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# Fifth International Congress on Familial Mediterranean Fever and Systemic Autoinflammatory Diseases

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## **Fifth International Congress on Familial Mediterranean Fever and Systemic Autoinflammatory Diseases** *Rome, Italy, 4–8 April, 2008*

The Fifth International Congress on Familial Mediterranean Fever and Systemic Autoinflammatory Diseases (Rome, Italy, 4–8 April, 2008) reviewed developments in the field of innate immunity and discussed their relevance to the pathogenesis of associated diseases. The meeting gathered over 300 participants from 32 countries. New modes of inheritance of autoinflammatory diseases, animal models, novel related genes and the remarkable efficacy of IL-1 $\beta$  blockade in most of these diseases were emphasized.

The Fifth International Congress on Familial Mediterranean Fever and Systemic Autoinflammatory Diseases, organized by R Manna (Rome, Italy) and A Martini (Genoa, Italy), was held in Rome, from the 4th to the 8th of April, 2008. This meeting provides a forum every 2.5 years for clinicians and scientists to discuss developments in the field of autoinflammatory diseases [1]. This term was first applied to the hereditary periodic fever (HPF) syndromes, but now includes a number of both inherited and multifactorial systemic autoinflammatory disorders, several of which were discussed at the congress.

JW van der Meer (Nijmegen, Holland) addressed the topic of fever of unknown origin (FUO) in the postgenomic era. He highlighted the difficulties encountered in establishing a diagnosis, as well as some recent advances in investigating these patients, with emphasis on HPF. Some new tools in the diagnostic armamentarium include fluorodeoxyglucose-positron emission tomography and utilization of 16S ribosomal DNA sequencing as part of the diagnostic protocol in FUO patients.

D Kastner (Bethesda, MD, USA), during a wide-ranging talk entitled 'The Systemic Autoinflammatory Diseases *Quo Vadis?*', discussed the expanding scope of autoinflammatory diseases

and emphasised the clinical overlaps that exist between some of these conditions, indicating that they might usefully be considered as a genetic and pathogenic continuum [2]. He proposed digenic inheritance as a paradigm for familial Mediterranean fever (FMF) inheritance, as recent data indicate that one FMF gene mutation (*MEFV*) may be sufficient in some patients, in the presence of some other modifying genes, to cause the inflammatory phenotype. He also discussed the feasibility of conducting large-scale, genome-wide association studies, using a very high single-nucleotide polymorphism density to investigate idiopathic febrile syndromes. Other themes included the utility of knock-in mice and microarrays to study the function of HPF proteins.

The meeting comprised of eight sessions in total, divided according to different disease categories; we will attempt to review the highlights of each session.

### Sessions

#### ***Pathways of innate immunity***

D Golenbock (Worcester, UK) focused on Toll-like receptors (TLRs), discussing signal transduction by lipopolysaccharide (LPS) and its receptor family, including the LPS-binding proteins and the TLR4 coreceptor, MD-2. He emphasized

that MD-2, and not LPS, is a soluble endogenous ligand for TLR4. The TLR4/MD-2 complex plays a key role in antibacterial defenses.

ME Bianchi (Milan, Italy) discussed evidence that trauma and tissue damage are recognized via receptor-mediated detection of intracellular proteins, termed 'alarmins', released by dead cells. Alarmins are a subgroup of damage-associated molecular patterns of which HMGB1 is a founding member, with others including IL-1 $\alpha$ , heat-shock proteins and thymosins.

F Martinon (Boston, MD, USA) spoke about the inflammasome. IL-1 $\beta$  production occurs in three major stages: transcription, maturation and exportation. The number of inflammasome activators is rapidly increasing and includes urate crystals, DNA, RNA and, more recently, asbestos and silica [3], in addition to pathogens. Inflammasome formation is regulated by SGT1 and HSP90.

Mechanisms of IL-1 $\beta$  secretion were discussed by A Rubartelli (Genoa, Italy). Export of IL-1 $\beta$  is an active process, not occurring through the endoplasmic reticulum and Golgi body. IL-1 $\beta$  secretion is a two-step process, involving endolysosomal vesicles, with the first signal, such as the TLR ligand, resulting in pro-IL-1 release. A second signal, such as ATP, causes maximal production of IL-1 $\beta$  [4]. C Dinarello (Denver, CO, USA) concentrated on caspase-activated cytokines and the IL-1 homologs, IL-1F7b and IL-1F710. LPS-induced IL-1F7 downregulates TNF and IL-6, as well as other proinflammatory cytokines, but has no effect on IL-10. In summary, IL-1F7 is an inhibitory member of the IL-1 $\beta$  family.

R Flavell (New Haven, CT, USA) focused on innate immunity driving adaptive immunity. He discussed NALP3 deficiency *in vivo*, which leads to defective caspase-1 activation in *NALP3*<sup>-/-</sup> macrophages, and how silica and asbestos activate the NALP3 inflammasome. Macrophages produce reactive oxygen species (ROS) in response to silica; ROS are required for silica-induced IL-1 $\beta$  *in vivo* maturation, but this is upstream of NALP3 engagement *in vivo*. Aluminum adjuvants cause dendritic cell activation and produce a Th2 response.

R Slim (Montreal, Canada) spoke on the identification of a defective maternal gene, *NALP7*, responsible for recurrent moles, and ongoing work to elucidate the pathophysiology of molar pregnancies was also described [5].

### **NALP-related diseases**

Cryopyrin-associated periodic syndrome (CAPS) is caused by *CIAS1/NALP3* mutations and includes three phenotypes. H Hoffman (San Diego, CA, USA) considered CAPS as a clinical continuum and presented a trial of rilonacept (IL-1 Trap) resulting in prevention of symptoms (further developed in the 'novel treatments' session). R Goldbach-Mansky (Bethesda, MD, USA) has set up a large, prospective study that shows a dramatic response to anakinra in neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurological, cutaneous and articular (CINCA) patients, including the CNS and inner-ear problems. Together, these results establish anti-IL-1 $\beta$  therapies as the standard treatment for CAPS [6].

I Jéru (Paris, France) searched for novel causative genes in CAPS phenotypes that were mutation negative. A total of two mutations in *NALP12* were identified [7].

### **From MEFV to FMF**

J Chae (Bethesda, MD, USA) has generated knock-in mouse models for FMF. The homozygous knock-in mice with the FMF-causing mutations show profound inflammatory phenotypes, but heterozygotes are healthy; knock-in/knockout hemizygotes are also healthy. S Ozen (Ankara, Turkey) emphasized the high number of heterozygote patients with typical clinical symptoms [8] and offered a number of hypotheses, including unidentified rare or nonexonic *MEFV* mutations, genetic heterogeneity, digenism, genetic modifiers, environmental and epigenetic factors.

R Manna (Rome, Italy) presented the clinical features of FMF and the specificities of the disease, as seen in Italy [9]. In addition, A Livneh (Tel Hashomer, Turkey) and H Ozdogan (Istanbul, Turkey) reviewed the current options for FMF treatment and concluded that, currently, there is no alternative to colchicine, although thalidomide and etanercept may be effective as additional therapies in colchicine-resistant cases of FMF [10]. A promising, randomized, multicenter, double-blinded trial with rilonacept is ongoing. Other highlights included a presentation by M La Regina (Rome, Italy), who surveyed clinical centers from eight countries and pinpointed considerable variations in colchicine use, 35 years after its introduction. T Kallinich (Berlin, Germany) demonstrated that S100A12 is a sensitive surrogate marker for disease monitoring in FMF. In untreated patients, high concentrations of S100A12 may help to differentiate FMF from other conditions. Several presentations from Bethesda (MD, USA) concerned the pathophysiology of FMF.

### **From mevalonate kinase deficiency to periodic fever**

J Frenkel (Utrecht, The Netherlands) reviewed the evidence that a deficiency of geranylgeranylated proteins is likely to cause increased IL-1 $\beta$  secretion in patients with mevalonate kinase deficiency (MKD) [11]. He also showed that impaired isoprenoid biosynthesis induces caspase-1 activation in a Rac1-PI3k-dependent fashion. He suggested that Rac1 is a target for therapy, as Rac1 inhibition decreases IL-1 $\beta$  secretion.

J Drenth (Nijmegen, The Netherlands) discussed the value of serum IgD levels in patient assessment. In a series of 50 patients with clinical MKD, the sensitivity was 79% and the specificity was 27% [12]. He also described genetic heterogeneity; *MVK* mutation-positive patients were younger at first attack, with more cutaneous involvement. A number of reports have described the efficacy of anakinra in MKD.

### **New insights for TRAPS**

A Simon (Nijmegen, The Netherlands/Bethesda, MD, USA) reviewed the pathogenic consequences of TNF receptor (TNFR)-trafficking abnormalities in TNFR-associated periodic syndrome (TRAPS). Abnormal disulfide-linked oligomerization

results in endoplasmic reticulum retention and altered signaling by TNFR1 mutants [13]. She also found increased activation of c-Jun and p38, but not NF- $\kappa$ B.

I Todd (Nottingham, UK) described his findings using mutant TNFRs in transfection systems and concluded there was little, if any, expression of mutant TNFR1 (C33Y) on the cell surface [14].

M Gattorno (Genoa, Italy), in a talk entitled 'Lessons from TRAPS patients', compared data from various transfection systems and those on patients' cells; the latter studies show NF- $\kappa$ B activation [15,16], whereas transfection systems do not. He described four TRAPS patients who responded well to anakinra, although there are also reports of TRAPS patients unresponsive to IL-1 $\beta$  blockade.

### **Expanding spectrum of autoinflammatory diseases**

D Kastner (Bethesda, MD, USA) indicated that the mechanisms by which *PSTPIP1* mutations lead to the syndrome of pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) are unclear, but suggested that this protein prevents normal pyrin inhibition of ascorbic acid activation. Clinical aspects of PAPA were reviewed, with anti-TNF (infliximab) being suggested as a possible therapy.

H El-Shanti (IA, USA) described the increased recognition of chronic recurrent multifocal osteomyelitis (CRMO) and potential treatments, which include bisphosphonates and infliximab. Majeed syndrome, a form of CRMO, is associated with mutations in *LPIN2* [17].

A Martini (Genoa, Italy) reviewed clinical heterogeneity in systemic-onset juvenile idiopathic arthritis (soJIA), with and without joint involvement, depending on response to anti-IL-1 $\beta$ . M Hofer (Lausanne, Switzerland) explained that clinical distinction of periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) from genetically defined HPF remains difficult. It is proposed to define tighter clinical criteria for this diagnosis.

A Gul (Istanbul, Turkey) overviewed clinical features and epidemiology of Behçet's disease, as well as focusing on the *HLA-B51* locus and the role of receptors for natural killer cells (killer cell immunoglobulin-like receptor [KIR]), while I Koné-Paut (Paris, France) discussed the inherent difficulties of diagnosing Behçet's disease in children due to lack of specific criteria and low incidence below 16 years of age. An international cohort study for pediatric Behçet's (PED-BD) has been established.

A Simon presented Schnitzler syndrome, a clinical entity with a poorly understood pathophysiology, and C Wouters (Leuven, Belgium) and M Chamailard (Lille, France) reviewed two diseases associated with *NOD2* mutations, Blau syndrome and Crohn's disease, respectively [18].

Posters describing possible new genes were selected. A Rösen-Wolff (Dresden, Germany) revealed novel mutations in caspase-1 in five patients with a TRAPS-like phenotype, all leading to a decrease in IL-1 $\beta$ . P Ferguson (Iowa City, IA, USA) described a mutation in the cherubism gene, associated with skin and bone pathology. M André (Clermont-Ferrand, France) screened *NOD2* and *PSTPIP1* as candidate genes in aseptic abscesses

and found a significant association with a microsatellite 5' upstream of *PSTPIP1*.

### **New insights into amyloidosis**

P Hawkins (London, UK) overviewed amyloidosis in auto-inflammatory diseases and highlighted the critical role of serum amyloid A (SAA) in development of amyloid A (AA) amyloidosis, whatever the cause. He presented a 15-year study on both natural history and response to various treatments, which emphasized the clinical value of monitoring SAA protein and the absolute necessity to maintain the level as low as possible, with a target of under 5 mg/l.

G Hatemi (Istanbul, Turkey) presented a series of 26 patients, with AA amyloidosis of very diverse causes, treated with anti-TNF agents. The overall effect over 1 year seems to be beneficial in terms of renal function. However, the number of deaths and adverse effects is high in this series. L Obici (Pavia, Italy) discussed the current state of development of drugs that interfere with amyloid fibril formation, and presented data from the international eprodisate study, suggesting their benefit on renal function. Doxycycline also stimulates amyloid fibril clearance, and trials are in progress to treat transthyretin amyloidosis. An association of two serum amyloid P (SAP) inhibitors developed by P Hawkins, namely CPHPC and an anti-SAP antibody, are effective at blocking amyloid formation in a mouse model.

### **Novel treatments in autoinflammatory diseases**

O Della Casa Alberighi (Genoa, Italy) considered development of rare diseases and the remarkable efficacy of IL-1 $\beta$  inhibition was emphasized. JB Kuemmerle-Deschner (Tubingen, Germany) presented clinical trial findings of ACZ885, a monoclonal antibody to IL-1 $\beta$ , and H Lachmann (London, UK) presented findings in patients with cryopyrinopathies. Response to rilonacept appears to remain stable at 48 weeks, but caution is necessary due to potentially serious adverse effects. The positive effect of rilonacept in a murine model of gout was underlined by R Torres (Tarrytown, NY, USA). The session finished on an upbeat note with a presentation by P Miettunen (Calgary, Canada) of a preliminary study of pamidronate therapy in children with CRMO.

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