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Review article

Autophagy dysfunction in autoinflammatory diseases

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ABSTRACT

Autoinflammatory diseases (AUIDs) are a genetically heterogeneous group of rheumatic diseases characterized by episodic inflammation linked with dysregulated innate immune responses. In this review, we summarize the molecular mechanisms altered by disease-associated variants in several AUIDs, including *NOD2*-associated diseases, TNF receptor-associated periodic syndrome (TRAPS), familial Mediterranean fever (FMF) and hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), and highlight the roles dysregulated autophagy plays in disease pathogenesis. Autophagy is a conserved eukaryotic pathway for the elimination of cellular stressors, such as misfolded proteins, damaged organelles, or intracellular microorganisms. It is now recognized that autophagy also functions to control inflammation through regulatory interactions with innate immune signaling pathways. AUID-associated genetic variants are known to directly activate inflammatory signaling pathways. Recent evidence also indicates that these variants may also cause impairment of autophagy, thus augmenting inflammatory responses indirectly. Intriguingly, these variants can impair autophagy by different mechanisms, further implicating the autophagic response pathway in AUIDs. These discoveries provide evidence that autophagy could be investigated as a new therapeutic target for AUIDs.

Contents

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1. Introduction

Autoinflammatory diseases (AUIDs) were originally termed by Dr. Kastner's research group in 1999 to describe several heritable rheumatic disorders that present as self-limited episodes of fever and serosal, synovial, or cutaneous inflammation [1]. The term *autoinflammatory* disease is preferable to *autoimmune* disease as it is now understood that AUIDs result from dysregulated innate immune responses and generally lack the presence of autoantibodies. Classic members of this disease family include familial Mediterranean fever (FMF), TNF receptor–associated periodic syndrome (TRAPS), cryopyrin-associated periodic syndrome (CAPS) and hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) (Table 1) [2]. Presently, AUIDs represent a large spectrum of rheumatic and inflammatory disorders, including more than 40 monogenic diseases [3], as well as polygenic diseases including Crohn's disease (CD), adult onset Still's disease (AOSD), Behçet's disease, gout, and systemic juvenile idiopathic arthritis (sJIA) [4].

The genetically defined AUIDs can be classified into 5 groups based on the predominant pro-inflammatory cytokines or inflammatory pathway driving the disease [3]. These groups include: (1) Interleukin (IL)-1-mediated AUIDs; (2) Interferon (IFN)-mediated AUIDs; (3) NF-κB-mediated diseases; (4) AUIDs caused by persistent macrophage activation; (5) AUIDs with yet uncharacterized pivotal pro-inflammatory mediators. As our understanding of detailed pathogenic mechanisms has increased, it has laid a foundation for the investigation and selection of more effective therapies for these relatively rare diseases. For instance, patients with CAPS spectrum, an IL-1-associated AUID, therapeutically respond to IL-1 blockade by Anakinra, Rilonacept and Canakinumab [5]. Similarly, the classic AUIDs like FMF, TRAPS and HIDS are also currently classified as IL-1-mediated AUIDs, yet they tend to have a more variable response to IL-1 inhibition, indicating that other pathways in these diseases may play more important roles in their pathogenesis. Therefore, a more complete understanding of underlying disease mechanisms may provide newer and more effective therapeutic choices.

2. Candidate molecular mechanisms of the disease pathogenesis in AUIDs

2.1. General pathogenesis of AUIDs

The mechanisms by which disease-causing genetic variants lead to the flares of AUIDs vary significantly, but they all primarily impact pattern recognition receptors (PRRs) that trigger innate immune responses [3,6]. PRRs are located either on the cell surface or in the cytosol, recognizing pathogen-associated molecular patterns (PAMPs) in bacteria, viruses and fungi. PRRs also recognize danger-associated molecular patterns (DAMPs) elicited by cell injury [7]. Most PRRs can be classified into one of five families consisting of the Toll-like receptors (TLRs), C-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid inducible gene I (RIG-I)-like receptors (RLRs), and absent in melanoma 2 (AIM2)-like receptors (ALRs) [8]. PRRs on the cell surface include most TLRs and CLRs, while the intracellular receptors include NLRs, ALRs, RLRs and TLR3, 7, 8, and 9. The AUID-associated mutants of PRRs and related adaptors are all intracellular. For example, variants in NLR family member *NLRP3* (NLR family pyrin domain containing 3) are found in CAPS [9], *NLRC4* (NLR family CARD domain containing 4) mutations are linked to macrophage activation syndrome (MAS) [10], *NOD2* variants are associated with Blau syndrome (BS) [11], and mutations in RLR family member *MDA5* (melanoma differentiation gene 5) are found in Aicardi-Goutières syndrome 7 [12].

Variants associated with AUIDs drive pathogenesis by both direct and indirect effects on PRR function. One mechanism is that the result of a genetic variant causes the hyperactivation of a PRR directly. Activated PRRs generate various innate immune responses, including transcription of proinflammatory mediators and non-transcriptional functions, such as induction of phagocytosis, autophagy, cell death, and cytokine maturation [13]. The inflammasome, a highly organized complex induced by activated intracellular PRRs, such as NLRP3, NLRC4 and AIM2, proteolytically process the inactive form pro-IL-1β into mature, active IL-1β [14], which is the key cytokine resulting in the symptoms of group 1 AUIDs. The structure of canonical inflammasomes, such as NLRP3 and AIM2 inflammasome, usually consist of 3 parts: PRR, an adaptor protein ASC [apoptosis-associated speck-like protein containing CARD (caspase recruitment domains)] that contains a Pyrin domain (PYD) and CARD, as well as the protease caspase-1 which mediates the processing of IL-1β [14]. The ASC adaptor acts as a molecular bridge binding to PRRs via PYD-PYD interactions and interacting with caspase-1 through CARD-CARD binding. Some CARD containing PRRs (such as NLRC4) can directly recruit caspase-1 without the adaptor ASC (Fig. 1). Mutations in PRRs may constitutively activate inflammasomes in the absence of activating signals from PAMPs or DAMPs, resulting in high levels of IL-1β secretion.

Table 1
Classic members of monogenic autoinflammatory diseases.

Diseases	Gene	Protein	Inheritance	Prominent clinical features
FMF	*MEFV*	Pyrin	AR/AD	Episodic fever, serositis, oligoarthralgia, erysipelas-like eruption on the lower extremities, serositis, amyloidosis
TRAPS	*TNFRSF1A*	TNFR1	AD	Episodic fever, myalgia underlying rash, oligoarthralgia, periorbital edema, serositis, steroid response
HIDS	*MVK*	Mevalonate kinase	AR	Fever, rash, arthralgia, abdominal pain, diarrhea, conjunctivitis, cervical lymphadenopathy, splenomegaly
CAPS	*NLRP3*	Cryopyrin	AD	Fever, urticarial rash, cold intolerance, conjunctivitis, arthralgia, hearing loss and central nervous system involvement

FMF, familial Mediterranean fever; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; HIDS, hyper-gammaglobulinemia D syndrome; CAPS, cryopyrin-associated periodic syndromes; AR, autosomal recessive; AD, autosomal dominant.

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