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Review

An Update on Familial Mediterranean Fever

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Abstract: (1) Background: Familial Mediterranean Fever (FMF) is the prototypal autoinflammatory disease, characterized by recurrent bursts of neutrophilic inflammation. (2) Methods: In this study we look at the most recent literature on this condition and integrate it with novel information on treatment resistance and compliance. (3) Results: The canonical clinical presentation of FMF is in children with self-limited episodes of fever and polyserositis, associated with severe long-term complications, such as renal amyloidosis. It has been described anecdotally since ancient times, however only recently it has been characterized more accurately. We propose an updated overview on the main aspects of pathophysiology, genetics, diagnosis and treatment of this intriguing disease. (4) Conclusions: Overall, this review presents the all the main aspects, including real life outcome of the latest recommendation on treatment resistance of FMF, a disease, that not only helped understanding the pathophysiology of the auto inflammatory process but also the functioning of the innate immune system itself.

Keywords: Familial Mediterranean Fever; colchicine; colchicine resistance; children; autoinflammatory disease; Interlukin-1 Inhibitors

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1. The Historical Background

Familial Mediterranean Fever (FMF) is the oldest and the most frequent autoinflammatory disease. It is a hereditary periodic fever syndrome characterized by self-limited episodes of fever and polyserositis associated with severe long-term complications, such as renal amyloidosis. FMF was particularly frequent in populations originating from the Mediterranean basin, such as Turks, Armenians, Jews, and Arabs [1]. The MEFV gene (from MEditerranean FeVer), located on the short arm of chromosome 16, was described for the first time in 1997 by the International and the French Consortium [2]. The protein encoded by the MEFV gene was initially called "Marenostrin" in reference to the Latin name of the Mediterranean Sea. Alternatively, the name "Pyrin" was given by the International Consortium in reference to the Greek name for fever.

Before the identification of the causative gene, the description of the disease can be traced back to the ancient history of Mediterranean populations, in which the Galen were among the first to report it almost two thousand years ago. This condition continued to be part of Mediterranean history throughout the centuries despite migrations and the merging of different cultures and people. In 1945, Siegal defined "benign paroxysmal peritonitis" as an under-diagnosed and "unusual clinical syndrome" in himself and other patients: "The characteristics of this disorder are constant and distinctive. The syndrome is characterized by recurrent paroxysms of severe abdominal pain with fever which may be as high as 105° F [=~41.6 °C]. Chilliness or a shaking chill may accompany the attacks. Involvement of the peritoneum is indicated by the subjective symptom of marked abdominal soreness and the objective finding of widespread, exquisite direct and rebound tenderness" [3]. The name Familiar Mediterranean Fever was given in 1955 by Professor Heller and his study group [1], which became universal.

In 1972, the first anecdotal observations on the efficacy of colchicine were provided by Goldfinger [4]. This event represented a revolution in the management of FMF, decreasing the frequency and intensity of the attacks and preventing renal amyloidosis, the most worrisome complication of uncontrolled FMF. Amyloid A (AA) amyloidosis results from continuous inflammation and unrestrained secretion of acute phase reactants. Colchicine was able to reduce the incidence of amyloidosis by reducing the levels of sub-clinical inflammation [5].

2. Epidemiology

FMF is prevalent in countries surrounding the Mediterranean Sea, especially affecting Turks, Arabs, Armenians, and Non-Ashkenazi Jews. Turkey is probably the country with the greatest prevalence, which is reported to be 1:1000 overall, with interregional differences. A nationwide multicentre study performed in Turkey [6] shows that patients with FMF originate mainly from the non-Mediterranean regions, with over 70% of the cases from central and eastern Anatolia and the inner Black Sea regions. Additional studies have revealed further differences in distribution, with the north-western region of Turkey having a prevalence as low as 6:10,000 [7]. Similarly, in Italy, the distribution of cases varies between northern and southern districts, the latter having a much higher occurrence of FMF. This phenomenon may be explained, at least partially, by the ancient colonization of the area by Greeks and Arabs and by the Jews' migratory fluxes [8].

It is possible that MEFV mutations arose in pre-Biblical times and that Jews, being genetically isolated, might represent the most likely candidate founder population for several common MEFV mutations [9], with a prevalence in Israel of roughly 1–2:1000. In the Armenian population, the same prevalence has been calculated [10]. Additionally, the carrier rate of FMF mutations in Armenians was shown to be 1:5, as high as in North African and Iraqi Jews and Turks but lower than in Moroccan Jews (1:3.5) and Muslim Arabs (1:4.3). Such an elevated number of carriers, resulting from a founder effect, does not correlate with the real prevalence of patients with a diagnosis of FMF, since the detection of a single mutation (heterozygosity) does not help in making the diagnosis [11].

It has also been hypothesised in the past that the high carrier rate of the MEFV gene mutations in certain populations is the result of an evolutionary advantage against tuberculosis [12] or brucellosis [13]. The recent insights on the role of the pyrin inflammasome as a crucial sensor against infection from microbes producing exotoxins outlined the possible selective advantage of MEFV carriers towards the infection of *Yersinia pestis* during different devastating plagues hitting the Mediterranean basin during the centuries [14].

In addition to the above countries, FMF is found in North African countries, Greece, Crete, France, Germany, and the US. In most of these countries, the presence of FMF is largely related to robust emigration from Mediterranean countries. Many studies have shown the presence of different severity in FMF according to the country of residence, totally or partially independent of the pathogenicity of MEFV variants and ethnicity. The incidence of amyloidosis is much higher in Turk and Armenian patients living in their country of origin with respect to the same population emigrating to northern Europe or the US [15]. The same phenomenon was also reported in children by the international Eurofever registry, which showed how children living in Western Europe displayed a less severe disease activity independently from their ethnicity [16]. These observations likely reflect the burden of environmental factors (i.e., infections) as possible triggers for a more robust inflammatory response in Mediterranean countries.

Finally, a milder form of FMF is also present in Japan, with a lower prevalence of abdominal manifestations, a higher median age of onset, and a lower frequency of complications (AA amyloidosis) as compared to Mediterranean patients, probably due to differences in MEFV gene mutations [17].

3. Pathogenesis

Pyrin, the protein product of the MEFV gene, is an immunoregulatory molecule made up of 781 amino acids, interacting with the inflammasome components that can be activated in response to microbes. The protein is mainly expressed in granulocytes and dendritic cells and within serosal and synovial fibroblasts [18].

Pyrin contains an N-terminal eponymous PYD domain, central B-box zinc finger, bZIP transcription factor, coiled-coil domains, and a C-terminal B30.2 domain (Figure 1). Most FMF causative mutations are found in the B30.2 domain [19]. The distinctive structure of the PYD domain (amino acids 1–300), identified for the first time when the MEFV gene was cloned, was not analogous to any other protein domain known at the time; hence, it was named the PYD or PYRIN domain. Since its discovery, it has been found in more than 20 proteins regulating inflammation [20]. It is responsible for the homotypic interaction with ASC, an apoptosis-associated speck-like protein that promotes the activation of caspase-1 [21]. Typically, ASC oligomerises with one of the NLRP proteins and with procaspase-1 through homotypic CARD (Caspase recruitment domain) interactions to make up the inflammasome. This complex brings two molecules of precursor pro-caspase-1 into close proximity, leading to autocatalysis and, therefore, the release of the active catalytic p20 and p10 domains of caspase-1 [22]. Caspase-1, in turn, cleaves the pro-form of IL-1β into its active form (Figure 2).

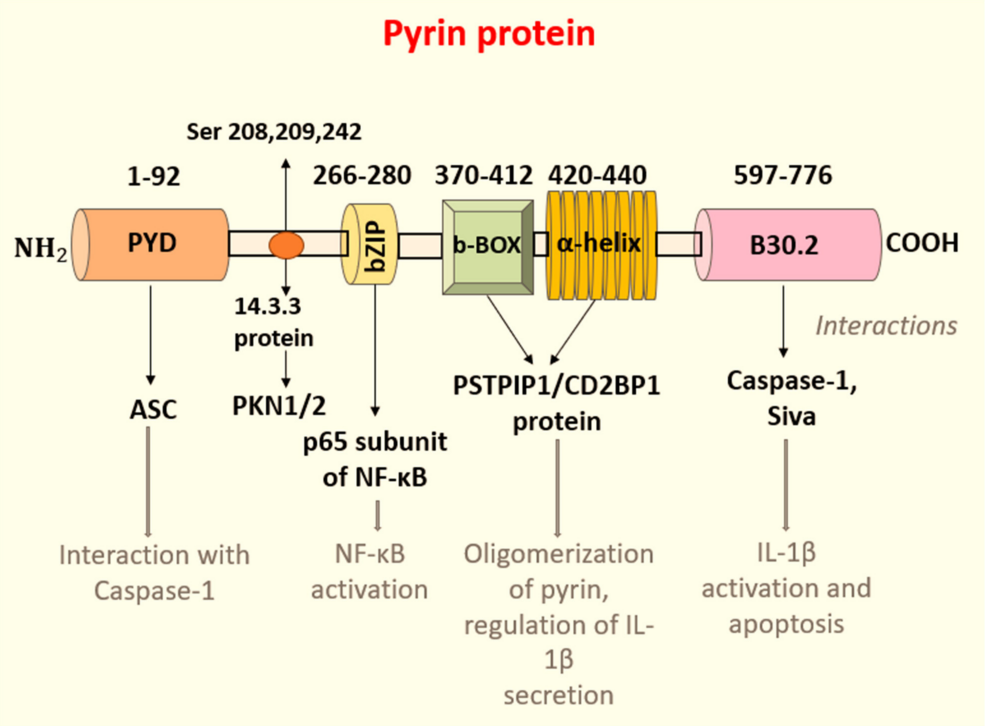

Figure 1. Schematic representation showing the pyrin protein. Pyrin is an approximately 95 kDa protein made up of five domains: a PYD or PYRIN domain (1–92), bZIP transcription factor domain (266–280), B–box zinc finger (370–412), α–helix coiled–coil domain (420–440), and a C–terminal B30.2 domain (597–776). The N–terminal PYD domain is responsible for the interaction with ASC (apoptosis–associated speck–like protein with a caspase recruitment domain), which, in turn, mediates the CARD (caspase recruitment domain) CARD homotypic interface with caspase–1. The bZIP transcription factor basic domain promotes NF–kB activation via the interaction with its subunit p65. The B–box zinc finger and the α–helix domain are involved in the oligomerization of pyrin and the regulation of IL–1β secretion. The B30.2 domain harbours most of the FMF–causing mutation and is functionally important in the activation of the pyrin inflammasome. B30.2 interacts with caspase–1 and pro–apoptotic protein Siva. Three residues of pyrin, serines 208, 209, and 242, are responsible for interacting with the 14.3.3 regulatory molecule that participates in the phosphorylation via PKN 1/2 (serine/threonine protein kinase C–related kinase 1/2).