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Review

Autoinflammation and autoimmunity: Bridging the divide

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ABSTRACT

As soon as autoinflammatory diseases (AIDs) emerged as new entities, they have been linked to the well known world of autoimmunity. In fact, AIDs and systemic autoimmune diseases (ADs), share some characteristics: they start with the prefix "auto" to define a pathological process directed against self; they are systemic diseases, frequently involving musculoskeletal system; both include monogenic and polygenic diseases. From the pathogenetic point of view, they are characterized by a chronic activation of immune system, which eventually leads to tissue inflammation in genetically predisposed individuals. Nevertheless, the specific effectors of the damage are different in the two groups of diseases: in AIDs the innate immune system directly causes tissue inflammation, whereas in ADs the innate immune system activates the adaptive immune system which, in turn, is responsible for the inflammatory process.

Mutations in inflammasome-related proteins, particularly in NOD-like receptor (NLR) genes, have been strongly associated to the occurrence of AIDs, whereas the link between inflammasome and ADs is less clear. However, a role for this multiprotein-complex in some ADs can be postulated, since a wide spectrum of endogenous danger signals can activate NLRs and inflammasome products, including IL-1ß, can activate adaptive immunity. An association between single nucleotide polymorphisms (SNPs) localized in the inflammasome gene NLRP1 and systemic lupus erythematosus has recently been reported.

AIDs and ADs are currently subdivided into two different groups, but looking at their similarities they might be considered as a single group of diseases with a large immune pathological and clinical spectrum which includes at one end pure ADs and at the other end pure AIDs.

Contents

1. Introduction . . . 22
2. Similarities and differences between autoinflammatory and autoimmune diseases . . . 23
   2.1. Innate and adaptive immune effectors involved in autoinflammatory and autoimmune diseases . . . 23
   2.2. Genetic background . . . 24
   2.3. Pathogenetic triggers . . . 24
   2.4. Clinical aspects . . . 25
      2.4.1. Age at the onset . . . 25
      2.4.2. Signs and symptoms . . . 25
      2.4.3. Disease morbidities . . . 26
   2.5. Biomarkers . . . 27
   2.6. Therapy . . . 27
3. Conclusions . . . 28
References . . . 28

1. Introduction

Autoinflammatory diseases (AIDs), also called periodic fever syndromes, refer to a group of rare, hereditary, recurrent, unprovoked inflammatory disorders which occur in the absence of infection [1–3]. These diseases primarily include familial Mediterranean fever (FMF), tumor necrosis factor (TNF) receptor-associated periodic fever syndrome

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(TRAPS), hyperimmunoglobulinemia D and periodic fever syndrome (HIDS), cryopyrin-associated periodic syndrome (CAPS) including familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and neonatal onset multi-system inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA).

Some other diseases characterized by episodes of acute, apparently inexplicable inflammation have recently been classified in this group, including pyogenic disorders (pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA), chronic recurrent multifocal osteomyelitis syndrome (CRMO), Majeed's syndrome), immune-mediated granulomatous diseases (Blau's syndrome, Crohn's disease), and idiopathic febrile syndromes (systemic-onset juvenile idiopathic arthritis (sJIA), periodic fever with aphthous stomatitis, pharyngitis, and cervical adenopathy syndrome (PFAPA), and Behçet's syndrome), as shown in Table 1.

As soon as AIDs emerged as new entities, they were linked to the well known world of autoimmunity.

A preliminary observation is that these two types of diseases, AIDs and autoimmune diseases (ADs), share some characteristics: they start with the prefix "auto" to define a pathological process directed against self; they are systemic diseases, frequently involving skin and musculoskeletal system; they include monogenic and polygenic diseases.

From the pathogenetic point of view, they are characterized by a chronic activation of the immune system, which eventually leads to tissue inflammation in genetically predisposed individuals.

Nevertheless, the specific effectors of damage are different in the two groups of diseases: in AIDs the innate immune system directly causes tissue inflammation, whereas in ADs the innate immune system activates the adaptive immune system which, in turn, is responsible for the inflammatory process (Fig. 1) [4].

ADs exhibit distinct major histocompatibility (MHC)-associated haplotype susceptibility [4], whereas AIDs do not have associations with MHC class II haplotypes.

Patients affected with AIDs compared to those with ADs do not have autoantibodies or autoreactive antigen-specific T cells driving the disease process; in AIDs monocyte–macrophages rather than T and B cells are responsible for inflammation and damage [4].

Table 1
Classification of autoinflammatory and systemic autoimmune diseases.

Autoinflammatory diseases		Autoimmune diseases	
Monogenic diseases	Polygenic diseases	Monogenic diseases	Polygenic diseases
FMF	Still's disease	APS type I	Rheumatoid arthritis
TRAPS	Crohn's disease	IPEX	SLE
CAPS FCAS, MWS, NOMID	Behçet's disease	ALPS	Systemic sclerosis
HIDS	Gout	C1q deficiency	Polymyositis
Blau's syndrome	sJIA		Dermatomyositis
PAPA syndrome			Sjögren syndrome
CRMO			UCTD
DIRA			MCTD
Majeed's syndrome			Overlap syndromes
IL-10 deficiency			

FMF: familial Mediterranean fever; TRAPS: TNF receptor-associated periodic syndrome; CAPS: cryopyrin-associated periodic syndrome; FCAS: familial cold auto-inflammatory syndrome; MWS: Muckle–Wells syndrome; NOMID: neonatal-onset multisystem inflammatory disease; HIDS: hyper-immunoglobulinemia D syndrome; PAPA: pyogenic arthritis, pyoderma gangrenosum and acne; DIRA: deficiency of the interleukin-1 receptor antagonist syndrome; IL: interleukin; sJIA: systemic juvenile idiopathic arthritis; CRMO: chronic recurrent multifocal osteomyelitis syndrome; C1q: complement fraction 1q; APS: autoimmune polyendocrinopathy syndrome; IPEX: immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; ALPS: autoimmune lymphoproliferative syndrome; SLE: systemic lupus erythematosus; UCTD: undifferentiated connective tissue disease; MCTD: mixed connective tissue disease;

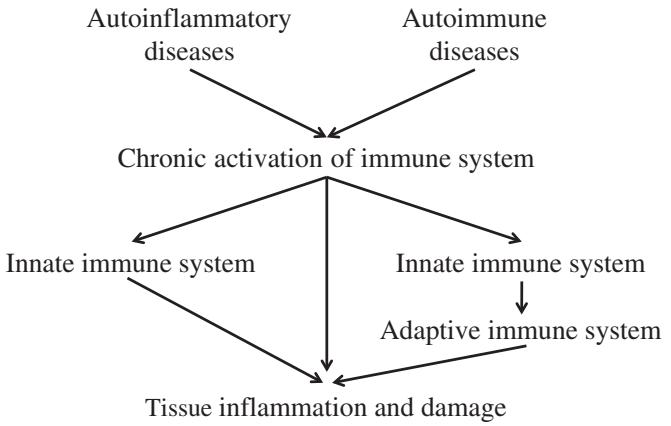

Fig. 1. What is autoimmune and what is autoinflammatory: a schematic pathogenetic pathway of autoinflammatory and autoimmune diseases.

2. Similarities and differences between autoinflammatory and autoimmune diseases

2.1. Innate and adaptive immune effectors involved in autoinflammatory and autoimmune diseases

Innate immunity represents the first barrier in host immune defense; it identifies pathogens or other harmful triggers inducing an inflammatory process with the aim of blocking their diffusion, and activates adaptive immunity.

The effector cells of innate immunity are phagocytes, including macrophages, dendritic cells and other antigens presenting cells (APC) [4]. Innate immunity acts through pattern recognition receptors (PRR) which bind to highly conserved structures expressed by pathogens (pathogens associated molecular patterns, PAMPs) or by damaged cells (damage associated molecular patterns, DAMPs).

Three classes of PRR have been identified: the Toll-like receptors (TLRs), the retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) and the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) [5].

Their recognition of foreign molecules is followed by the activation of intracellular signal transduction pathways, which induces the expression of genes including interferon (IFN) alpha, IFN-β, TNF and interleukin (IL)-1 gene sequences. A dysregulation of these receptors, mostly excessive or prolonged activation, may lead to the development of both AIDs and ADs [6].

Involvement of TLRs in ADs, such as systemic lupus erythematosus (SLE), has been demonstrated in experimental models [7] which leads to the production of type I IFNs [8].

Activation of the NLR proteins, NLRP3 (also known as NALP3 or cryopyrin), NLRP1, and NLRC4 results in the formation of large protein complexes termed inflammasomes. Two types of inflammasomes have been described: the NALP1 inflammasome and the NALP3, or cryopyrin, inflammasome [5].

The inflammasome serves as a molecular platform which mediates the activation of pro-caspase-1, which cleaves the proforms of IL-1ß and IL-18 to the active forms. Inflammasome activation is crucial for host defense to pathogens.

AIDs have been strongly linked to mutations in inflammasome-forming NLR [9]. In fact, the majority of patients with AIDs have mutations in either pyrin, cryopirin, or TNF receptor super-family genes [10].

The role of inflammasome in autoimmunity is less clear. Nowadays there are no convincing genetic links between inflammasome-inducing NLRs and ADs. Nevertheless, a role for the inflammasome in some ADs can be postulated, considering the wide spectrum of endogenous danger signals that activate NLRs, among which ultra violet (UV) radiation and double stranded DNA have been reported [11,12], and