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Review

The hereditary autoinflammatory disorders uncovered

Donato Rigante [a], Antonio Vitale [b], Orso Maria Lucherini [b], Luca Cantarini [b,*]

[a] Institute of Pediatrics, Policlinico A. Gemelli, Università Cattolica Sacro Cuore, Largo A. Gemelli 8, 00168 Rome, Italy
[b] Interdepartmental Research Center of Systemic Autoimmune and Autoinflammatory Diseases, Rheumatology Unit, Policlinico "Le Scotte", Università di Siena, Viale Bracci 1, 53100 Siena, Italy

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ABSTRACT

There is a thriving interest in the field of hereditary autoinflammatory disorders (HAID), a gamut of heterogeneous conditions deriving from an aberrant orchestration of innate immunity, unified by the common feature of seemingly unprovoked inflammation, which might be systemic or occur in localized niches of the organism. Recurrent fever and episodic inflammation in the joints, serosal membranes, skin, gut, and other organs are the common denominator of HAID. Mutations in the inflammasome-related genes have been associated with different HAID, showing the intimate link existing between interleukin-1 (IL-1)-structured inflammasome and their pathogenesis. Differential diagnosis of HAID can be challenging, as there are no universally accepted diagnostic protocols, and near half of patients may remain without any genetic abnormality identified. The use of IL-1-antagonists has been associated with beneficial effects in a large number of HAID associated with excessive IL-1 signalling, such as cryopyrin-associated periodic syndromes, familial Mediterranean fever, and deficiency of IL-1 receptor antagonist. This review will discuss about the key-clues of HAID which might guide for an early recognition and drive decisions for treatment.

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The innate immunity is the first-line defense barrier of a living being, which has been preserved throughout the evolution, based on different white blood cells, as neutrophils, macrophages, dendritic and natural killer cells, but also the complement system and proinflammatory signalling proteins, with the cytokine interleukin 1 (IL-1) displaying a managerial role. Hereditary autoinflammatory disorders (HAID) are a group of hereditable monogenic conditions in which the most typical and striking feature is the exaggerated innate immune response which leads to the recurrence of episodic sterile inflammation, followed by symptom-free periods of variable duration [1]. The term "autoinflammatory" was coined to underscore the absence of pathogens, circulating autoantibodies, or self-reactive T cells [2]. To date, nearly all mutations that have been linked to HAID disrupt inflammatory signalling pathways within the innate immune system: this disruption generates a vast spectrum of inflammatory symptoms and systemic signs affecting multiple organs, deriving by the activation of the inflammasome, which is a multimeric cytosolic protein complex, containing procaspase 1, the adapter protein PYCARD (also known as ASC) and a sensor protein belonging to the NOD-like receptor (NLR) family, that link microbial products, microcrystals, and metabolic stress to the proteolytic processing of pro-IL-1β into its biologically active IL-1β [3]. IL-1β, secreted by stimulated monocytes and macrophages, and to a lesser degree by several other cell types, including neutrophils, keratinocytes, epithelial and endothelial cells, lymphocytes, smooth muscle cells, and fibroblasts, is considered the prototypic multi-functional cytokine with protean effects in nearly all body districts, either alone or in combination with other cytokines [4]. Since its cloning in the early 1980s [5], the discovery of IL-1β heterogeneous biological activities has significantly increased our understanding in the pathogenesis of several diseases, including HAID. Pro-IL-1β is biologically inactive and must be converted to 17 kDa IL-1β in order to function, under a specific inflammasome-mediated mechanism involving caspase 1 and a tight feedback-control operated by several naturally occurring inhibitors, such as IL-1 receptor antagonist (IL-1Ra) and other soluble receptors [6]. Fig. 1 briefly depicts the most relevant mechanisms of IL-1β activation in HAID.

* Corresponding author at: Interdepartmental Research Center of Systemic Autoimmune and Autoinflammatory Diseases, Università di Siena, Siena, Italy.
E-mail address: cantariniluca@hotmail.com (L. Cantarini).

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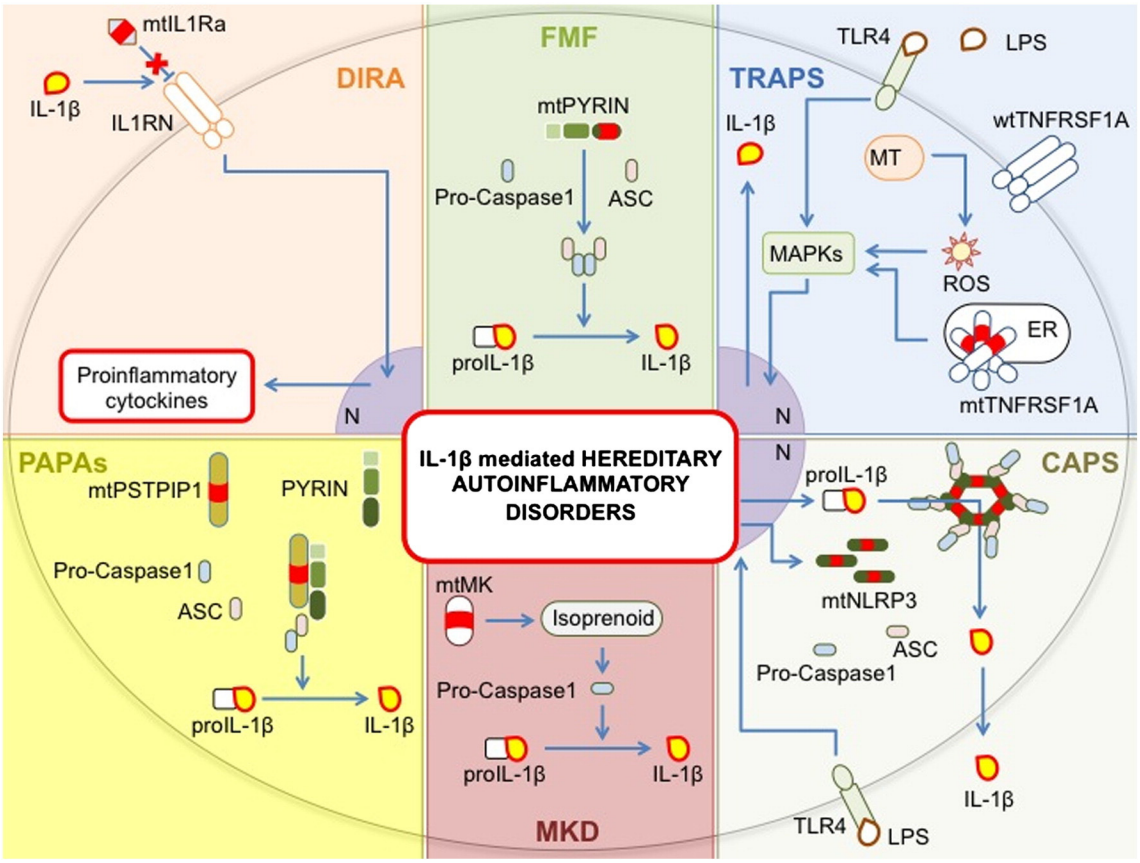

Fig. 1. Mechanisms of IL-1β activation in the hereditary autoinflammatory disorders. Familial Mediterranean fever (FMF), cryopyrin-associated periodic syndromes (CAPS), mevalonate kinase deficiency syndrome (MKD) and PAPA syndrome (PAPAs) are due to mutations on pyrin, cryopirin, mevalonate kinase enzyme (MK) and PSTPIP1 genes respectively, and are associated to enhanced pro-caspase 1 activation, leading to increased IL-1β processing and secretion. Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) is due to mutation in TNF receptors (named TNFRSF1A), which enhance the inflammatory response by the intracellular accumulation of mutated TNFRSF1A (mtTNFRSF1A) in the endoplasmic reticulum (ER). mtTNFRSF1A intracellular accumulation activate ER-stress response and increased mitochondrial (MT) levels of reactive oxygen species (ROS), which in turn amplifies the inflammatory response and sustains MAPK activation (JNK and p38). Deficiency of the interleukin-1 (IL-1) receptor antagonist (DIRA) is due to mutations on the gene coding for IL-1 receptor antagonist (IL-1Ra), which lead to the loss of IL-1β inhibitory function and IL-1α signalling, finally impairing the IL-1β-dependent inflammatory cascade. **Abbreviations:** Toll-like receptor 4 (TLR4); interleukin 1 receptor antagonist (IL1RN); wild type TNFRSF1A (wtTNFRSF1A); nucleus (N); mutated NLRP3 (mtNLRP3); mutated MK (mtMK); mutated PSTPIP1 (mt PSTPIP1); interleukin 1 receptor antagonist (IL1Ra).

During the last two decades several IL-1-targeting agents have been developed: some of these compounds have been used only in experimental models of disease, others have been tested in clinical trials, but only a few are currently available for clinical use and have widened new therapeutic horizons for people with HAID [7]. Fig. 2 offers a synthetic illustration of the available IL-1-targeted therapies.

This review is an ideal journey in the land of these newly defined conditions, in which a genetically mediated excessive IL-1 signalling is directly or less clearly linked to the pathogenesis of HAID, explaining why the use of IL-1 inhibitors is consistently associated with the resolution of inflammatory manifestations in the former set of diseases or with partial efficacy in the latter.

Familial Mediterranean fever (FMF) is an autosomal recessive inherited disease, the most prevalent among HAID worldwide, mostly affecting people of Middle Eastern descent who live around the Mediterranean sea areas, caused by loss-of-function mutations within the *MEFV* gene [8]. Pyrin is the product of the *MEFV* locus which works as an intracellular regulator of IL-1 production [9]. Conflicting results have been reported regarding the effect of full-length pyrin and FMF-associated pyrin mutants on IL-1β production [10]. Mutations can be found throughout the *MEFV* gene, though patients with the most severe forms of FMF carry missense mutations in the B30.2/SPRY domain at the C-terminal end of pyrin, which is necessary for its interaction with caspase 1 [11]. Patients experience self-limiting attacks characterized by one-to-three-days duration episodes of fever with inflammation of the serosal, synovial, or cutaneous tissues, usually starting during childhood or teenage years and recurring with variable frequency. Severe abdominal and chest pain are the most typical inflammatory symptoms occurring in more than 90 and 40% of patients, respectively. A typical attack may frequently mimic an acute abdomen. Suggestive for diagnosis if present is a recurrent erysipelas-like eruption on the calf. The clinical pictures can be distinguished into three major clinical phenotypes: type one, which is the "classical" picture; type two, where reactive AA amyloidosis is found as the first clinical manifestation of the disease in otherwise asymptomatic individuals; and type three, considered as the 'silent' homozygous or mix heterozygote state, in which two *MEFV* mutations are detected without signs or symptoms of FMF or AA amyloidosis [12]. The development of systemic amyloidosis, due to the deposition of a cleavage product, serum amyloid-A (SAA), one of the acute reactants produced during disease flares, is the deadly long-term complication of FMF: the products of amyloidogenesis can be deposited in a number of organs, including kidneys, adrenal glands, liver, spleen, thyroid gland, and heart [13]. Diagnosis of FMF remains clinical and requires information about ethnic background, family history, and response to colchicine, a tricyclic alkaloid extracted from lily plants, since specific laboratory tests of confirmation are not available [14]. According to the so-called Tel Hashomer criteria a definitive diagnosis of FMF requires the presence of two major criteria (recurrent febrile episodes accompanied by serositis, AA amyloidosis without apparent predisposing disease, favourable response to colchicine test) or one major and two minor criteria (recurrent febrile episodes, erysipelas-like eruption, FMF in a

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