




## New and future perspectives in familial Mediterranean fever and other autoinflammatory diseases

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**Received:** August 13, 2024

**Accepted:** August 19, 2024

**Published online:** August 26, 2024

**Citation:** Çam V, Ercan Emreol H, Ozen S. New and future perspectives in familial Mediterranean fever and other autoinflammatory diseases. Arch Rheumatol 2024;39(3):331-338. doi: 10.46497/ArchRheumatol.2024.10911.

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### ABSTRACT

Systemic autoinflammatory diseases are a group of disorders characterized by sterile episodes of inflammation resulting from defects in the innate immune system. In contrast to classical autoimmune diseases, where circulating autoantibodies and the adaptive immune system are involved, these conditions involve excessive presence of proinflammatory cytokines leading to inflammatory attacks. Excessive cytokine production, functional mutations in regulatory pathways, excessive interferon production, defects in the nuclear factor-kappa B signaling pathway, abnormal protein folding, and complement activation are the mechanisms leading to autoinflammatory diseases. A defect in the mTOR pathway and trained immunity are newly discovered possible causes in pathogenesis. Early onset and severe forms of classical rheumatological diseases have been more frequently associated with autoinflammatory diseases in the last decade. Therefore, monogenic autoinflammatory diseases should be considered in rheumatic diseases with family history, consanguinity, early onset, and severe disease. The combination of functional and genotyping research will help to identify unclassified patients. The optimal treatment strategy remains uncertain, functional studies such as interferon signature and cytokine profiling, may prove valuable in guiding the treatment process. Stem cell transplantation strategies in autoinflammatory diseases with partial response to biological therapies can be considered. Autoinflammatory diseases are becoming increasingly complex and are bringing new perspectives to already known rheumatic diseases. Although we have effective treatments, we are still far from personalized recommendations.

**Keywords:** Autoinflammation, autoinflammatory diseases, Familial Mediterranean fever.

Systemic autoinflammatory diseases are a group of disorders characterized by sterile episodes of inflammation resulting from defects in the innate immune system. In contrast to classical autoimmune diseases, where circulating autoantibodies and the adaptive immune system are involved, these conditions involve excessive presence of proinflammatory cytokines leading to inflammatory attacks. In addition to recurrent fever attacks, clinical inflammation can affect the skin, serosa, central nervous system, gastrointestinal system, lungs, and heart. Although onset is usually in childhood, the findings may be subtle, and diagnostic delays can occur due to the rarity of the disease and the variety of symptoms. Some autoinflammatory diseases (e.g., Schnitzler syndrome, VEXAS syndrome) present in adulthood.

Familial Mediterranean fever (FMF), NLRP3 (NOD-like receptor [NRL] family pyrin

domain-containing 3)-associated autoinflammatory diseases (NLRP3-AID), mevalonate kinase deficiency, and TRAPS (tumor necrosis factor [TNF] type 1A receptor-associated periodic fever syndrome) constitute the recurrent fever syndrome group, in which the interleukin (IL)-1 pathway is primarily affected.<sup>1</sup> Excessive cytokine production, functional mutations in regulatory pathways, excessive interferon (IFN) production, defects in the nuclear factor-kappa B (NF-κB) signaling pathway, abnormal protein folding, complement activation, and defects in the mTOR pathway are well-recognized mechanisms. Moreover, in polygenic diseases such as systemic juvenile idiopathic arthritis (pediatric Still disease), more than one pathway appears to be affected.

The discovery of the genes that cause AIDs has enabled more appropriate diagnosis and targeted treatment. It became clear that different variants in some genes may be associated with different

AIDs (e.g., in the MEFV gene, FMF, and PAAND). In recent years, early and severe presentations with symptoms similar to those observed in autoimmune diseases have been genetically and functionally linked to AIDs. AIDs remain a fascinating field with rapidly advancing progress. In this article, we aimed to summarize current developments in autoinflammatory diseases and discuss future perspectives.

## PATHWAYS AND NEW HORIZONS

The innate immune system responds to extracellular or intracellular pathogens or damage-associated molecular patterns (DAMPs) with inflammation and defense. The process is controlled by numerous mechanisms that regulate the excess of the immune response. Autoinflammatory diseases occur due to abnormalities that can occur at every stage and regulation of the immune response. Recognition of pathogen-associated molecular patterns (PAMPs), such as viral RNA and bacterial lipopolysaccharides, or endogenous DAMPs released from damaged cells, through pattern recognition receptors of phagocytes, is the first step of the innate immune response. Pattern recognition receptors have components that trigger specific responses in different cellular layers. Toll-like receptors located on the cell surface or in endosomes provide transcription of IFN regulatory factors that trigger the production of NF- $\kappa$ B and type 1 IFN. The NLR family located in the cytosol also recognizes DAMPs and PAMPs. They stimulate the transcription factor NF- $\kappa$ B, leading to activation of genes encoding inflammatory proteins. Inflammasomes (pyrin, NLRP3), which are multiprotein complexes found in the cell cytosol, detect microorganism products and endogenous molecular residues and activate caspase-1. Activated caspase-1 cleaves pro-IL-1 $\beta$  and triggers acute inflammation. In addition, caspase-1 causes damage to the cell membrane by causing oligomerization of a protein called gasdermin D. Death of dendritic cells and macrophages results in the release of IL-1 $\beta$ .

RIG-like receptors are specialized to recognize viral RNA. Transcription is cytosolic DNA sensors that ultimately bind to the endoplasmic reticulum membrane adaptor protein called STING

(stimulator of IFN genes). STING stimulation activates the TBK1 (TANK-binding kinase 1) IRF3 (IFN regulatory factor 3) by phosphorylation. Type 1 IFNs bind to IFN receptors and promote the expression of IFN-stimulated genes via the JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathway.

Disorders in the regulation of the mentioned pathways are also involved in the pathogenesis of autoinflammatory diseases. For example, in the absence of cellular stress, NF- $\kappa$ B bound to the inhibitor of  $\kappa$ B is inactive. Ubiquitination leads to proteasome-mediated degradation of the inhibitor of  $\kappa$ B, resulting in activation of NF- $\kappa$ B. LUBAC (linear ubiquitin assembly complex) is a protein complex that enables the formation of linear ubiquitin chains (HOIP, HOIL-1, and SHARPIN). It stabilizes the structures that enable the activation of NF- $\kappa$ B. Deubiquitinases, such as A20 and OTULIN, act as negative regulators of the NF- $\kappa$ B pathway by cleaving ubiquitin chains. Another example of lack of regulation is the lack of IL-1 receptor antagonists and IL-36 receptor antagonists. These cause strong and continuous cytokine release. Finally, in adenosine deaminase 2 (ADA2) deficiency, the disruption of the balance between M1 and M2 in favor of M1 macrophages leads to the release of proinflammatory cytokines.

Recently, there have been several developments regarding the role of the mTOR pathway in the pathogenesis of autoinflammatory diseases. Loss-of-function mutations in the SKIV2L gene cause trichohepatoenteric syndrome 2, which is characterized by diarrhea, skin lesions, brittle hair and immunodeficiency. In a mouse model, loss of SKIV2L activated the mTORC1 pathway in both keratinocytes and T cells independently of IFNs.<sup>2</sup> Another exciting development involving the mTOR pathway was the demonstration of the role of mTORC1 signaling in linking the spectrum of inflammation in Still's disease and macrophage activation syndrome using a combination of model and human studies.<sup>3</sup> In both studies, there was a response to rapamycin under experimental conditions. In addition, the latter study suggested that the mTORC1 signature in Still's disease was associated with disease severity and response to treatment. Another group studied the mTOR pathway in FMF.<sup>4</sup> Receptor-interacting protein kinase 3 was involved in the transcriptional regulation of MEFV through negative control

of mTOR signaling, and they showed that the inhibition of mTOR activity upregulated MEFV expression and pyrin inflammasome activation.<sup>4</sup>

An exciting and current new pathway of autoinflammatory diseases is the trained immune response. Trained immunity is the memory of the innate immune system, understood as the long-term functional reprogramming of innate immune system cells following exogenous or endogenous stimuli.<sup>5</sup> This reprogramming leads to a stronger inflammatory response to the secondary stimulus through epigenetic changes, such as DNA acetylation and methylation,<sup>6</sup> metabolic pathways, such as glycolysis and cholesterol synthesis, or transcriptional pathways. Trained immunity has been described in monogenic autoinflammatory diseases such as inflammasomopathies and TRAPS. However, it is not yet clear whether trained immunity determines a patient's sensitivity to a particular treatment. Finally, Magnotti et al.<sup>7</sup> showed that steroid hormone catabolites activated pyrin in a B30.2-dependent manner. This data was important since it occurred in the absence of RhoA inhibition, providing a good explanation for why stress triggers FMF attacks.

## EXPANDING THE CLINICAL SPECTRUM

The initial autoinflammatory diseases were recognized by signs and symptoms of fever, rash, and serositis. However, the clinical spectrum for these diseases has expanded considerably. Early onset and severe forms of classical rheumatological diseases have been more frequently associated with autoinflammatory diseases in the last decade. Table 1 summarizes these associations.

New autoinflammatory diseases are defined everyday, and thus, the spectrum of symptoms is enlarging. For example, disabling pansclerotic morphea, a recently described scleroderma mimic, is characterized by rapidly progressive deep fibrosis. It has a unique presentation with absence of autoantibodies, lack of response to immunosuppressive therapies for systemic sclerosis, contracture, joint ankylosis, and complications such as squamous cell carcinoma. Disabling pansclerotic morphea is caused by monoallelic gain-of-function mutations encoding the STAT4 (signal transducer and activator of

transcription 4) gene<sup>8</sup>. Case reports have shown that targeting the JAK-STAT pathway may be effective.<sup>8</sup>

The VEXAS syndrome, defined in 2020, showed that patients previously diagnosed with relapsing polychondritis, Sweet syndrome, myelodysplastic syndrome, or vasculitis are associated with a somatic mutation (UBA1) that presents in adulthood.<sup>9</sup>

Classifying or defining all autoinflammatory diseases is beyond the scope of this article. However, the importance of investigating monogenic autoinflammatory diseases in rheumatic cases with early onset, atypical course, and family history or consanguinity should be emphasized.

## CHANGING CRITERIA, EVOLUTION OF ALGORITHMS, AND UNANSWERED QUESTIONS

In early years when only a few autoinflammatory diseases were known, FMF diagnostic criteria such as the Tel Hashomer, Livneh, and Yalçinkaya-Özen criteria provided a framework for clinicians.<sup>10-12</sup> These criteria were based on clinical findings. The specificity was low, as patients with TRAPS and hyper immunoglobulin D syndrome genetic mutations were also met these criteria.<sup>13</sup> With the increasing diversity of autoinflammatory diseases and the relative development of genetic research, clinical criteria had to be supplemented by genotype. Eurofever-Paediatric Rheumatology International Trials Organisation (PRINTO) criteria responded to this need. New classification criteria detailing clinical features, as well as genetic validation, have been developed for FMF, CAPS (cryopyrin-associated periodic syndrome), TRAPS, mevalonate kinase deficiency, and PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) syndrome. These criteria provided high specificity and sensitivity for FMF, as well as other autoinflammatory diseases.<sup>14</sup> The concept of confirmatory and nonconfirmatory genotypes referred to by the Eurofever-PRINTO criteria was tried to be resolved by an expert committee consisting of members of the EMQN (European Molecular Genetics Quality Network) and members of the ISSAID (International Society of

<b>Table 1.</b> Main clinical features of autoinflammatory diseases			
	Inheritance	Gene	Findings
<b>Those characterized by vasculitis, vasculopathy, panniculitis</b>			
DADA	AR	CERC1	PAN mimic. However, absence of thrombocytosis, frequent stroke, livedo racemosa, low Ig levels, lacunar infarct, early age of onset and consanguinity
HA20	AD	TNFAIP3	Behçet's disease mimic. Fever, oral, GI and genital ulcerations, arthritis, uveitis. Early age of onset, severe course, frequent GI involvement, autoimmune features possible
CANDLE/PRAAS	AR/AD	PSMA3/PSMB8/PSMB4/PSMB9/PSMB4/PSMB8/PSMB9/PSMB10/POMP	Nodular exanthema, panniculitis, lipodystrophy, basal ganglia calcifications, hepatosplenomegaly
SAVI	AD	TMEM173	Erythema-purpuric lesions, ischemic ulcerative skin disease, necrosis of extremities, interstitial lung disease
FCL	AD	TREX1	Chilblain lesions, livedo reticularis
ORAS	AR	OTULIN	Lipodystrophy, Hypergammaglobulinemia, early-onset of neutrophilic panniculitis, recurrent or severe infections
NEMO/NDAS	XL	IKBKKG	Conical teeth, progressive B-cell lymphopenia, hypogammaglobulinemia
<b>Those characterized by macrophage activation syndrome</b>			
NLRC4-related autoinflammatory diseases	AD	NLRC4	MAS, urticarial rash, early-onset nonspecific enterocolitis
CDC42-AID	AD	CDC42	MAS, urticarial rash
IL18PAP-MAS	?	?	Pulmonary alveolar proteinosis, clubbing, MAS
<b>Those characterized by arthritis</b>			
COPA	AD	COPA	High titer RF positive arthritis, hemorrhagic interstitial lung disease
LACC1	AR	LACC1	Systemic JIA, chronic polyarthritis
BLAU	AR	NOD2	Polyarthritis, hypertrophic tenosynovitis (boggy synovitis), chronic uveitis
<b>Those characterized by SLE</b>			
FCL	AD	TREX1	Early-onset familial chilblain lupus, retinal vasculopathy with cerebral leukodystrophy
IFIH1	AD	IFIH1	Chilblain lesions, livedo reticularis
<b>Those characterized by early-onset sarcoidosis</b>			
BLAU	AR	NOD2	Polyarthritis, hypertrophic tenosynovitis (boggy synovitis), chronic uveitis
<b>Those characterized by psoriasis/neutrophilic dermatoses</b>			
DITRA	AR	IL36RN	Generalized pustular psoriasis, fever
DIRA	AR	IL1RN	Fever, multifocal osteomyelitis, CNS vasculitis
CAMPS	AD	CARD14	Plaque or pustular psoriasis, skin ulcers, arthritis, fever
<b>Those characterized by uveitis</b>			
NAIAD	AD	NLRP1	Uveitis, corneal dyskeratosis, hemolytic anemia, failure to thrive, eosinophilia
HA20	AD	TNFAIP3	Anterior uveitis, retinal vasculitis, CNS vasculitis
BLAU	AR	NOD2	Chronic uveitis, cataract, glaucoma, amaurosis, polyarthritis, hypertrophic tenosynovitis (boggy synovitis)
<b>Those characterized by lung disease</b>			
SAVI	AD	TMEM173	Erythema-purpuric lesions, ischemic ulcerative skin disease, necrosis of extremities, interstitial lung disease
COPA	AD	COPA	High titer RF positive arthritis, hemorrhagic interstitial lung disease
IL18 PAP-MAS	?	?	Pulmonary alveolar proteinosis, clubbing, MAS
AR: Autosomal recessive; PAN: Polyarteritis nodosa; AD: Autosomal dominant; GI: Gastrointestinal; XL: X-Linked; MAS: Macrophage activation syndrome; RF: Rheumatoid factor; JIA: Juvenile idiopathic arthritis; CNS: Central nervous system.			



Systemic Auto-Inflammatory Diseases).<sup>15</sup> In cases carrying one pathogenic mutation or two variants of uncertain significance (VUS) variants that were not considered as confirmatory genotypes, clinical criteria gained weight. In addition, the trans combination (two alleles) of a pathogenic or possibly pathogenic variant with a rare or novel VUS was considered consistent with the diagnosis of clinical disease. This interpretation implicitly excluded previously reported cases in the cis position from the confirmatory genotype. It remains uncertain whether patients from nonendemic areas with only one VUS in the MEFV gene could be considered to have FMF.<sup>16</sup> This complex picture may be shaped by environmental and epigenetic effects. The microRNAs studied in FMF and NLRP3 emphasized the importance of epigenetic effects and may provide new targets for treatment.<sup>17</sup>

ISSAID/EMQN experts also recommended Sanger or single-gene targeted next-generation sequencing (NGS) in cases of high clinical suspicion for a specific disease or in the presence of biochemical promoters (e.g., enzyme activity for ADA2).<sup>15</sup> In the absence of a specific preliminary diagnosis, nontargeted NGS or exome/genome sequencing was recommended. Mosaicism in CAPS, TRAPS, and Blau syndrome and copy number variations in ADA2 deficiency and mevalonate kinase deficiency can be bypassed by the mentioned methods. If the disease is strongly suspected, molecular cytogenetic techniques and multiplex ligation-dependent probe amplification analysis are recommended for the first group, and deep sequencing NGS is recommended as an intermediate step for the second group.<sup>15</sup>

A task force of European and American experts proposed a diagnostic approach for type 1 interferonopathies. Due to the presence of clinically overlapping diseases or the presence of multiple genes causing a disease (e.g., CANDLE/PRAAS), they proposed NGS methods, such as targeted gene panel, whole exome sequencing, or whole genome sequencing, instead of Sanger or single gene targeting.<sup>18</sup> Following these efforts to better classify and define known autoinflammatory diseases, the next diagnostic step was the search for undiagnosed and unclassified autoinflammatory diseases.<sup>19</sup> It appears that the use of functional

studies in this way can fill the gaps left by genotype alone. An example of functional study-genotype combination is the *ex vivo* colchicine test developed by Van Gorp et al.,<sup>20</sup> which can distinguish pathogenic mutations from healthy controls and some VUS (E148Q, PS369S).

## MANAGEMENT

Colchicine has functions such as inhibition of pyrin and NLRP3 inflammasome formation, disruption of neutrophil motility and function, and microtubule destabilization and is an indispensable drug in FMF treatment with its effects on the RhoGTPase system. In addition to its efficacy on attacks, it significantly reduces complications over the years by preventing amyloid accumulation. Apart from FMF, it is also used effectively in patients with idiopathic recurrent pericarditis, PFAPA syndrome, Behçet's disease, and syndrome of undifferentiated recurrent fever.<sup>21</sup> It is more effective in PFAPA patients carrying MEFV mutation compared to other patients.<sup>22</sup> In a limited number of studies, intravenous formulations have also been tried in resistant patients and found to be effective.<sup>23</sup> However, it was unsuccessful in mevalonate kinase deficiency and CAPS in different studies and is not recommended.<sup>24</sup>

About 5% of FMF patients (with drug compliance) are resistant to colchicine.<sup>25</sup> IL-1 antagonists are the first-line drugs used successfully in these patients. The duration for treatment is still controversial. Biological drugs may not be needed when the triggering factors disappear.

Tocilizumab showed efficacy in some cases where IL-1 antagonists failed and in preventing amyloidosis. Tofacitinib experience is also available in a few limited cases.<sup>26</sup> Anti-TNF agents are effective in the presence of arthritis. However, the treatment decision may be challenging in FMF cases with comorbidities (e.g., chronic nonbacterial osteomyelitis, inflammatory bowel disease, and arthritis) resistant to colchicine and unresponsive to disease-modifying antirheumatic drugs. In these cases, tocilizumab or tofacitinib may be an option.<sup>27</sup> In a phase III study, efficacy against placebo was also demonstrated without significant side effects.<sup>28</sup>

Interleukin-1 antagonists are also successfully used in NLRP3-associated AIDs. Researchers are investigating specific inhibitors of the NLRP3 inflammasome, but no studies have advanced to phase-3 yet. Glyburide, an oral antidiabetic, showed promise, but studies could not progress to phase III due to toxicity at effective doses.<sup>29</sup>

Interferonopathies result from overproduction of type 1 IFN, which binds to IFNAR to mediate JAK-STAT signaling. Inhibition of JAK by tofacitinib, ruxolitinib, and baricitinib is an increasingly used approach for the treatment of interferonopathies. Although traditionally JAK inhibition was thought to treat inflammatory findings, one study reported neurological improvement in patients with aicardi goutieres syndrome.<sup>30</sup> This contrast complicates the follow-up of asymptomatic patients with a genetic diagnosis. Although JAK inhibitors may cause a risk of cardiovascular events in adult patients, they do not appear to be a valid risk for pediatric patients due to the absence of comorbidities. However, JAK2 is involved in growth hormone signaling; thus, whether baricitinib and ruxolitinib suppress growth may be a subject of investigation.

Anti-TNF drugs were successfully used in Haploinsufficiency of A20, OTULIN-related autoinflammatory syndrome, and ADA2 deficiency. However, the positive experience in ADA2 deficiency is related to patients with inflammatory phenotype. Anti-TNF drugs were ineffective in patients with immunological and hematological involvement.<sup>31</sup> Hematopoietic cell transplantation is curative in these cases. The risk of stroke in ADA2 deficiency may make the monitoring of anti-TNF drugs from the monoclonal antibody difficult. Etanercept or a disease-modifying antirheumatic drug concomitant with monoclonal antibodies may be an option due to the low risk of antibodies. There is no definite recommendation on how long anti-TNF treatment should be continued in ADA2 deficiency. The recommended approach is life-long adherence to the medication.<sup>31</sup>

Tadekinig alfa (IL-18 blockade) has been used in a few pediatric patients with NLRC4 mutation and in adult-onset Still's disease.<sup>32,33</sup> Anifrolumab has started to be used in lupus treatment. It may be

a good alternative to JAK inhibitors in the coming years. Biological treatment decision is difficult in undiagnosed autoinflammatory diseases. The optimal treatment strategy remains uncertain, functional studies such as interferon signature and cytokine profiling, may prove valuable in guiding the treatment process. Stem cell transplantation strategies in autoinflammatory diseases with partial response to biological therapies can be considered. However, for example, in the case of ADA2 deficiency, mortality can rise to 20%, and a donor is not always available. This situation suggests that gene therapies may also be considered in the future, with their own handicaps.

In conclusion, autoinflammatory diseases are becoming increasingly complex and are bringing new perspectives to already known rheumatic diseases. Although we have effective treatments, we are still far from personalized recommendations. Future research and international collaborations are expected to make significant contributions to the recognition and management of rare autoinflammatory diseases.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Conception and design of research: V.Ç., H.E.E., S.Ö.; Drafted, edited and revised manuscript: S.Ö.; Approved final version of manuscript: V.Ç., H.E.E., S.Ö.

**Conflict of Interest:** The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

**Funding:** The authors received no financial support for the research and/or authorship of this article.

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