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Cytokine signatures in hereditary fever syndromes (HFS)

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ABSTRACT

Hereditary fever syndromes (HFS) include a group of disorders characterized by recurrent self-limited episodes of fever accompanied by inflammatory manifestations occurring in the absence of infection or autoimmune reaction. Advances in the genetics of HFS have led to the identification of new gene families and pathways involved in the regulation of inflammation and innate immunity. The key role of several cytokine networks in the pathogenesis of HFS has been underlined by several groups, and supported by the rapid response of patients to targeted cytokine blocking therapies. This can be due to the direct effect of cytokine overproduction or to an absence of receptor antagonist resulting in dysbalance of downstream pro- and anti-inflammatory cytokine networks.

The aim of this study was to present an overview and to discuss the major concepts regarding the cellular and molecular immunology of HFS, with a particular focus on their specific cytokine signatures and physiopathological implications. Based on their molecular and cellular mechanisms, HFS have been classified into intrinsic and extrinsic IL-1β activation disorders or inflammasomopathies, and protein misfolding disorders. This review integrates all recent data in an updated classification of HFS.

Contents

Abbreviations: AIDs, autoinflammatory disorders; AIM2, absent in melanoma 2; ALR, AIM2–like receptor; AP-1, activator protein 1; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; ATP, adenosine triphosphate; CAPS, cryopyrin-associated periodic syndromes; CARD, caspase recruitment domain; CC, coiled coil; CINCA, chronic infantile neurological cutaneous and articular syndrome; CRP, C-reactive protein; DAMP, danger-associated molecular pattern; DIRA, deficit in IL-1 receptor antagonist; DITRA, deficit in IL-36 receptor antagonist; dsDNA, double stranded DNA; ESR, erythrocyte sedimentation rate; FCAS, familial cold autoinflammatory syndrome; FCU, familial cold urticarial; FMF, familial Mediterranean fever; HFS, hereditary fever syndromes; HIDS, hyperimmunoglobulinemia D syndrome; HIN, hematopoietic expression, interferon-inducible nature, and nuclear localization; HMG-CoA, 3-hydroxy-3-methylglutaryl CoA; ICAM-1, intercellular adhesion molecule 1; IL-1R1, IL-1 receptor type I; IL-1RA, IL-1 receptor antagonist; LRR, leucin rich repeat; MBL, mannose binding lectin; MKD, mevalonate kinase deficiency; MVK, mevalonate kinase; MWS, Muckle-Wells syndrome; MICA, major histocompatibility complex, MHC class-I-chain-related type A; MYD88, myeloid differentiation primary response gene 88; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLR, nod-like receptor; NLRP12AD, NLRP12-associated disorders; NOD, nucleotide-binding oligomerization domain; NOMID, neonatal onset multisystemic inflammatory disease; PBMCs, peripheral blood mononuclear cells; PI3K, phosphoinositide-3-kinase; PKB, protein kinase B; PLA_2, phospholipase A_2; PMN, polymorphonuclear neutrophils; PYD, pyrin domain; RAC1, ras-related C3 botulinum toxin substrate 1; RANK, receptor activator of NF-κB; ROS, reactive oxygen species; SAA, serum smyloid A; sIL-2R, soluble IL-2 receptor; sTNFr, soluble TNF receptors; TNF, tumor necrosis factor; TNFRSF1A, tumor necrosis factor receptor superfamily, member 1A; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; TRAPS11, TNFRSF11A-associated disorder; TRIF, TIR-domain-containing adapter-inducing interferon-β; T3SS, type III secretion system.

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1. Introduction

Autoinflammatory disorders (AIDs) are a group of inherited diseases characterized by unprovoked episodes of systemic inflammation. These disorders differ from autoimmune diseases as their pathogenesis is not mediated by self-reactive antibodies or T lymphocytes [1]. Another distinction between these two groups of disorders is the primary role of the innate immune system in mediating autoinflammatory diseases, versus the recognized importance of the adaptive immune system in autoimmune disorders [2]. Given the broad spectrum of autoinflammatory diseases, this review will focus on hereditary fever syndromes (HFS) which constitute the most important subgroup of AIDs. HFS are characterized by recurrent self-limited episodes of fever accompanied by severe inflammation, without apparent infectious etiology [3]. They include six clinically and genetically characterized disorders, namely the familial Mediterranean fever (FMF), which is the most frequent, the Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), the Mevalonate kinase deficiency/HyperImmunoglobulinemia D syndrome (MKD/HIDS), the Cryopyrin-associated periodic syndromes (CAPS), the NLRP12-associated disorders (NLRP12AD) and the recently described TNFRSF11A-associated disorder (TRAPS11) [3–5]. CAPS include syndromes mediated by *NLRP3* mutations, namely Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS) formerly termed familial cold urticaria (FCU) and the chronic infantile neurological cutaneous and articular syndrome also known as neonatal onset multisystemic inflammatory disease (CINCA/NOMID) [3,6]. The differential diagnosis of HFS relies on clinical information, in addition to the mode of inheritance, age of onset, family history, ethnic background and more recently genetic data [7] (Table 1).

Table 1
Genetic, clinical and therapeutic features of HFS, DIRA and DITRA.

		Disease name	Mode of inheritance	Gene (localization)	Protein	Age at onset	Fever	Other clinical manifestations	Drugs/treatment
Hereditary fever syndromes	Inflammasomopathies	FCAS	Autosomal dominant	*NLRP3/CIAS1* (1q44)	Cryopyrin	<6 months	Variable	Urticarial skin rash, conjunctivitis, joint pain, drowsiness, headache, and nausea	High-dosage corticosteroids IL-1 inhibitors
		MWS	Autosomal dominant	*NLRP3/CIAS1* (1q44)	Cryopyrin	Infancy	Variable	Non-itchy rash, painful and swollen joints, and hearing loss	IL-1 and TNF-α inhibitors
		CINCA	Sporadic or Autosomal dominant	*NLRP3/CIAS1* (1q44)	Cryopyrin	Infancy	Variable	skin rash, joint involvement, chronic meningitis	IL-1 and TNF-α inhibitors
		NLRP12AD	Autosomal dominant	*NLRP12* (19q13)	NLRP12	Infancy	Variable	Skin rash, lymphadenopathy, aphthous ulcers, and abdominal pain	Steroidal/ nonsteroidal anti-inflammatory drugs IL-1 and TNF-α inhibitors
		FMF	Autosomal recessive	*MEVF* (16p13.3)	Pyrin	<20 years	1–4 days	Serositis, sterile peritonitis, monoarthritis, pleuritis, and skin erythema	Colchicine IL-1 and TNF-α inhibitor
	Metabolic dysregulation leading to IL-1β secretion	MKD	Autosomal recessive	*MVK* (12q24)	Mevalonate kinase	<1 year	3–7 days	Lymphadenopathy, abdominal pain, and skin rash	Steroids
	Protein misfolding disorders	TRAPS	Autosomal dominant	*TNFRSF1A* (12p13)	p55 TNF-receptor	<20 years	>1 week	Abdominal pain, erythematous macules, peritonitis, myalgias, arthralgias, and periorbital oedema,	High-dosage corticosteroids IL-1 and TNF-α inhibitors
		TRAPS11	Autosomal dominant	*TNFRSF11A* (18q22)	RANK	<20 years	>1 week	Abdominal pain and headaches. Macular rash or erythema nodosum noted in some patients. One case with recurrent pharyngitis.	Not noted
Deficit in receptor antagonist diseases		DIRA	Autosomal recessive	*IL1RN (2q14)*	IL-1RA	Infancy	–	Periostitis,sterile multifocal osteomyelitis, and pustolosis	IL-1 inhibitors
		DITRA	Autosomal recessive	*IL36RN*	Il-36RA	Variable	Variable	High-grade fever, generalized pustular psoriasis, and asthenia	Acitretin, Steroids IL-1 and TNF-α inhibitors