CONGRESS REPORT

Familial Mediterranean fever (FMF) and beyond: a new horizon. Fourth International Congress on the Systemic Autoinflammatory Diseases held in Bethesda, USA, 6–10 November 2005

S Ozen, H M Hoffman, J Frenkel, D Kastner

Ann Rheum Dis 2006;**65**:961–964. doi: 10.1136/ard.2006.052688

Autoinflammatory diseases are characterised by seemingly unprovoked inflammation. They can be categorised as: hereditary (monogenic) autoinflammatory diseases, complex (polygenic/multifactorial) autoinflammatory diseases, and diseases where the course is affected by mutations in the defined autoinflammatory disease genes. Identification of the inflammatory pathways involved has opened up new areas of research which have implications for the treatment of these disorders and the pathogenesis of common inflammatory diseases.

The Fourth International Congress on the Systemic Autoinflammatory Diseases—''Familial Mediterranean Fever (FMF) and Beyond—was held in Bethesda, USA, 6–10 November 2005. As noted in the opening session of the meeting, the autoinflammatory diseases are a group of disorders characterised by seemingly unprovoked inflammation but lacking high titre autoantibodies or antigen-specific T cells.[1] This term was first applied to the hereditary periodic fever syndromes, but now includes a number of both inherited and acquired disorders, several of which were discussed at the congress. Although not originally defined as such, the systemic autoinflammatory diseases usually affect the molecules and cells of the innate, rather than the adaptive, immune system.

CLINICAL HIGHLIGHTS

We will review the clinical highlights of the congress under three categories:

- Hereditary (monogenic) autoinflammatory diseases
- Complex (polygenic/multifactorial) autoinflammatory diseases
- Diseases where the course is affected by mutations in the defined autoinflammatory disease genes.

Hereditary (monogenic) autoinflammatory diseases

These diseases are often associated with mutations in one of several proteins involved in innate immune pathways. This family of disorders includes the hereditary recurrent fevers: FMF, the cryopyrinopathies (defined below), tumour necrosis factor (TNF) associated periodic syndrome (TRAPS), and hyper IgD syndrome (HIDS). These diseases are all characterised by systemic inflammation with high acute phase inflammatory markers and especially high serum amyloid A levels.[1 2]

FMF

FMF is the most common of these illnesses and is characterised by recurrent, self limited, febrile episodes with serositis, synovitis, and occasionally, skin involvement.[1–3] Attacks are often associated with high levels of acute phase reactants.[4] This disease usually presents in childhood and primarily affects people of eastern Mediterranean background. It is usually inherited in an autosomal recessive pattern, and most patients have mutations in *MEFV*, which codes for the protein pyrin (also known as marenostrin). Avi Livneh reviewed the features of FMF and drew attention to the differences of disease expression between patients living in the eastern Mediterranean and those living in the USA. The importance of the serum amyloid A level in treatment monitoring and prevention of amyloidosis was also presented. FMF has an excellent response to colchicine and this feature is used as a diagnostic feature to differentiate FMF from other diseases. Treatment of amyloidosis by the new emerging anti-cytokines appears promising. Fibrillex, a glycosaminoglycan-mimetic drug inhibiting fibril formation, has shown some promise, but requires more study.

Several presentations concerned the function of pyrin and pathogenesis of FMF. Pyrin seems to have an important role in the regulation of IL1β activation, exerting both positive and

See end of article for authors' affiliations

Correspondence to: Professor S Ozen, Department of Paediatrics, Hacettepe University, Ankara 06100 Turkey; sezaozen@hacettepe.edu.tr

Accepted 4 April 2006
Published Online First 10 April 2006

Abbreviations: ASC, apoptosis associated speck-like protein with a caspase-recruitment domain; CAPS, cryopyrin associated periodic syndromes; CINCA, chronic infantile neurological cutaneous articular syndrome; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyper immunoglobulin D syndrome; IL, interleukin; *MEFV*, gene for Mediterranean fever; MWS, Muckle-Wells syndrome; NOMID, neonatal onset multisystem inflammatory disease; PAMPs, pathogen associated molecular patterns; PAPA, pyogenic arthritis with pyoderma gangrenosum and acne; PFAPA, periodic fever adenopathy pharyngitis and aphthous stomatitis; PSTPIP1, proline serine threonine phosphatase-interacting protein 1; SoJIA, systemic onset juvenile idiopathic arthritis; TNF, tumour necrosis factor; TRAPS, tumour necrosis factor associated periodic syndrome

negative regulatory effects depending on the experimental conditions. Previously published data from mice harbouring a truncated form of pyrin indicate an inhibitory effect of pyrin on IL1β activation,[5] and it has been proposed that FMF associated pyrin mutants exhibit less inhibition of IL1β processing. Other in vitro data presented from Emad Alnemri's laboratory suggest that pyrin can also complex with ASC (apoptosis associated speck-like protein with a caspase-recruitment domain) to activate caspase-1 and consequently IL1β.[6] JaeJin Chae presented unpublished data suggesting that the interaction of pyrin with caspase-1 cleaves pyrin, resulting in an N-terminal fragment which mediates NF-κB activation. This in turn is responsible for transcription of pro-IL1 and other inflammatory cytokines in the nucleus. He presented data showing that mutated pyrin is more susceptible to cleavage, resulting in enhanced signalling and inflammation. Additional studies in mice, cell lines, and patients' leucocytes will be required to determine the relative contributions of these and other pathways in the pathogenesis of FMF.

Elegant reviews of the clinical features of TRAPS, HIDS, and the cryopyrinopathies including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease/chronic infantile neurological cutaneous articular syndrome (NOMID/CINCA), were presented.

Cryopyrinopathies

Three dominantly inherited syndromes previously thought to be distinct entities, FCAS, MWS, and NOMID (also known as CINCA), are all caused by mutations in *CIAS1* (also known as *NALP3* or *PYPAF1*), which codes for the cryopyrin protein.[1 4] They are grouped as cryopyrinopathies, or cryopyrin associated periodic syndromes (CAPS), and represent a clinical continuum of disease severity, with FCAS as the mildest and NOMID the most severe.[7–10] All are characterised by fevers and a rash that is often urticarial, usually presenting in infancy (or up to the second decade in MWS). Features unique to each disease include the precipitation of attacks by generalised cold exposure (FCAS), progressive sensory hearing loss (MWS), and more severe central nervous system involvement including optic nerve inflammation/papilloedema, chronic aseptic meningitis, mental retardation, as well as facial dysmorphia (NOMID). The musculoskeletal involvement ranges from arthralgia (FCAS) to synovitis (MWS) to arthropathy with premature ossification and overgrowth (NOMID). However, the borders between these three phenotypes are becoming increasingly less distinct as more patients are identified. Encouraging results have been presented with anti-IL1 treatment,[7 8] and Raphaela Goldbach-Mansky presented data from a large trial of anakinra in NOMID indicating efficacy in reducing inflammation of the central nervous system.

Cryopyrin forms a macromolecular complex with ASC, CARDINAL (CARD8), and caspase-1 called the inflammasome, which mediates caspase-1 and IL1β activation. Data presented by Alnemri suggest that mutant cryopyrin is less soluble than wild-type cryopyrin, resulting in the formation of large protein complexes and increased inflammasome activation.[6] These in vitro data are supported by ex vivo experiments using cultured leucocytes from patients with CAPS showing increased IL1 responses with stimulation. Additionally, the function of cryopyrin is supported by in vivo data observed in patients with FCAS after cold challenge and in patients with NOMID participating in studies at the NIH.

TRAPS

TRAPS is an autosomal dominant disorder characterised by febrile episodes often lasting more than 1 week that can also include abdominal pain, pleurisy, myalgia, arthritis, rash, and periorbital oedema. Mutations of the p55 TNF receptor gene have been shown in these patients.[11] Anti-IL1 treatment emerges as a treatment option in patients when anti-TNF treatment fails.

It was initially suggested that TRAPS was caused by shedding defects in the p55TNF receptor. However, recent studies suggest that the picture is more complex because the cleavage of the receptor varies with the mutation and cell type.[1] It may be that multiple mechanisms, including decreased ligand binding, downstream trafficking, or signalling defects, or effects on apoptosis, also contribute to the TRAPS phenotype.

HIDS

HIDS is a rare autosomal recessive autoinflammatory disease. It is caused by an inborn error of metabolism: mevalonate kinase deficiency. It causes impairment of the complex isoprenoid biosynthesis pathway. Clinically, the disease is characterised by 3 to 7 day long fever attacks, accompanied by tender lymphadenopathy, rash, aphthous ulcers, and joint and gastrointestinal involvement. Data from the international HIDS registry (http://www.hids.net, accessed 7 April 2006) on some 90 patients with the confirmed metabolic defect were presented by Joost Drenth. In comparison with other periodic fever syndromes, amyloidosis is rare. A possible explanation was provided by Jeroen van der Hilst, who found that in an in vitro system impaired isoprenoid biosynthesis reduced AA amyloid deposition.[12]

The link between impaired isoprenoid biosynthesis and HIDS remains poorly understood. Current evidence favours a role for impairment of just one of the several branches of isoprenoid biosynthesis: the generation of geranylgeranyl pyrophosphate. The ultimate inflammatory phenomena appear to be caused by IL1β and, secondarily, TNFα and IL6.[13] The clinical effect of anti-IL1 strategies appears promising but requires further study.

Other related rare diseases

While the hereditary autoinflammatory diseases share many clinical features, the proteins altered in these monogenic disorders also share structural features, and participate in the same pathways regulating inflammation. Pyrin and cryopyrin both possess an N-terminal PYRIN domain, which is involved in protein-protein interactions that are important in the regulation of inflammatory caspases. Cryopyrin has other structural features, such as a leucine-rich repeat domain involved in the recognition of pathogen associated molecular patterns (PAMPs), which are seen in other proteins associated with autoinflammatory disease. One such protein is the NOD2 or CARD15 (caspase activating recruitment domain 15). Mutations in the gene that codes for NOD2 have been associated with Crohn's disease, a common inflammatory bowel disease, and Blau syndrome, a dominantly inherited disorder characterised by granulomatous arthritis, uveitis, and rash.

Pyrin has been shown to interact directly with a cytoskeletal protein called proline serine threonine phosphatase-interacting protein 1 (PSTPIP1). Mutations in the gene that codes for this protein are associated with pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) syndrome, a disease manifested by episodes of mono- or oligoarticular sterile pyogenic arthritis, purulent skin lesions, and severe cystic acne. Disease associated mutations of PSTPIP1 have previously been shown to increase its interaction with pyrin.[14] One form of (murine) chronic recurrent multifocal osteomyelitis was found to be linked to PSTPIP2.[15]

Work from Deborah Gumucio's lab has detailed a number of distinct interactions between pyrin and the cytoskeleton.

Firstly, pyrin itself tends to localise in sites of active actin polymeration, such as the leading edge of migrating cells and the polymerising actin tails of *Listeria monocytogenes* (unpublished data). The pyrin-interacting protein ASC also localises to sites of polymerising actin, but does so independently of pyrin. On the other hand, formation of characteristic ASC specks seems to require the microtubules, but not the actin machinery. PSTPIP1 promotes actin reorganisation when overexpressed, and forms delicate fibrils that are dependent upon microtubules for their integrity (unpublished data). These multiple connections between pyrin and its interaction partners with elements of both the actin and microtubular network may explain aspects of FMF disease aetiology (massive neutrophil influx) as well as the efficacy of colchicine treatment.

Complex (polygenic/multifactorial) autoinflammatory diseases

A number of polygenic or multifactorial autoinflammatory diseases were discussed at the meeting, including Behçet's disease, periodic fever with adenopathy pharyngitis and aphthous stomatitis (PFAPA), and systemic onset juvenile inflammatory arthritis (SoJIA).

Behçet's disease

It has been suggested that Behçet's disease may be included in the autoinflammatory diseases because of certain clinical similarities, such as its episodic nature and the importance of granulocytes in disease pathogenesis. Behçet's disease differs from the disorders discussed above in that it is not monogenic, exhibits well documented HLA associations, and often requires immunosuppressive treatment.

Periodic fever adenopathy pharyngitis and PFAPA syndrome

Periodic fever adenopathy pharyngitis and PFAPA syndrome is another periodic disease characterised by marked cyclic episodes of inflammation. It shares several clinical features with the hereditary autoinflammatory diseases. However, there is no familial association and it usually remits before adolescence, suggesting a role for environmental factors. Additional study is needed for this relatively common disorder of children, and understanding its link to the inflammatory pathways involved in monogenic disorders will be particularly interesting.

SoJIA

Virginia Pascual presented her elegant results in SoJIA demonstrating that serum from patients induces the transcription of innate immunity genes, including IL1β, in healthy peripheral blood mononuclear cells.[16] IL1 was found to be a major mediator of the inflammatory cascade that underlies this disease and represents a target for treatment in some patients. Nevertheless, Patricia Woo presented data showing that some patients with SoJIA do not respond to anti-IL1 treatment, suggesting a degree of disease heterogeneity that may be explained with pharmacogenomic studies.

Additional disorders

A few additional disorders were also discussed as possible autoinflammatory diseases, based on symptomatology, pathophysiology, or effective treatments, such as macrophage activation syndrome and adult onset Still's disease. Schnitzler syndrome, a disorder with features reminiscent of HIDS and cryopyrinopathies and a high IgM level, may yet be another *acquired* autoinflammatory syndrome.

Diseases where the course is affected by the mutations in the known autoinflammatory disease genes

Another theme was the role of autoinflammatory disease gene mutations on the course or development of common inflammatory diseases. Previously published data suggest that *MEFV* mutations may affect the occurrence and/or course of Crohn's disease, vasculitis, and juvenile rheumatoid arthritis.[17 18] The association of vasculitis with autoinflammatory diseases and FMF was reviewed, suggesting that *MEFV* mutations may contribute to the development of vasculitis.[18] Vasculitides were found to be increased in a registry of 3000 Turkish patients with FMF.[19] Seza Ozen suggested that the predominance of Henoch-Schönlein purpura and polyarteritis nodosa in FMF can be explained by the important role of neutrophils in both diseases, the geographic distribution, or other environmental factors. The lack of ANCA and nuclear antibodies was highlighted and this may be due to the high pentraxin (C reactive protein and serum amyloid P) levels in these patients.[20]

CONCLUSION

The study of autoinflammatory diseases is shedding light on our understanding of inflammation and innate immunity. The identification of the molecular basis of these relatively rare diseases has opened up new areas of research which have implications for normal immune function and common inflammatory diseases. The elucidation of the inflammatory pathways involved in these disorders has also provided new effective treatments for these diseases, as seen by the success of anti-IL1 and anti-TNF treatments. International cooperation, which was exemplified at this meeting, is necessary to improve the care of patients with these illnesses.

Authors' affiliations

S Ozen, Department of Paediatrics, Hacettepe University, Ankara, Turkey
H M Hoffman, Department of Paediatrics, University of California at San Diego, La Jolla CA, USA
J Frenkel, Department of General Paediatrics, University Medical Centre Utrecht, The Netherlands
D Kastner, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda MD, USA

REFERENCES

1 **Stojanov S**, Kastner DL. Familal autoinflammatory diseases: genetics, pathogenesis and treatment. *Curr Opin Rheumatol* 2005;**17**:586–99.
2 **Livneh A**, Langevitz P, Zemer D, Padeh S, Migdal A, Sohar E, *et al*. The changing face of familial Mediterranean fever. *Semin Arthritis Rheum* 1996;**26**:612–27.
3 **Ozen S**. Renal amyloidosis in familial Mediterranean fever. *Kidney Int* 2004;**65**:1118–27.
4 **Samuels J**, Ozen S. FMF and the other autoinflammatory syndromes: evaluation of the patient with recurrent fever. *Curr Opin Rheumatol* 2006;**18**:108–17.
5 **Chae JJ**, Komarow HD, Cheng J, Wood G, Raben N, Liu PP, *et al*. Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis. *Mol Cell* 2003;**11**:591–604.
6 **Yu JW**, Wu J, Zhang Z, Datta P, Ibrahimi I, Taniguchi S, *et al*. Cryopyrin and pyrin activate caspase-1, but not NF-kappaB, via ASC oligomerization. *Cell Death Differ* 2006;**13**:236–49.
7 **Hoffman H**, Rosengren S, Boyle D, Cho J, Nayar J, Mueller J, *et al*. ''Interleukin-1 receptor antagonist prevents cold-associated inflammation in familial cold autoinflammatory syndrome,'' *Lancet* 2004;**364**:1779–85.
8 **Hawkins PN**, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004;**50**:607–12.
9 **Leys C**, Eschard C, Motte J, Prieur AM, Kalis B, Bernard P. Chronic infantile neurological, cutaneous, and articular syndrome with severe early articular manifestations. *Pediatr Dermatol* 2005;**22**:222–6.
10 **Neven B**, Callebaut I, Prieur AM, Feldmann J, Bodemer C, Lepore L, *et al*. Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU. *Blood* 2004;**103**:2809–15.

11 **McDermott MF**, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, *et al*. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell* 1999;**97**:133–44.
12 **Bodar EJ**, van der Hilst JC, Drenth JP, van der Meer JW, Simon A. Effect of etanercept and anakinra on inflammatory attacks in the hyper-IgD syndrome: introducing a vaccination provocation model. *Neth J Med* 2005;**63**:260–4.
13 **Frenkel J**, Rijkers GT, Mandey SH, Buurman SW, Houten SM, Wanders RJ, *et al*. Lack of isoprenoid products raises ex vivo interleukin-1beta secretion in hyperimmunoglobulinemia D and periodic fever syndrome. *Arthritis Rheum* 2002;**46**:2794–803.
14 **Shoham NG**, Centola M, Mansfield E, Hull KM, Wood G, Wise CA, *et al*. Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc Natl Acad Sci USA* 2003;**100**:13501–6.
15 **Ferguson PJ**, Bing X, Vasef MA, Ochoa LA, Mahgoub A, Waldschmidt TJ, *et al*. A missense mutation in pstpip2 is associated with the murine autoinflammatory disorder chronic multifocal osteomyelitis. *Bone* 2006;**38**:41–7.
16 **Pascual V**, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med* 2005;**201**:1479–86.
17 **Ozen S**, Bakkaloglu A, Yilmaz E, Duzova A, Balci B, Topaloglu R, *et al*. Mutations in the gene for familial Mediterranean fever: do they predispose to inflammation? *J Rheumatol* 2003;**30**:2014–18.
18 **Fidder H**, Chowers Y, Ackerman Z, Pollak RD, Crusius JB, Livneh A, *et al*. The familial Mediterranean fever (MEVF) gene as a modifier of Crohn's disease. *Am J Gastroenterol* 2005;**100**:338–43.
19 **Tunca M**, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, *et al*. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. *Medicine (Baltimore)* 2005;**84**:1–11.
20 **Ozen S**, Bakkaloglu A. C reactive protein: protecting from lupus in familial Mediterranean fever. *Ann Rheum Dis* 2005;**64**:786–7.