Review

Familial Mediterranean fever in 2003.
Pathogenesis and management

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent febrile inflammatory attacks of the serosal and synovial membranes. It is currently regarded as a member of the hereditary periodic fever syndromes, and a subset of the autoinflammatory diseases (1). Autoinflammatory diseases are distinct recurrent inflammatory episodes without the production of high titer autoantibodies or antigen-specific T-cells (2). FMF is not a truly "periodic" disease since recurrent attacks are neither regular nor predictable. It has been estimated that there are more than 100,000 FMF cases worldwide (3). Other members of this new family of disorders are quite rare, and therefore FMF is probably the only hereditary autoinflammatory disease that an average clinician will ever encounter during his professional lifetime. Principally studies published from 2002 onwards will be dealt with in the following discussion.

Pathogenesis

FMF was defined as an independent clinical entity in 1945 by S. Siegal who himself was an FMF patient. Siegal hypothesised that the attacks were due to allergy (4). Later proposals to explain its pathogenesis such as etiocholanolone (a metabolite of testosterone) or abnormal cathecolamine metabolism could not be confirmed by other investigators. Meanwhile, Matzner *et al.* observed that FMF patients had decreased levels of complement 5a inhibitor activity in their serosal and synovial fluids (5, 6). This observation was attractive for a number of reasons. It could, for example, explain to a certain extent the recurrent attacks and anatomic location that characterises the clinical picture, but the discovery of the

gene causing FMF (called MEFV) and the protein encoded by this gene (pyrin) radically changed the direction of investigations (7, 8).

About 30 mutations have been detected in a short time, the most severe one being the M694V mutation. Today, however, it is generally agreed that utilization of genetic analysis as a diagnostic tool is not acceptable because of various discrepancies in the phenotypic expression of the genotypes (9, 10). Recent studies confirmed previously reported findings that M694V or the serum amyloid A (SAA) alpha/alpha genotype homozygosity significantly increased the risk of amyloidosis (11, 12), but there was no correlation between M694V homozygosity and the development of amyloidosis in a large group of patients from Turkey (13).

The N terminal of the pyrin protein contains a sequence of 90 amino acids called the pyrin domain (14). This is one of four domains that actively participate in apoptosis, the others being the death domain, (DD) the death effector domain (DED), and the caspase activating and recruitment domain (CARD) (15,16). It has been found that each domain can interact only with its similar counterpart (homotypic interaction) (17). A pivotal compound in this system is a protein called ASC (apoptosis-associated speck-like protein with a caspase recruitment domain). This protein has a pyrin domain and a CARD domain (Fig. 1). When there is a stimulus for inflammation, ASC interacts with the CARD of procaspase 1 (IL-1 converting enzyme or ICE) and induces a cascade which leads to the formation of IL-1 and other cytokines that inhibit apoptosis (18-20). However, if pyrin interacts with the pyrin domain of the ASC it can no longer interact with the procaspase; thus the production of IL-
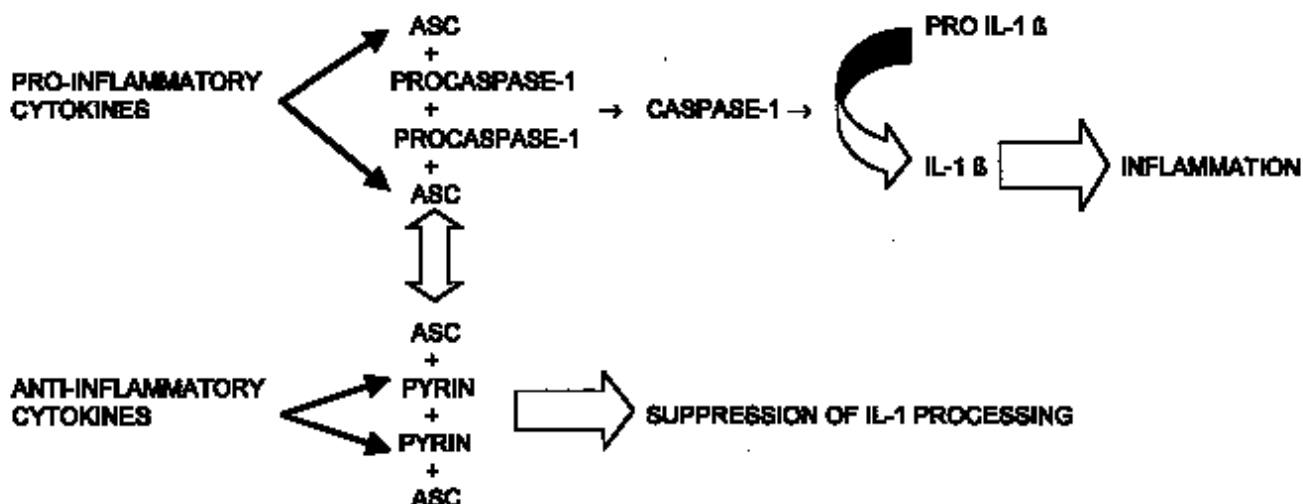
Fig. 1. Proposed role of pyrin, competing with caspase-1 for ASC (apoptosis-associated speck-like protein with a caspase recruitment domain).
Functional domains of the proteins:Procaspase-1 = CARD + 10 kDa and 20 kDa polypeptides; Caspase-1 = Two 10 kDa and two 20 kDa subunits (heterotetramer); ASC = CARD + PyD; Pyrin = PyD + B-box zinc-finger + Coiled-coil + B30.2
Adapted and reprinted from Figure 6 (pg. 601), Chae JJ, Komarow HD, Cheng J, Wood G, Raben N, Liu PP, Kastner DL: Targeted disruption of pyrin, the FMF protein,causes heightened sensitivity to endotoxin and a defect in macropha ge apoptosis. *Mol Cell* 2003;11:591-604,Copyright 2003,with permission from Elsevier.

1 is inhibited and normal apoptosis is allowed. These two processes depress the inflammatory reaction in response to the stimulus.

In patients with FMF, the gene encoding pyrin is defective due to the mutations it bears. It would therefore be expected to interact poorly with ASC, thereby allowing it to react with the procaspase, leading to IL-1 production, the inhibition of apoptosis, and enhancement of the inflammatory burst. Thus it is assumed that inhibition of the apoptosis of leukocytes and the production of IL-1 are two mutual processes underlying the acute attacks of FMF. This "apoptosis inhibition" hypothesis is quite plausible and reasonable, but seems overly simple. It has various limitations because it does not explain several findings and observations seen in the clinic and reported previously in the literature.

The theory for example is not in line with the observations of Ozen *et al.*, who reported that apoptosis is enhanced in the neutrophils of FMF patients (21). Furthermore, in a study by Gumucio *et al.* no difference could be demonstrated between the effect of wild type pyrin and mutated pyrin with regard to their interaction with the ASC protein and their effect on cell death (18). Another query which requires explanation is the possible (if any) interaction between the main mutations that are present in the C-terminal site and the pyrin domain which is present at the N-terminal site of the protein. The last but not least important concern is the lack of explanation for the periodic nature of this disease. If the heightened sensitivity to endotoxin observed in the mouse model can be shown in human beings, this could explain the episodic nature of FMF and the fact that an exaggerated inflammatory response can be triggered by negligible bacteremias (22).

While a couple of years ago the hypothesis that FMF represents a disorder in leukocyte apoptosis could have appeared tenable, there are a number of experiments – some already published and some still in course – which would suggest that the pathogenesis is more complex. Probably cytokine processing, apoptosis, and NF-kappa B activation are all involved in this cascade of inflammation.

A great deal of progress has been made in the cloning and isolation of the gene associated with FMF. However, the above mentioned questions and doubts – although may have remote explanations – remind us that we still have a long way to go in order to understand the mystery of this fascinating disease.

Clinical aspects and the follow up of patients

While exciting results are emerging from molecular studies, there are a number of unresolved clinical issues. FMF is still a largely unrecognised disease. As was recently pointed out, erroneous diagnostic and therapeutic decisions with potentially serious consequences are not uncommon (23). Colchicine does not significantly increase the risk of teratogenicity and routine amniocentesis in the second trimester would seem to be unjustified (24, 25), yet many couples are discouraged from using the drug during conception and pregnancy. A prospective study on a sufficiently large number of pregnant patients would be conclusive on this point.

Any patient who is continuously receiving a drug treatment needs regular follow up and FMF patients represent no exception to this rule. Colchicine is essentially a safe drug, although therapeutic levels may approach the toxic range, particularly in patients with renal or hepatic dysfunction and in the elderly (26, 27). The subject most at risk is the post-renal transplant patient who is taking cyclosporin and colchicine concomitantly. Cyclosporin may also have a detrimental effect on graft survival in FMF patients (28). Neverthe-

less, occasionally patients without overt risk factors may present with severe colchicine toxicity. Therefore, informing the patient and family of the signs and symptoms of myo-neurotoxic complications would be more rational than the frequent assessment of his/her renal, hepatic and haematological status. The patient may be seen once every 3 months initially, then twice a year. Annual check-ups including urinanalysis and a clinical blood count should usually suffice from the third year onwards, with other tests to be decided on an individual basis.

There is fairly clear evidence that some FMF patients have ongoing subclinical inflammation between their acute attacks (29, 30). It has been shown that even a minimally elevated CRP constitutes not only a clue but also an independent risk factor for atherosclerosis (31). Instead of simply using the clinical response as the criterion, periodic CRP and SAA measurements should be utilized for the optimisation of colchicine therapy.

The number of elderly FMF patients who have been on colchicine for decades is increasing. Inevitably these patients will begin taking other drugs for such ailments as hypertension, hyperlipidemia and diabetes mellitus. There have already been reports on adverse interactions of colchicine with drugs utilized for above-mentioned illnesses (32) and this issue will need closer attention.

Treatment of FMF

More than 30 years after its introduction as an effective drug for FMF, colchicine remains the single agent at our disposal. The acute attacks and amyloidosis that are seen in FMF can be effectively avoided by the administration of colchicine regularly at the optimum dosage of 1.5 – 2.0 mg/day. The drug can also induce the regression of amyloid deposits to a certain extent (33). True resistance to colchicine is probably rare, but even committed patients have occasional severe attacks. Other adjunct treatment candidates to colchicine such as interferon alpha, thalidomide, anti-TNF agents and plant extracts require further clinical trials to obtain definitive results regarding their efficacy (34-36).

In conclusion, FMF retains its reputation as a disease that is of great interest to clinicians and basic scientists alike. Most of the very recent studies have been directed toward its pathogenesis and the structural and functional relationships of pyrin with other members of the family of autoinflammatory diseases. Meanwhile, large-scale clinical and genetic studies covering several thousands of FMF patients have been completed. There is no doubt that these investigations will provide us with a better understanding of our patients.

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