

Molecular and Genetic Characteristics of Hereditary Autoinflammatory Diseases

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Abstract: Autoinflammatory diseases are defined as recurrent "unprovoked" inflammatory events which do not produce high-titer autoantibodies or antigen-specific T cells. There are currently eight hereditary forms of these diseases: Familial Mediterranean fever (FMF), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), chronic infantile neurologic cutaneous articular (CINCA) syndrome or neonatal-onset multisystem inflammatory disease (NOMID), pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) and Blau syndrome. Apart from FMF (which has a prevalence of about 0.1 percent among non-Ashkenazi Jews, Armenians, Turks and Arabs), they are very rare disorders. FMF and HIDS are autosomal recessive diseases, all the other members of the family are autosomal and dominantly transmitted. Their common clinical features are recurrent and usually short attacks of synovitis and various skin eruptions; abdominal pain and fever are also frequently observed. The genes of all of these diseases have been discovered and, with the exception of HIDS, it was found that the proteins they encode share certain domains taking part in innate immunity and apoptosis. Thus it was evident that hereditary autoinflammatory diseases may help us understand better a number of important and prevalent pathologic events. We have reviewed the recent and rapidly accumulating knowledge on the molecular aspects of these disorders.

INTRODUCTION

Autoinflammatory diseases are defined as recurrent inflammatory events without any recognizable pathogens. They do not produce high-titer autoantibodies or antigen-specific T cells [1, 2]. There are currently eight hereditary forms of these diseases and probably there will be more additions to this list in the future [3, 4]:

1. Familial Mediterranean fever (FMF, MIM249100)[†],
2. Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS, MIM260920),
3. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS, MIM142680),
4. Muckle-Wells syndrome (MWS, MIM191900),
5. Familial cold autoinflammatory syndrome (FCAS, MIM120100),
6. Chronic infantile neurologic cutaneous articular (CINCA) syndrome or neonatal-onset multisystem inflammatory disease (NOMID, MIM607115),
7. Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA, MIM604416),
8. Blau syndrome (MIM186580).

[†]MIM: Mendelian inheritance in man classification number. (Source: <http://www.ncbi.nlm.nih.gov/Omim>)

Genotyping analyses of all these diseases are registered at the web site <http://fmf.igh.cnrs.fr/infevers> [5]. The mutation information cited in this manuscript has been derived from this web site and the date of our inquiry was December 31, 2003.

FAMILIAL MEDITERRANEAN FEVER (FMF, MIM249100)

Familial Mediterranean fever (FMF) is the most commonly encountered member of autoinflammatory diseases. FMF is characterized by recurrent febrile inflammatory attacks of serosal and synovial membranes which respond favourably to colchicine treatment [6]. Secondary (AA) amyloidosis is the main and potentially lethal complication of the disease.

There have been occasional reports of true dominant inheritance of FMF with variable penetrance but FMF is essentially an autosomal recessive disease [7, 8]. Its prevalence among susceptible ethnic groups (non-Ashkenazi Jews, Armenians, Turks and Arabs) is between 1/500-1/2000, and the carrier rate is about 20% in these populations. Since the discovery of its gene which is called *MEFV*, located at 16p13, 76 mutations have been detected, 43 of them are true mutations, there are 24 polymorphisms and 9 of them are unknown [9, 10]. There are

discrepancies in phenotypic expression of the genotypes, thus making genotyping analyses obsolete for definite diagnosis [11, 12].

A patient with a positive family history of FMF, who has developed AA type amyloidosis without experiencing typical attacks of the disease, is classically defined as "phenotype II" [13]. This variant of the disease is probably quite rare [14-16]. After the availability of genetic analysis, a more proper definition of phenotype II would be a patient with AA amyloidosis and positive family history of FMF, without a predisposing disease, and/or 2 *MEFV* mutations, and/or developing classical FMF attacks after the diagnosis of amyloidosis.

On the other hand, substantial number of FMF patients have no demonstrable mutations while some of the asymptomatic relatives may be homozygous or compound heterozygous. The latter are called "phenotype III" cases [12, 17, 18].

It is generally accepted that being M694V homozygous predisposes to a more severe phenotype and that M694V and/or serum amyloid A (SAA) alpha/alpha genotype homozygosity or male gender significantly increase the risk of amyloidosis [19-22]. However the correlation between being M694V homozygote and development of amyloidosis was not confirmed in a large group of patients from Turkey [23]. Four different mutations on this locus have already been detected (M694V, M694I, M694Del and M694L). Interestingly, in an extensive animal study, several of the true mutations of FMF were found to exist as wild type without overt signs of the disease, but not a single wild type mutation could be demonstrated on the 694 locus [24]. The authors of this study, along with other investigators have proposed that an ongoing subclinical inflammatory response would provide a survival benefit to the carriers [25]. Several other studies have also found higher than normal levels of acute phase reactants in FMF patients during the attack-free intervals [26, 27]. On the other hand, there is increasing evidence that being a carrier of some of the FMF mutations may predispose to and augment the clinical expression of various chronic inflammatory diseases [28-31].

The FMF gene encodes a protein of 781 amino acids and is called pyrin. Most of the mutations are located at the C-terminal of the protein. However recent information on the putative function of pyrin is more related to its N-terminal, which has a sequence of 90 amino acids and called pyrin domain [32]. Pyrin domain is one of four domains participating in apoptosis: death domain, (DD) death effector domain (DED), and caspase activating and recruitment domain (CARD) [33, 34]. Each domain can interact only with its similar counterpart which is called homotypic interaction [35]. In this system a protein called ASC (apoptosis-associated speck-like protein with a caspase recruitment domain) has a pivotal role since it has both a pyrin domain and a CARD domain. When there is a stimulus for an inflammation, ASC interacts with the CARD of procaspase 1 and induces a cascade which leads to the formation of IL-1 β and other apoptosis inhibiting cytokines [36-38]. Pyrin competes with procaspase for ASC and if pyrin interacts with the pyrin domain of the ASC it can no longer interact with the procaspase, thereby inhibiting the production of IL-1 β and allow normal apoptosis. In patients with FMF

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pyrin is defective, therefore it interacts poorly with the ASC, allowing it to react with the procaspase, leading to IL-1 β production, inhibition of apoptosis and enhancement of the inflammatory burst. The heightened sensitivity to endotoxin observed in the mouse model may explain the episodic nature of FMF and that an exaggerated inflammatory response can be triggered by negligible bacteremias [39].

HYPERIMMUNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME (HIDS, MIM260920)

Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) is also autosomal and recessively inherited. The syndrome was first described in 1984. HIDS is characterized by recurrent attacks of fever, severe abdominal pain, diarrhea, oligoarthritis and arthralgia with mainly cervical lymphadenopathy and erythematous macules or papules. Serum levels of IgD are persistently elevated (>100IU/mL) in almost all of the patients [40]. Contrary to what the name of this entity suggests, IgD itself does not seem to be the cause of the inflammatory attacks. The frequency and severity of the attacks do not correlate with IgD levels. Besides there are other conditions like pregnancy, diabetes mellitus and cigarette smoking, in which IgD levels are over normal levels [41]. Slight elevations are also reported in a minority of cases with FMF, TRAPS and PAPA [42, 43].

The prevalence of HIDS is much lower than FMF and the cases are mostly from The Netherlands, France and Northern Europe. Its gene (MVK) is located at 12q24 and encodes the enzyme mevalonate kinase [44]. Mevalonate kinase catalyzes the ATP-dependent phosphorylation of mevalonic acid to form mevalonate 5-phosphate, which plays a key role in regulating cholesterol biosynthesis. Its activity is subject to feedback regulation by the branch-point intermediates geranyl diphosphate, farnesyl diphosphate and geranylgeranyl diphosphate. The subcellular localization of mevalonate kinase may be in the cytosol or in peroxisomes [45]. Up to this date 24 true mutations on various exons were detected, along with 6 polymorphisms and 3 unknown. Most of the patients have the V3771 mutation and about 20% are homozygous for this mutation. The second most common mutation is I268T [46].

Mevalonate kinase activity is not absent but reduced in HIDS. Patients with severe mevalonic aciduria however, have almost no enzymatic activity. These patients differ from patients with HIDS with regard to clinical as well as genetic wise. Mutations related with HIDS are distributed throughout the coding region of the gene, whereas mutations associated with mevalonic aciduria are found mainly between codons 243 and 334. Three cases by now, had overlapping features of HIDS and mevalonic aciduria [46].

Acute-phase proteins, C-reactive protein (CRP) and soluble type-II phospholipase A2 (PLA2), IL-6, and tumor necrosis factor alpha (TNF alpha), IL-1 receptor antagonist (IL-1ra), the soluble TNF receptors p55 (sTNFr p55) and p75 (sTNFr p75) were found to be significantly higher with attacks of HIDS. Also urinary mevalonate levels are elevated during attacks [47]. The mechanism of MVK deficiency and the observed cytokine release leading to inflammatory attacks are not fully understood.

TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED PERIODIC SYNDROME (TRAPS, MIM142680)

Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is a rare autosomal dominant disease. It was initially called "familial Hibernian fever" because the first recognized cases were from "Hibernia", the name given to Ireland by the Romans [48]. There have been ever increasing cases from Western Europe and various ethnic groups, including Armenians, Sephardic Jews, Arabs and Japanese [49-52]. The disease is characterized by recurrent attacks of fever, abdominal pain, migratory myalgia, rash, and periorbital edema. The attacks usually continue for several days to weeks but much shorter variants have also been observed. The median age of onset of TRAPS is 3 years [53]. Its gene (TNFRSF1A) is located at 12p13 and 47 mutations have been reported, 35 of them are true mutations and the most frequent mutation is R92Q, there are 10 polymorphisms and 2 unknown [54]. It has been reported that of the 100 cases with TRAPS, 14 had systemic amyloidosis. AA amyloidosis is more common among patients with cysteine mutations compared to non-cysteine ones [55]. The TNFRSF1A gene encodes 55 kDa tumor necrosis factor receptor 1. In normals, stimulation through TNF- α receptors activates cytokine secretion and also metalloprotease mediated cleavage of the receptors from the cell surface to the circulation where they act as an inhibitor of TNF- α . The autoinflammatory phenotype of TRAPS may be, to some extent, due to impaired downregulation of

membrane TNFR1 and diminished shedding of potentially antagonistic soluble receptor [56]. However this proposed mechanism is not consistent with all TRAPS mutations [57]. Most of the mutations result in amino acid substitutions within the first 2 cysteine-rich domains of the extracellular portion of the receptor. These mutations have higher penetrance of phenotype [54]. Some mutations such as R92Q and P46L have very low penetrance but there is some evidence that they may play a role in various inflammatory rheumatic diseases [53, 58, 59].

MUCKLE-WELLS SYNDROME (MWS, MIM191900), FAMILIAL COLD AUTOINFLAMMATORY SYNDROME (FCAS, MIM120100), CHRONIC INFANTILE NEUROLOGIC CUTANEOUS ARTICULAR (CINCA) SYNDROME OR NEONATAL-ONSET MULTISYSTEM INFLAMMATORY DISEASE (NOMID, MIM607115)

Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS) and chronic infantile neurologic cutaneous articular (CINCA) syndrome or neonatal-onset multisystem inflammatory disease (NOMID) have several similarities in their clinical and genetic features. They are all autosomal dominant diseases.

MWS is characterized by recurrent episodes of urticaria, fever and polyarthralgia. Sensorineural deafness and secondary amyloidosis may also occur later in life [60]. In FCAS, these recurrent episodes are triggered by generalized exposure to cold and almost all of the patients have an onset before age one. Deafness is not encountered and amyloidosis is less probable than MWS [61, 62]. The clinical characteristics of CINCA syndrome are nonpruritic urticarial skin rash; deforming arthropathy of knees, feet, elbows and hands; and chronic meningitis with mental retardation. The patients have a short stature, head enlargement, saddle back nose and short and thick extremities with clubbing of fingers. CINCA syndrome is the most severe of the above mentioned three diseases [63].

Although most of the patients are from Europe or America a few cases from India and Thailand have been diagnosed. A single mutation may cause both MWS and FCAS [64, 65]. Some cases may disclose an overlapping phenotype, a further evidence of close relation of these entities [66]. It has also been suggested that MWS and CINCA syndrome are in fact the same disease with different degrees of severity [67].

The mutated gene (CIAS1) is located at 1q44 and encodes a protein with various names, called cryopyrin, PYPAF1 and NALP3. Cryopyrin is one of the recently described pyrin domain proteins (PYD) which play a role in the regulation of NF κ B activity, cytokine processing and apoptosis. Cryopyrin has an N-terminal pyrin domain (PYD), a nucleotide-binding site (NACHT subfamily), and a leucine-rich repeat (LRR) region [68]. The gene is highly expressed in polymorphonuclear leucocytes and chondrocytes [69, 70]. Up to the end of 2003 forty one mutations were detected, 30 of them true mutations, 10 polymorphisms and 1 unknown. All of the mutations are located on exon 3 [71].

CIAS1 mutations have been found in only 6 of the 13 patients with clinical diagnosis of CINCA and this may point to the genetic heterogeneity of the disease [72]. The same investigators found that IL-1beta, tumor necrosis factor, IL-3, IL-5, and IL-6 were increased in a mutation positive patient. This finding is more important in the context of the role of CIAS1 in IL-1 regulation. The activation antigen CD10/NEP was found to be hyper-expressed in neutrophils of 3 patients with CINCA syndrome and was proposed as a marker of the inflammatory process [73].

It has been shown that co-expression of cryopyrin and its binding partner, ASC, induce apoptosis and NF-kappaB activation and is negatively regulated by pyrin [37]. The nucleotide-binding site (NBS) domain of cryopyrin, which is a member of NACHT subfamily, has been suggested to be similar to ATPases. As most of the mutations are located at this region where intermolecular contacts occur, its defect would disrupt various functions of the protein [74].

PYOGENIC STERILE ARTHRITIS, PYODERMA GANGRENOSUM, ACNE (PAPA, MIM604416)

Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) is another rare autosomal dominant syndrome with recurring inflammatory attacks leading to destructive joint lesions. Patients have also aphthous stomatitis, headache and abdominal pain and attacks last about 4 days [75]. Its gene (CD2BP1/PSTPIP) has been located at 15q24 which encodes CD2-binding protein 1 (CD2BP1), an adaptor protein involved in cytoskeletal organization. There are 2 known mutations at this gene [76]. It has been recently shown that this protein also interacts with pyrin [77].

BLAU SYNDROME (MIM186580)

Blau syndrome is an autosomal dominant disease characterized by granulomatous arthritis with papular rash and uveitis [78]. Its gene (CARD15 or NOD2) is located at 16q12 with three known mutations. The gene encodes a 1040-amino-acid protein (called CARD15) whose nuclear binding site domain (NACHT) is shared by cryopyrin [79].

Mutations have been detected in the leucine-rich repeat (LRR) domain at the C-terminal of the same protein in Crohn's disease cases [80]. The two separate observations of more than expected frequencies of Crohn's disease, and inflammatory bowel disease in general, among FMF patients further increase the intriguing relations of this group of disorders [81, 82]. The recently reported close locations and even one identical variation of CIAS1 and NOD2/CARD15 mutations in highly conserved regions is interesting [83, 84].

CONCLUSION

Great progress has been made in our comprehension of the periodic fever syndromes as well as the molecular basis of inflammation in general. The common pathology these syndromes seem to share is an inborn error of inflammation, which forms the basis behind the term autoinflammation [85].

Accumulation of data will be reflected in designing future therapies and may also provide insights into the pathogenesis of other inflammatory diseases.

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