes were reported only by 4 patients lasting on average between three and five days. Three patients presented a single episode of pericarditis, that is rather unusual in the classical clinical picture of CAPS. Notably pericarditis was also observed in in one additional patients with the same variants belonging to a different cohort (35).

The significance of V198M mutation is unclear since it has been associated with several CAPS phenotypes. Rowczenio *et al*. (36) described the clinical phenotype associated with *NLRP3* V198M mutation in 19 subjects. Interestingly, an association with a clear CAPS phenotype was found only in 5 patients, with a wide variability from typical FCAS to NOMID/CINCA phenotype.

The Q703K variant of *NLRP3* has still an unknown pathogenic significance. Up to a recent past it has been considered to be both a clinically unremarkable polymorphism and a low-penetrance mutation (37). However, recent evidences have shown that monocytes from patients carrying the Q703K variant display an higher secretion of IL-1_ upon stimulation (38), pointing out the possible pathogenic effect of this functional polymorphism. The long-term clinical course in a small cohort of 7 adult patients presenting with periodic fever attacks and carrying the Q703K mutation in the *NLRP3* gene has been recently described (39). According to this preliminary experience all patients were characterised by symptoms consistent with recurrent inflammatory syndrome, presenting with a mild FCAS-like phenotype (39). Further studies on a larger population will help to identify the actual pathogenic role, if any, of this variant.

IL-1 blockade is the treatment of choice in patients with CAPS (24, 40-43). The long term efficacy and safety of anakinra in paediatric CAPS patients has been described in two distinct cohorts of patients. These two studies indicate that anakinra treatment is safe and effective on the long term and provide a dramatic amelioration of the quality of life of the patients (44, 45). More recently Sibley *et al*. published an open-label, long-term follow-up study on a cohort of 26 CINCA/NOMID patients treated with anakinra 1–5 mg/kg/day for at least 36 months (46). A sustained improvement in clinical and laboratory variables were observed during all the period of the study. Despite a general good control of clinical manifestations (including hearing loss, ocular manifestations and headache) and laboratory parameters, few patients displayed a persistent even if mild inflammation of CNS that was associated in few patients, with the progression of hearing loss. Overall, anakinra was well-tolerated and no major adverse effects were observed (46). The long-term safety and efficacy of anakinra was also recently reported in paediatric and adult patients affected with MWS (47).

A two-year open-label study has recently confirmed the efficacy and safety of the monoclonal antibody anti IL-1β (canakinumab) in 166 adult and paediatric patients with different CAPS phenotypes (48). Of 141 patients with an available relapse assessment, 90%

did not relapse, their CRP/ SAA levels normalised by day 8, and remained in the normal range thereafter. Upward adjustments of dose or frequency were needed in 24.1% patients mostly children with a severe CAPS phenotype (CINCA/NOMID). Serious adverse events (AE) were reported in 18 patients (10.8%) and were mainly infections responsive to standard treatment. The safety and efficacy of canakinumab was also recently evaluated in 19 Japanese patients with CAPS (49). A complete response was achieved in 18 (94.7%) patients with some requiring a dose and/or a frequency adjustment to attain full clinical response. The majority of patients (77.8%) were in remission at week 24 (49). The first experience on the use of canakinumab in daily clinical practice in 13 paediatric CAPS patients was recently reported (50). Globally, patients with a mild-intermediate MWS phenotype displayed a complete control of disease activity maintaining the initial dosage of 2 mg/kg (or 150 mg) every 8 weeks, independently of their age. Conversely, the majority of CINCA patients required to increase the dosage to 4 mg/kg (or 300 mg) and a progressive increase of the dosing frequency (50), thus showing that patients with a more severe phenotype deserve higher doses and, conceivably, a more frequent drug administration since the beginning of the treatment.

TNF Receptor Autoinflammatory Syndrome (TRAPS)

Novel insights in the pathogenesis

Several hypotheses have been proposed to explain the biological dysfunction derived from the presence of Tumour Necrosis Factor Receptor (TNFR)-1 mutants causing TRAPS. Either defective TNFR1 shedding, TNF-induced apoptosis and NFκB activation, and aberrant activation of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) have been suggested. Only recently, Bulua *et al*. identified a novel putative mechanism by providing evidence that ROS of mitochondrial origin increase in TRAPS and promote the LPS-driven production of proinflammatory cytokines (51). Namely, analysis of both embryonic fibroblasts from TNFR1 mutant mice and PBMC purified from TRAPS patients, revealed the presence of elevated ROS, and treatment with antioxidants dampen LPS-induced inflammatory cytokine production. Interestingly, the Authors ruled out nicotinamide adenine dinucleotide phosphate (NADPH) as source of proinflammatory ROS. On the contrary, the use of drugs inhibiting mitochondrial ROS significantly reduced LPS-induced release of proinflammatory cytokines (51). One of the most widely accepted pathogenic mechanism in TRAPS is based on the concept that in these patients the trafficking of mutated TNFR1 is impaired, and the mutant receptor eventually accumulates in ER. Thus, it is conceivable that accumulation of TNFR1 in the ER may trigger ER stress and mitochondrial ROS production. The interplay of enhanced ROS production and endoplasmic reticulum stress pathways as potential mechanism in TRAPS pathogenesis, based on the intracellular retention of the TNFR1 has been further investigated (52). The Authors explored the hypothesis that mutations in the extracellular domain of the TNFR1 interfere with the physiological receptor folding, leading to intracellular accumulation which may activate a non-traditional unfolded protein response (UPR) involving X-box binding protein 1 (XBP1). According to this work, activation of the XBP1 pathway independently of classical UPR may enhance ROS production, thus suggesting the convergence of ER stress pathway and enhanced ROS generation in the presence of TNFR1 mutants. Actually, the Authors provided evidence of increased sXBP1 (*i.e*. the active transcription factor of XBP) and elevated ROS in PBMC from TRAPS patients, in the absence of signs of classical UPR (52).

In line with this evidence, and in agreement with hypotheses recognising mutant TNFR1 impaired clearance and intracellular accumulation as a main pathogenic hit, our recent study identified autophagy as an additional key mechanism involved in TRAPS pathogenesis (53). Autophagy is a well recognised pathway involved in the elimination of insoluble aggregates in cell biology. By analysing both primary PBMC from patients and human cell lines transiently transfected with mutant forms of *TNFRS1A*, this work demonstrated the presence of defective autophagy in TRAPS, and unveiled its contribution to the clearance of the mutant protein, as well as TRAPS-associated induction of NFκB. In particular, adding the *in vitro* refolding inducer geldanamycin (GA), it was possible to rescue cells from the accumulation of unfolded mutant TNFR1, to restore formation autophagosomes, and to decrease the mutant protein-mediated NFκB activation (53). Interestingly, by restoring autophagy in monocytes freshly isolated from TRAPS patients, a dramatic reduction of LPS-induced IL1β production was also obtained, consistent with data in the literature suggesting that IL1β secretion is prevented by autophagy (53). This findings further support the rationale for the apparent paradox that the most effective therapy in TRAPS is based on the inhibition of IL1β signalling cascade rather than TNFR1-mediated pathway.

Clinical and therapeutic novelties

In a recent study Bulua *et al*. reported the experience of 15 TRAPS patients enrolled in a prospective, open-label, dose-escalation study using etanercept (54). Despite the overall beneficial effects both on clinical manifestations and laboratory parameters, most of the patients discontinued the treatment during a ten-year follow-up being the median duration of treatment of 3.3 years. The main reasons for discontinuation were the lack of efficacy and injection site reactions. During the follow-up period 6 patients switched to IL-1 blockade (anakinra) with a good response (53).

Recently published data from the Eurofever registry confirm the better performance of IL-1 blockade on anti-TNF treatment in TRAPS patients (55). In fact, even if etanercept was beneficial in 32 of the 37 patients, only 11 (30%) experienced a complete response. Conversely, 79% of patients treated with anakinra displayed a complete response (absence of clinical manifestations and

normalisation of acute phase reactants) and five more patients had a partial response (55). The same good results have been preliminary reported in one TRAPS patients treated with the anti-IL-1 monoclonal antibody (canakinumab) (56).

Interim data of open-label 4-month canakinumab therapy and 5-month follow-up involving 20 active TRAPS patients has been recently presented, showing the complete control of clinical manifestations and persistent normalisation of acute phase reactants (57). These data support the pivotal role of IL-1β in the pathogenesis of TRAPS, but need to be confirmed in a larger number of patients.

Other diseases

Periodic fever associated with *mevalonate kinase deficiency (MKD)* is associated to mutations in the mevalonate kinase (*MVK*) gene (58). A recent French and Belgian multicentre study has analysed the clinical spectrum associated to mutations of the MVK gene in 50 patients (59). Fever episodes began during the first 6 months of life in 60% of patients and before the age of 5 years in almost all of them (92%). The patients displayed the full range of the clinical spectrum from the severe phenotype of mevalonic aciduria (characterised by a severe neurological impairment with a chronic systemic inflammation) to the milder phenotype dominated by recurrent fever episodes only, also know with the term of Hyper IgD syndrome. Recurrent and/or severe infections were observed in 13 patients, hypogammaglobulinaemia in 3 patients. Interestingly, the development of renal angiomyolipoma was observed in 3 patients. The disease remained highly active in 54% of surviving symptomatic patients followed up for >5 years, whereas disease activity decreased over time in the other 46% of patients (59).

New insights for the treatment came from some small studies and from a large cohort of patients collected by the Eurofever registry.

The efficacy and safety of IL-1-targeting drugs, anakinra and canakinumab, in 11 patients with MKD has been recently (60). Anti-IL-1-targeting drugs were used continuously in all but one patient who received anakinra on demand. Daily anakinra (nine patients) or canakinumab injections every 4–8 weeks were associated with complete remission in four cases and partial remission in seven (60).

Data on from Eurofever registry recently showed the response to treatment in 67 MKD patients (55). NSAIDs and corticosteroids were reportedly used mainly on-demand therapy. Corticosteroids induced a complete response in 8 (24%) and a partial response in another 22 (67%). In seven complete responders, corticosteroids, was referred as the only therapeutic strategy. Anakinra was effective in 24 (89%) of 27 patients inducing complete remission in 6 (22%). Etanercept was effective in 11 (65%) of 17 treated patients, with only one complete response (55).

Blau syndrome, or familial juvenile systemic granulomatosis, is an autosomal-dominant, disease characterised by a non-caseating granulomatous inflammation affecting the joint, the skin, and the uveal tract and associated to mutation of CARD15/NOD2 gene (61, 62). Mutations in the nucleotide-binding domain of NOD2 have been shown to alter its signal transduction properties in response to muramyl dipeptide (MDP). In a recent paper, Mo *et al*. clarified some molecular mechanisms regulating the assembly of NOD2-containing signalling complexes (63). Using purified recombinant protein, the authors showed that NOD2 binds and hydrolyses ATP. Binding of NOD2 to muramyl dipeptide and homo-oligomerisation of NOD2 are enhanced by ATP binding, suggesting a model of the molecular mechanism for signal transduction that involves binding of nucleotide followed by binding of muramyl dipeptide and oligomerisation of NOD2 into a signalling complex (63).

The morphologic and immunohistochemical characteristics of granulomas in patients with NOD2-related Blau syndrome have been recently compared with those of patients affected with Crohn's disease (64). Interestingly, biopsy specimens from Blau patients were characterised by the presence polycyclic granulomas with large lymphocytic coronas, extensive emperipolesis of lymphocytes within multinucleated giant cells, fibrinoid necrosis and fibrosis. In contrast, biopsy specimens from patients with Crohn's disease showed simple granulomas with subtle/absent lymphocytic coronas, sclerosis of the surrounding tissue, and polymorphonuclear cells. In both patient groups prominent IFN-γ expression was found in and around granulomas (64).

Pyogenic Sterile Arthritis, Pyoderma Gangrenosum and Acne (PAPA) syndrome is a disorder caused by mutations of gene coding for the CD2-binding protein 1 (CD2BP1), or *PSTPIP1*(65) (66). The manifestations of this disorder are pyogenic gangrenosum, cystic acne, and pyogenic sterile arthritis which represents the most common symptom of the disease. So far, only isolated case reports have been described. Demidowich *et al*. recently described the clinical phenotype of 5 new patients (67). Besides the classical triad, a number of other unusual manifestations have been described, such as severe colonic inflammation and recurrent otitis. One patient presenting the E250K mutation presented a peculiar clinical "systemic" phenotype characterised by hepatosplenomegaly, lymphoadenopathy and anaemia (67). Notably Holzinger *et al*. have described a larger cohort of patients carrying the same E250K mutation. Indeed these patients display the same peculiar "systemic" phenotype described in the patient by Demidowich *et al*. and are also characterised by high serum levels of zinc and calprotectinemia (68).

Majeed's syndrome was firsly described in three related Arab children presenting an association of chronic recurrent multifocal osteomyelitis, congenital dyserythropoietic anaemia and inflammatory dermatosis were described by Majeed *et al*. (69) and subsequently associated to mutation of the *LPIN2* gene (70). A recent report describes the over production of IL-1β by monocytes of 2 brothers carrying LPIN2 mutations and a good response to anti-IL-1 treatment (71), thus showing the possible pivotal involvement of this cytokine also in this condition.

DIRA (deficiency of the interleukin-1–receptor antagonist) is a recently identified autosomal recessive autoinflammatory syndrome, due to the deficiency of the interleukin-1–receptor antagonist, which begins around birth with multifocal osteomyelitis, periostitis, and pustulosis (72). Most of the patients described after the first report, display homozygous truncating mutations in the *IL1RN* gene (72, 73), however the first patient with an compound heterozygous of *IL1RN* has been recently also described (74). As a result of these mutations, no interleukin-1–receptor antagonist (IL1RA) protein is secreted, which inhibits the pro-inflammatory cytokines interleukin-1 and interleukin-1β (72). The response to anakinra was dramatic in all treated patients (72-74).

A similar mechanism has been recently identified as the cause of the newly identified DITRA (*deficiency of the interleukin-36 receptor antagonist)* syndrome, clinically characterised by a familiar generalised pustular psoriasis (75). This is a rare, life-threatening inflammatory disease characterised by repeated flares of diffuse, erythematous, pustular rash with high-grade fever and general malaise. Linkage analysis identified homozygous mutation in the gene coding for the IL-36Ra, the receptor antagonist of three proinflammatory cytokines: IL-36α, IL-36β and IL-36γ (IL-1F6, IL-1F8, and IL-1F9). Mutations of IL-36Ra affect the interaction of the protein with the receptor, thus reducing its anti-inflammatory action, especially at the level of patients' keratinocytes (75).

Recently, a gain of function mutations of CARD14 have been found to be associated in large multiplex families in which pustular psoriasis segregated as an autosomal-dominant Mendelianan trait (76), called *CARD14-mediated pustular psoriasis (CAMPS)*. CARD14 is prevalently localised in epidermal keratinocytes. Cultured keratinocytes from individuals carrying CARD14 mutations showed an up-regulation of NF-κB activity (76). Interestingly, both DITRA and CAMPS are examples of autoinflammatory disease dominated by an almost exclusive skin involvement, due to the prevalent expression of the mutated protein at the level of keratinocytes.

Finally, a novel autoinflammatory disease involving the immunoproteosome has been recently characterised form the molecular point of view. Indeed, a common molecular defect involving one component of the immunoproteasome, a protein called PSMB8 (proteasome subunit beta type 8) has been associated to three previously independent clinical syndromes: joint contractures, muscle atrophy, microcytic anaemia and *panniculitis-induced childhood-onest lipodystrophy (JMP), Nakajo-Nishimura syndrome,* and *chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE disease)* (77). These conditions are characterised by skin rash, early onset panniculitis, arthritis and dactilitis with the progressive development of severe lipodistrophy and joint contractures (77-79). The immunoproteasome is a multisub-unit protease that collaborates with the ubiquitine system for the degradation of non-lysosomal proteins in all eukariotic cells after activation by pro-inflammatory stimuli, such as IFN-γ. Mutations of PSMB8 lead to an impaired expression of the protein and to a defect of the proteasome assembly and activity (80). The consequent accumulation of ubiquitinated protein causes an over-activation of a number of pro-inflammatory intracellular pathways. Monocytes from patients with CANDLE syndrome showed an hyperphosphorylation of STAT-1 after IFN-γ stimulation (79), elucidating a novel pathway of inflammation associated to autoinflammatory disorders.

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