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Autoinflammation: Lessons from the study of familial Mediterranean fever

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ABSTRACT

Autoinflammatory disorders represent a heterogeneous group of systemic inflammatory diseases caused by genetic or acquired defects in key components of the innate immunity. Familial Mediterranean fever (FMF) is the most common among the other clinical phenotypes of the rare hereditary periodic fevers (HPFs) syndromes. FMF is associated with mutations in the *MEFV* gene encoding pyrin and is characterized by recurrent, often stress-provoked attacks of fever and serositis, but sometimes also by chronic subclinical inflammation. FMF is prevalent in Greece and other countries of the eastern Mediterranean region. Over the last 17 years, our group has focused on FMF as a model suitable for the research on innate immunity and particularly the role of neutrophils. Therefore, the study of Greek patients with FMF has yielded lessons across several levels: the epidemiology of the disease in Greece, the spectrum of its clinical manifestations and potential overlaps with other idiopathic inflammatory conditions, the demonstration of its rather complex and heterogeneous genetic background and the suggestion of a novel mechanism involved in the crosstalk between environmental stress and inflammation. Mechanistically, during FMF attack, neutrophils release chromatin structures called neutrophil extracellular traps (NETs), which are decorated with bioactive IL-1β. *REDD1* (regulated in development and DNA damage responses 1), that encodes a stress-related mTOR repressor, has been found to be the most significantly upregulated gene in neutrophils during disease attacks. Upon adrenergic stress, REDD1-induced autophagy triggers a pyrin-driven IL-1β maturation, and the release of IL-1β-bearing NETs. Consequently, not only the mode of action of IL-1β-targeting therapies is explained, but also new treatment prospects emerge with the evaluation of old or the design of new drugs targeting autophagy-induced NETosis. Information gained from FMF studies may subsequently be applied in more complex but still relevant inflammatory conditions, such as adult-onset Still's disease, gout, ulcerative colitis and Behçet's disease.

1. Introduction

Autoinflammatory disorders (AIDs) comprise a heterogeneous group of systemic inflammatory diseases caused by genetic or acquired disturbances in key regulatory molecules of innate immunity and lacking an apparent primary role of T and B lymphocytes [1,2]. Since the introduction of the term autoinflammation by Daniel Kastner 20 years ago [3], the spectrum of AIDs is continuously expanded including not only the group of the so-called monogenic hereditary periodic fever syndromes (HPFs), but also multifactorial, polygenic diseases, such as adult-onset Still's disease (AOSD), as well as common metabolic disorders, namely gout and low-grade inflammation of type 2 diabetes that leads to atherosclerosis [2,4,5]. The concept of autoinflammation was further boosted by the identification of the critical role of the NOD-Like Receptor (NLR) family, pyrin domain containing 3 (NLRP3) inflammasome in the maturation of IL-1β [6], and the realization that neutrophils and IL-1β are the main mediators of tissue damage in the majority of AIDs [4,7]. Thus, the term IL-1β-mediated AIDs is commonly used today to collectively describe diseases that are characterized by sterile inflammation and a favorable response to IL-1β inhibition, in the absence of cognate autoreactivity, such as high-titer autoantibodies or autoantigen-specific T lymphocytes [4,8].

Familial Mediterranean Fever (FMF) is the oldest known and the most common HPF [5,9]. It is caused by mutations in the Mediterranean fever (*MEFV*) gene that encodes the protein pyrin. Affecting over 100,000 people worldwide, it is most prevalent in the eastern Mediterranean region, where Greece is located as well, and causes life-long illness with a significant impact on patients' quality of life and the health care systems [10–12]. Clinically, it is characterized by recurrent, self-limited attacks of fever and serositis often triggered by various

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environmental stressors. In some patients, persistent subclinical inflammation may be the only evidence of disease. Such individuals are generally unaware of their condition and, therefore, have an increased risk of developing serious complications, amyloidosis being the most important [13,14].

Due to its relatively high prevalence and distinctive clinical presentation, FMF is the best studied monogenic IL-1β-mediated AID today [5,15]. Several scientific groups have conducted significant translational and clinical research shedding light onto the various aspects of the disease. Among them, our inflammation research group, www.inflathrace.gr, has contributed, over the last 17 years, important pieces of genetic, functional and clinical information. The knowledge gained has suggested that FMF may also serve as an excellent model for the study of neutrophil-driven IL-1β-mediated inflammation in humans that could help further understand the role of neutrophils in other more complex inflammatory diseases [16–18]. The following review discusses the main lessons learned during this journey and the remaining open questions that future research should address.

2. Genetics of FMF

A major breakthrough in the field of FMF and a launching event of the era of autoinflammatory diseases was the identification, almost simultaneously by two different research groups, of the *MEFV* gene as the genetic basis of FMF [19,20]. *MEFV* is located on the short arm of chromosome 16, it is composed of 10 exons and encodes a 781-amino acid protein called pyrin [7]. The three most common mutations in eastern Mediterranean populations, including Jews, Armenians, Arabs and Turks are M694V, followed by M680I and V726A, which are located in exon 10 and linked to severe disease phenotype and progression to amyloidosis [21–24]. Besides MEFV mutations, specific polymorphisms in the SAA1 gene [25] and country of residence [26] are also critical risk factors for amyloidosis.

Shortly after the identification of the role of the *MEFV*, we developed a RNA hybrid method, the non-isotopic RNase cleavage assay (NIRCA) as a rapid screening test of the entire *MEFV* coding sequence to select patients for subsequent Sanger sequencing [27]. Analysis of the results in the Greek population shows a similar pattern with the rest of the eastern Mediterranean populations, with M694V being the most common mutation, followed by M680I and V726A [28,29] (Table 1).

Table 1
Mutations in the *MEVF* gene, allele frequencies and total number of mutations per patient detected in FMF patients from mainland Greece (n = 152) and Crete (n = 71) (data from refs 29, 30).

Mutations	Mainland Greece	Crete
	Number of alleles of patients (%)	
M694V	80 (26.3)	39 (27.5)
M680I	39 (12.8)	0 (0)
V726A	21 (6.9)	7 (4.9)
E148Q	19 (6.3)	20 (14.1)
E230K	9 (3)	0 (0)
K695R	4 (1.3)	1 (0.7)
M694I	8 (2.6)	10 (7)
A744S	3 (1)	1 (0.7)
E148V	2 (0.7)	0 (0)
T267I	2 (0.7)	0 (0)
E167D	2 (0.7)	0 (0)
M680L	1 (0.3)	0 (0)
R761H	1 (0.3)	1 (0.7)
F479L	0 (0)	2 (1.4)
S702C	0 (0)	1 (0.7)
Number of mutated alleles per patient	**Number of patients (%)**	
2	65 (42.8)	24 (33.8)
1	62 (40.8)	35 (49.3)
0	25 (16.4)	12 (16.9)

However, a study of FMF patients from the island of Crete demonstrated that the mutational profile of Cretans is distinct, resembling more that of western Mediterranean populations (Spaniards and Italians) [30]. This suggested that from a point onwards these Greek populations followed separate evolutionary lines, which was further confirmed in a meta-analysis [31] (Table 1).The carrier rate among healthy Greeks was also calculated at 0.7%, much lower than that observed in populations with high FMF prevalence, such as non-Ashkenazi Jews, Arabs, Armenians and Turks [29].

As more and more patients globally had their *MEFV* sequenced over the years, some challenging aspects of the FMF genetics became evident. Firstly, the list of sequence variants grew considerably long with plenty of them having questionable association with clinical FMF. Secondly, the disease does not always show a clear autosomal recessive inheritance pattern. Of the 349 sequence variants of *MEFV* currently listed in the INFEVERS database (http://fmf.igh.cnrs.fr/infevers/), merely 16% are considered pathogenic, while the rest are benign or of uncertain significance. Furthermore, a couple of unique *MEFV* sequence variants with special clinical associations were reported for the Greek population. Firstly, half of the FMF patients that didn't carry other *MEFV* mutations were homozygous for R202Q. In this patient group, the clinical presentation was slightly different from typical FMF (see below), but the response rate to colchicine was high [29]. Furthermore, the variant E225D was described for the first time in a family with recurrent fevers and polyserositis, adding it to the list of *MEFV* variants with potential significance that merit further evaluation [32]. Conversely, the NIRCA assay was used to screen for *MEFV* mutations patients with other idiopathic inflammatory diseases. In a study of patients with ulcerative colitis (UC) and rheumatoid arthritis (RA) we found that almost 30% of patients with UC carried at least one *MEFV* mutation compared to only 4% of RA patients. Interestingly, half of the UC patients carrying a mutation had inflammatory arthritis compared to none of the non-carrier UC patients [33]. This might suggest that the presence of *MEFV* mutations in the context of a multigenic inflammatory disease may have a modifying effect on the disease presentation, an issue that should be further investigated [34].

Although FMF has traditionally been considered an autosomal recessive disease, it does not always follow this inheritance pattern. In fact, in our Greek FMF cohort a homozygous state was found in 42.8% of the patients, a heterozygous state in 40.8%, while no mutation was detected in 16.4% of the patients [29]. Moreover, in the Cretan population, the percentage of FMF patients with no identifiable mutation in the MEFV gene was similar to that of the Greeks from the mainland [30] (Table 1). These results are in line with other groups reporting that up to 40% of patients with a clinical diagnosis of FMF carry a single or no *MEFV* mutation [35–37]. Furthermore, it seems that a gene dosage effect exists, as the proportion of patients with more severe disease was significantly higher among homozygotes than heterozygotes [29]. Researchers studying other ethnic groups have also suggested that FMF may be a true autosomal dominant disease, at least in some cases [38], that there may be a gene dosage effect or that there may be mutations in other genes, including *SAA1* [38,39], which modify the disease phenotype. These observations prompted us to search for genetic alterations outside the *MEFV* locus, such as the *SAA1* and the genes encoding toll-like receptor-2 (TLR-2), TLR-4 and the C5a receptor. However, no significant genetic or functional results were obtained, at least among the Greek population studied [40–42].

In summary, following over 17 years of *MEFV* genetic testing, it is concluded that within a great array of sequence variants, some, particularly those affecting exon 10, are associated with the classical FMF phenotype; others, like R202Q, are associated with “atypical FMF”, while others are benign or of unknown significance. This is also reflected in the recent proposal for the nomenclature of autoinflammatory disorders, in which FMF is classified within a larger group of syndromes collectively referred to as pyrin-associated autoinflammatory diseases (PAAD) [9,43]. On the other hand, as typical FMF has undoubtedly

been observed in patients heterozygous for a major mutation or carrying no mutation at all, we have adopted the clinically-driven approach for genetic testing, that is to reserve the test only for patients with an inflammatory syndrome characterized by periodicity and a self-limiting course. A positive genetic test in the context of a compatible clinical picture is confirmatory of the diagnosis, while a negative test does not definitely disprove the clinical diagnosis neither prevents a therapeutic trial of colchicine [24]. Besides, although the recent criteria for the classification of HPF include -for the first time-genetic testing for FMF, they allow the disease to be diagnosed solely on clinical grounds in the absence of a confirmatory genotype [44]. Finally, we do not routinely perform genetic test in asymptomatic siblings of FMF patients, unless there is evidence of persistent subclinical inflammation (e.g. raised acute-phase reactants) or a family history of FMF-related amyloidosis, although this is rather unusual in Greece [24,45].

3. Immunopathogenetic aspects

3.1. Pyrin and inflammasome

Despite the early identification of *MEFV*, encoding the protein pyrin, as the gene responsible for FMF, the role of pyrin in the innate immune processes is not yet fully understood. Pyrin is a cytosolic protein primarily expressed in neutrophils and monocytes/macrophages. It belongs to PYrin Domain (PYD)-containing proteins, a class of proteins that play an important role in the regulation of inflammation, such as NLRP3 (NLR family, PYD containing 3) and ASC (apoptosis-associated speck-like protein) proteins [46]. Upon proinflammatory signals NLRP3 interacts with ASC via PYDs to form the multiprotein platform of NLRP3 inflammasome. This leads to the activation of caspase-1 and the subsequent proteolytic maturation of pro-IL-1β to its bioactive secreted form [4].

Most of the data regarding pyrin function came from studies investigating monocytes/macrophages in experimental mouse models. FMF was initially thought to be a disease resulting from loss-of-function mutations in pyrin. It has been proposed that the interaction of pyrin with components of the NLRP3 inflammasome is inhibitory, and that mutations associated with FMF prevent this interaction [47,48]. However, studies with macrophages obtained from chimeric knock-in mice expressing the human $MEFV^{V726A}$ FMF mutation demonstrated that MEFV mutations are gain-of-function resulting in the activation of the NRLP3 inflammasome and IL-1β secretion through gasdermin D-mediated pyroptosis [49,50]. Recent experimental studies suggest that pyrin can also form its own inflammasome (pyrin inflammasome). In particular, Rho GTPases activate PKN1 and PKN2 kinases leading to pyrin phosphorylation that enables pyrin inhibitory binding by 14-3-3 proteins. Bacterial toxins or pyrin mutations are able to disrupt GTPase-mediated pyrin phosphorylation, leading to 14-3-3 dissociation, pyrin inflammasome activation and increased IL-1β production [51,52].

3.2. The role of autophagy and neutrophils

Autophagy is a fundamental intracellular degradation system aiming to maintain cellular homeostasis in response to metabolic stress and immunological stimuli. Inflammatory activity of neutrophils is often regulated by autophagy [53]. During this dynamic biological process, various cytoplasmic constituents are sequestered within double-membrane vesicles, called autophagosomes, and subsequently delivered to lysosomes for degradation (autolysosomes) [54]. Recent studies have reported that pyrin acts as a receptor for the autophagy-driven degradation of components of the NLRP3 inflammasome [55,56], further reinforcing the role of pyrin and autophagy as inhibitors of the inflammasome [57].

Although the neutrophil is the most abundant leukocyte type in the peripheral blood, it has largely been overlooked in immunology research, not only due to its brief lifetime and its seemingly limited repertoire of responses, but, perhaps most importantly, due to the difficulty in isolating and culturing it *in vitro*. However, recently the traditional concept that neutrophils comprise terminally differentiated cells with limited plasticity has been critically revised. Neutrophils express various receptors that give them the ability to respond quickly following instructive signals from the tissue environment and undergo transcriptional reprogramming leading to *de novo* synthesis of cytokines and other effector proteins [58,59]. Thus, neutrophils clearly constitute the prototypic cell type of innate immunity, committed to immediately sensing alarm signals and rapidly responding to them often at their own demise [60].

Acute inflammation, a paradigm of neutrophil-mediated inflammation has traditionally been thought of having an abrupt onset, swiftly reaching its peak and equally quickly subsiding, unless it transitions to chronic inflammation, involving other cell types, such as macrophages and lymphocytes. Given the analogy between neutrophil-mediated inflammation and the clinical presentation of FMF, as well as that the disease attacks are characterized by neutrophilia and massive influx of neutrophils to affected sites [14,61,62], FMF appears as a fine naturally-occurring model for the study of neutrophil physiology. Moreover, data from research on mechanisms implicated in the initiation and resolution of FMF inflammation may also extend to several other disorders belonging to the same spectrum (HPFs and other IL-1β-mediated AIDs).

Stimulated from the above data, we have focused on neutrophils, a cell population with high pyrin expression and a major contribution in FMF inflammatory attacks, in order to investigate the molecular pathogenic mechanisms that underlie autoinflammation. Initially, the mechanism of autophagy in neutrophils was studied, for the first time, demonstrating significantly lower levels of basal autophagy in neutrophils of FMF patients in remission compared to healthy individuals. This suggests that autoinflammation is associated with Mechanistic Target Of Rapamycin (mTOR) and autophagy dysregulation [63]. Later on, this was confirmed experimentally in macrophages by an independent group showing that pyrin acts as a selective autophagy receptor targeting inflammasome components, while its autophagic function is diminished by mutations associated with FMF leading to increased IL-1β production [55].

Next, the role of neutrophil extracellular traps (NETs) in FMF was investigated. NETs represent extracellular chromatin fibers that are released from activated neutrophils and are lined with various highly active neutrophil-derived proteins [64,65]. During FMF inflammatory attacks, neutrophils release large amounts of NETs in an autophagy-dependent manner. Notably, these NETs deliver to the extracellular space bioactive IL-1β, an established therapeutic target in FMF today. Moreover, IL-1β-bearing NETs amplify the IL-1β production by peripheral blood mononuclear cells (PBMCs), while dismantling of NET chromatin scaffold by DNase disrupts IL-1β activity, highlighting the importance of NETs in the regulation of FMF inflammation [16,17]. Also, the binding of mature IL-1β to NETs may explain why serum levels of IL-1β during disease attacks are low or even undetectable, when conventional assays lacking a DNA substrate are used for measuring this cytokine [8,13,17]. This is particularly important for the design of diagnostic assays in several NET-driven disorders, in which NET-bound cytokines are involved.

Homeostatically, NETs are able to downregulate further NET formation, facilitating the self-resolution of the attack via a negative feedback mechanism [16]. On the other hand, low autophagy levels in neutrophils from FMF patients make them resistant to NET formation and may protect patients from further FMF attacks, whereas induction of autophagy enhances NET release [16,17,63]. All the above provide convincing evidence that the autophagy/NET axis is tightly involved in the pathogenesis of FMF autoinflammation.

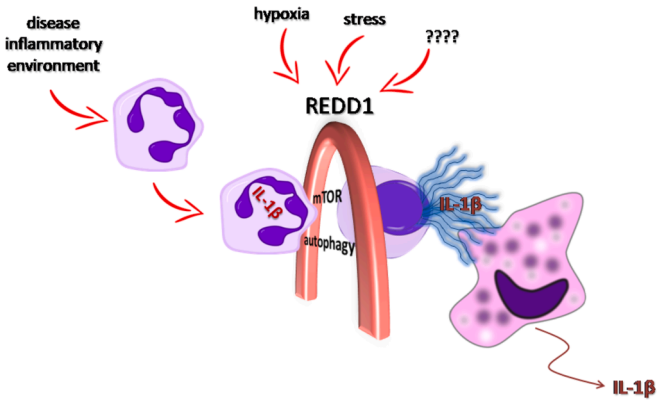

Fig. 1. REDD1 induction as a gateway to autophagy-driven NET-formation in autoinflammation. Naive neutrophils produce IL-1β upon priming by disease environment (first hit). Subsequently, REDD1 upregulation *via* stress agents, hypoxia or as yet undefined factors (second hit) unlocks mTOR/autophagy pathway leading to inflammatory IL-1β-bearing NETs. Bystander naive PBMCs can be also stimulated from NETs further amplifying IL-1β-mediated inflammatory responses. mTOR: Mechanistic Target Of Rapamycin; NETs: neutrophil extracellular traps; PBMCs: peripheral blood mononuclear cells; REDD1: regulated in development and DNA damage responses 1.

3.3. REDD1 as a gateway of autophagy-driven inflammation in FMF

Taking the above mechanism one step further, it was shown that REDD1 (regulated in development and DNA damage responses 1), a stress response protein, regulates neutrophil-dependent inflammatory response in FMF. *REDD1* was identified by RNAseq as the gene that showed the most significantly altered transcription in neutrophils during inflammatory attacks, upregulated by stress-associated stimuli, like adrenaline [17]. Since REDD1 is an inhibitor of the mTOR pathway [66,67], its role in the activation of autophagy in neutrophils was further investigated. In neutrophils from healthy donors, REDD1 activation seems to drive pyrin and NLRP3 into autolysosomes, where REDD1 is also co-localized with the inflammasome components. However, FMF associated mutations prevent the assembly of inflammasome components into autolysosomes, resulting in enhanced IL-1β production [17]. Furthermore, it was suggested that REDD1 activation in neutrophils offer the "second or NETotic hit" that induces the release of IL-1β-loaded NETs from the disease environment-primed neutrophils ("first or priming hit") through autophagy (Fig. 1) [16,17]. This "two hit mechanism" was also later demonstrated in several other NET-related disorders [68,69]. Taken together, during FMF attacks, REDD1 activation cannot suppress inflammasome activity through autophagy degradation, but instead it promotes NET formation, resulting in the release of NETs expressing high amounts of bioactive IL-1β [17,18].

Interestingly, previous studies have indicated that upon induction, REDD1 is able to dissociate 14-3-3 proteins from their substrate [70]. Since dissociation of 14-3-3 proteins from the pyrin inflammasome has been associated with its activation [9,51], one can assume that REDD1 up-regulation not only induces mTOR/autophagy-mediated NET formation, but is also involved in pyrin inflammasome (auto)activation.

The novel link between adrenergic stress and IL-1β-mediated inflammation, via REDD1-dependent regulation of neutrophil activation, is of significant importance in order to better understand the mechanism that drives FMF attacks in periods of stressful events [11,71]. It might also offer the mechanistic explanation behind the sympathomimetic metaraminol diagnostic test that has been used in previous decades to elicit an FMF attack [72].

Of note, it seems that the dysregulation of autophagy or/and NET formation pathways are common characteristics of autoinflammation since they are also implicated in AIDs more complex than FMF, such as AOSD, UC, Schnitzler's syndrome, Behçet's disease, gout and atherosclerosis [17,73–80]. In this context, REDD1 emerges as a key molecule that converts stress signals to inflammatory responses via the mTOR/autophagy pathway (Fig. 1), and a candidate biomarker to rule out infection in autoinflammatory disease patients [17,73,81].

4. Clinical phenotypes and therapeutic approaches

Apart from the genetic and basic research, the establishment of a cohort of Greek patients with FMF allowed the clinical description of the disease and the longitudinal follow up of those patients. As in other ethnic groups, Greek FMF patients manifest bouts of fever (88.2%), abdominal pain (87.5%) and monoarthritis (21.1%) and less frequently chest pain (12.5%) or skin rashes (2%) [29]. Amyloidosis is quite infrequent among Greeks with FMF (2.6%), while, interestingly, Henoch-Schönlein purpura occurred in 2.6% of Greek FMF patients, a co-morbidity later reported in Turkish children as well [82]. Also, cases of recurrent lymphocytic pleuritis and severe liver impairment in the context of FMF have been described [83,84].

A rather unique clinical observation among Greeks concerns those carrying no other mutation besides homozygous R202Q. In those patients, serositis, like pericarditis, occurs more often, while abdominal pain less frequently compared to patients carrying classic *MEFV* mutations, but the response rate to colchicine is high [29]. Similar results were subsequently reported for Turkish patients, suggesting that the R202Q variant may be associated with a slightly milder and modified form of the disease [85,86]. The main clinical manifestations of FMF in Greek population are depicted in Table 2.

Concerning treatment, Greek patients in general respond favorably to colchicine with only a handful of them not tolerating the drug. Over the years, among more than 150 Greek FMF patients, failure of colchicine to control the disease was observed in four, creating a need for an alternative treatment for these patients.

Subsequent to the aforementioned observations showing that neutrophils from FMF patients during disease attacks undergo spontaneous NETosis *in vitro* and that those NETs carry bioactive IL-1β [16,17], blockade of IL-1 appeared as a reasonable treatment option. Consequently, anakinra was administered during a disease attack to a patient with FMF whose disease had been resistant to colchicine, resulting in the remission of the attack over the next few hours [87]. Therefore, anakinra emerged as an effective treatment that could be given on demand to patients who enter a FMF flare despite colchicine, in order to prevent the full blow of the attack or to speed up remission. Indeed, this approach of on-demand anakinra for such cases has recently been supported by observations in a cohort of Turkish FMF patients as well [88]. Meanwhile, a monoclonal anti-IL-1β antibody became available for the treatment of another IL-1β-mediated disease, cryopyrin-associated periodic fever syndrome. The first patient with FMF ever

Table 2
Clinical manifestations and their cumulative incidence in FMF patients from mainland Greece (n = 152) and Crete (n = 71) (data from refs 29, 30).

Manifestation	Mainland Greece	Crete
	Prevalence (%)	
Fever	88.2	76
Abdominal pain	87.5	80
Monoarthritis	21.1	38
Thoracic pain	12.5	21
Serositis	11.8	NA
Myalgia	5.9	NA
Henoch-Schönlein purpura	2.6	NA
Amyloidosis	2.6	NA
Proteinuria	2.6	5.6[a]
Erysipelas-like erythema	2	11

[a] The patients declined renal biopsy, NA; Not Available.

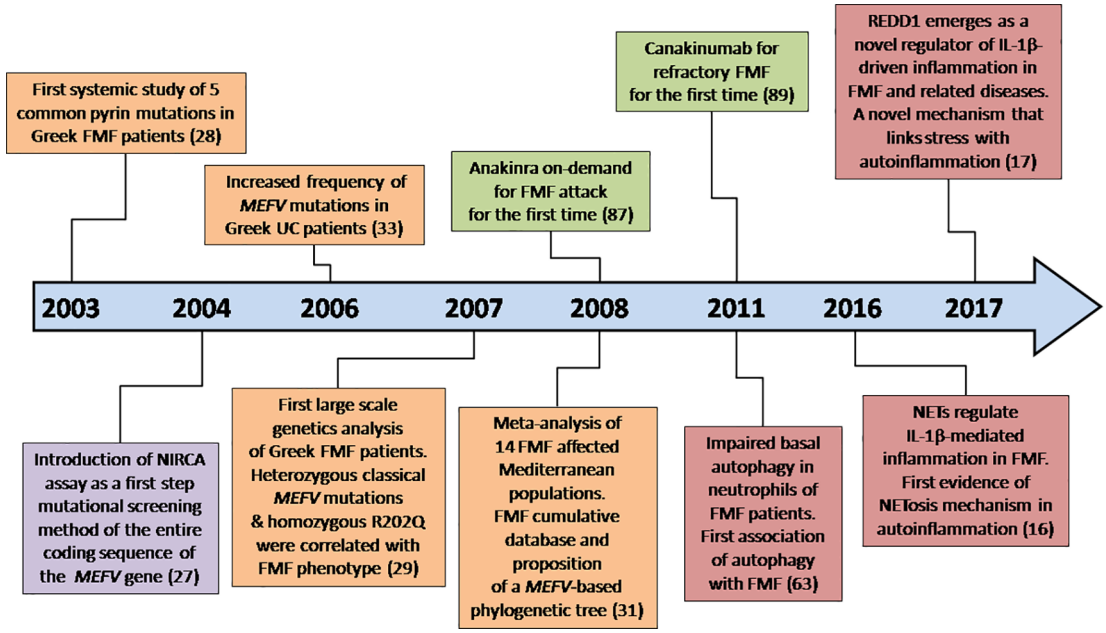

Fig. 2. Timeline of the main contribution of inflammation research group, www.inflathrace.gr, in the study of FMF as regards diagnosis (purple), genetics (light brown), treatment (green) and pathogenesis (magenta). NETs: neutrophil extracellular traps; NIRCA: non-isotopic RNase cleavage assay; UC: ulcerative colitis; REDD1: regulated in development and DNA damage responses 1.

reported to receive canakinumab, several years before this drug was licensed for the treatment of FMF, was one of our patients. Indeed, following canakinumab initiation, the patient's constitutional symptoms and arthritis, which had not previously responded adequately to colchicine and other immunomodulatory treatments, improved, while continued administration of canakinumab showed a sustained efficacy over time [89,90].

5. Acquired knowledge from FMF for the treatment of autoinflammatory diseases

The model of FMF was further applied in the study and treatment of other autoinflammatory diseases, like gout and AOSD. Indeed, neutrophils from patients during a gout attack or during an AOSD flare form NETs carrying active IL-1β [17,74,75,91]. Besides FMF, colchicine is a traditional treatment for gout, further highlighting the common inflammatory pathways operating in both apparently distinct diseases. Moreover, in FMF it was shown that colchicine acts by reducing intracellular IL-1β in neutrophils, thus suggesting a potential mechanism of colchicine action in gout as well [16]. Several publications have proposed anakinra for the treatment of refractory gout or AOSD several years before formal clinical trials were conducted [92–97]. Ultimately, following experimental and clinical evidence, both anakinra and canakinumab were approved for the treatment of AOSD and canakinumab for severe treatment-resistant gout [98,99].

Given that NETosis is associated with autophagy induction, another approach to suppress the release of IL-1β-laden NETs is to block autophagy. Several substances can inhibit neutrophil autophagy, such as hydroxychloroquine [100]. The latter is a non-immunosuppressive disease-modifying anti-rheumatic drug used for the treatment of systemic lupus erythematosus (SLE) and RA. Notably, it has recently been suggested that in SLE the immunomodulatory action of hydroxychloroquine may be mediated through its effects on neutrophil autophagy [81]. Moreover, in a case study of a patient with active AOSD who depended on high doses of glucocorticoids, the addition of hydroxychloroquine suppressed the formation of IL-1β-bearing NETs, while, from a clinical aspect, it allowed for a gradual weaning off glucocorticoids without loss of disease control [74].

Aside from diseases that IL-1 blockade is already an established treatment, the paradigm of FMF may help understand the involvement of neutrophils and the IL-1β pathway in more complex diseases, like RA and UC, and indicate new treatment targets. Indeed, it has been found that whole blood cells of RA patients have increased expression of the NLRP3 inflammasome and higher NLRP3-mediated IL-1β production upon TLR stimulation. This observation suggests that IL-1β plays a role in rheumatoid inflammation and explains the beneficial effect of anakinra in RA, although limited compared to other cytokine blockers [101]. Moreover, in active UC it was demonstrated that both colonic as well as peripheral blood neutrophils are prone to forming NETs bearing active IL-1β [73]. On the other hand, a subset of UC patients shows acute inflammation of musculoskeletal structures in parallel with active intestinal disease, which implies a cross-talk between the intestine and the musculoskeletal system [102,103]. Assuming that IL-1β-expressing peripheral neutrophils may also take part in this spread of inflammation, anakinra was administered to a couple of patients with active UC and acute sacroiliac pain. The rapid response of the musculoskeletal symptoms in both cases rendered support to the role of IL-1β in the pathogenesis of UC-related arthritis [73]. However, the benefit of IL-1 blockade in UC will be clarified through further research, including clinical trial data on the use of anakinra in active UC [104].

Finally, a more basic lesson taught from the study of FMF is to strive for a pathophysiological approach and aim for a targeted treatment of patients with acute non-infectious inflammation. For instance, in a patient with severe pustular psoriasis, which rapidly escalated up to the brink of a cytokine storm, reports of defects in the genes of the IL-1 family underlying cases of pustular psoriasis together with previous experience prompted the initiation of IL-1 blockade, which resulted in a successful outcome [105]. Taking the above into account, it is evident that neutrophils, IL-1β and autoinflammation may contribute in the pathogenesis of both monogenic AIDs, like FMF, as well as more complex inflammatory phenotypes. It is up to the clinician and researcher to pinpoint those cases, identify the underlying pathogenetic process and provide targeted treatment.

Table 3
"Lessons of autoinflammation" learned from the study of FMF in Greece and future perspectives in the field.

Lessons from FMF study	Future perspectives
• Phenotypic & genotypic characteristics of Greek FMF population	• New AIDs phenotypes and unclassified syndromes • NGS as a research & diagnostic tool in AIDs
• Beneficial therapeutic effect of IL-1 inhibition • Anti-IL-1 diagnostic challenge in undefined inflammatory syndromes • New modes of action for colchicine and HCQ	• New diagnostic/prognostic assays to discriminate infectious from sterile inflammation • Drug repositioning • New biologics against other members of IL-1 family • Selective small-molecule inhibitors against NLRP3 inflammasome
• REDD1-induced autophagy and NET-bound IL-1β as key mechanisms in autoinflammation	• Regulatory mechanisms underlying autophagy/NETs/IL-1β axis • Autophagy & NETosis-related candidate biomarkers and theurapeutic targets

AIDs: Autoinflammatory disorders; HCQ: Hydroxychloroquine; NETs: neutrophil extracellular traps; NGS: Next Generation Sequencing; NLRP3: NLR family pyrin domain containing 3; REDD1: regulated in development and DNA damage responses 1.

6. Lessons and open queries

The study of FMF in Greece during the last 17 years (Fig. 2) has improved our understanding of several aspects of autoinflammation, but has also generated new research questions (Table 3).

6.1. Genetic and clinical lessons

The first lesson came from pheno-genotyping of Greek FMF patients that allowed the description of the disease in Greece [28–31]. Mutations in the mainland Greece show a similar pattern with the eastern Mediterranean region [28,29], while Cretans share similarities with western Mediterranean populations [30]. In addition, it seems that homozygosity of the R202Q alteration is associated with atypical FMF phenotypes or act as a modifier in various inflammatory diseases. Obviously, 10 years later and taking into account current migration flows from the East, this needs to be updated, including also "atypical FMF" phenotypes, PAADs, others HPFs or unclassified syndromes that share an autoinflammatory phenotype [5,9,44]. This is particularly interesting given, nowadays, the availability of next generation sequencing technologies [106–108].

We have learnt more about the treatment of autoinflammatory syndromes by introducing biologic agents against IL-1β. Similarly to colchicine trial as a "criterion" for FMF diagnosis [24,109], anakinra administration is proposed as a clinical diagnostic tool for atypical inflammatory syndromes of undefined etiology [110]. However, this reflects an actual need for accessible and reliable assays for the differentiation of IL-1β-mediated autoinflammatory syndromes from infectious ones, so that time to diagnosis and effective treatment of patients is shortened. Vice versa, the application of anti-IL-1β therapies emerge as therapeutic options for refractory inflammatory disorders that appear to share pathophysiological characteristics with FMF, such as AOSD, gout, UC and Behçet's disease [17,73,74,77,91]. Moreover, new modes of anti-inflammatory action through the reduction of autophagy and/or IL-1β release from neutrophils have been uncovered for old drugs, such as hydroxychloroquine and colchicine, respectively [16,74,81]. Apparently, a better understanding of molecular pathways implicated in autoinflammation is expected to provide novel therapeutic approaches through drug repositioning or novel compounds that selectively target NLRP3 inflammasome or cytokines of the IL-1 family [111–113].

6.2. Immunoinflammation lessons from the study of neutrophils

The study of neutrophils as the major inflammatory player in FMF has taught us a new mode of IL-1β action: its dynamic delivery at sites of inflammation via NETs, which are also able to activate PBMCs, thus amplifying the inflammatory process [16,73,74]. In this respect, REDD1-driven autophagy may be an important switch mechanism that directs neutrophil functional plasticity towards NET formation (Fig. 1), and, consequently, neutrophil REDD1 expression could be a putative biomarker for several NET-driven diseases [18]. From this point of view, agents or signals that regulate REDD1 activity are of great importance and need to be further investigated.

Almost twenty years after the discovery of the *MEFV* gene and a decade after the introduction of anti-IL-1 treatments for FMF, the group of autoinflammatory diseases is still expanding as new genetic, functional and clinical information comes to our knowledge [9,43]. Despite this changing landscape, though, the study of FMF still remains the prototype for the basic and clinical research of autoinflammatory syndromes.

Declarations of interest

None.

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