# The Body against Self: Autoinflammation and Autoimmunity

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Autoinflammatory (AIF) diseases and autoimmune (AIM) diseases are characterized by an aberrant chronic activation of the immune system, leading to tissue inflammation and damage. In AIF diseases, the innate immune system is directly responsible for tissue inflammation, while in AIM diseases it activates the adaptive immunity, which becomes the main effector of the inflammatory process [1].

## GENETIC BACKGROUND

Genetic association studies highlighted the presence of gene mutations that predispose to the development of both autoinflammatory and autoimmune diseases [2,3]. Genes associated with AIF diseases encode for proteins of the inflammasome [2]. Mutations in genes coding for regulatory molecules of T and B cell signaling and in genes involved in Toll-like receptor (TLR)-interferon (IFN) and in tumor necrosis factor (TNF)-nuclear factor kappa B (NFκB) signaling pathways have been observed in patients affected with AIM diseases [3]. Recently, an association was reported between single-nucleotide polymorphisms (SNPs) localized in the inflammasome gene nucleotide-binding oligomerization domain-like receptor protein 1 (NLRP1) and systemic lupus erythematosus (SLE) [4].

## ENVIRONMENTAL TRIGGERS

In both autoinflammatory and autoimmune diseases, environmental as well as endogenous factors can elicit disease onset and flares. Infective agents may induce both AIF and AIM diseases, i.e., by interacting with TLR, as well as by molecular mimicry, bystander activation (expansion of previously activated T cells), and activation of T cells by microbial superantigens. In addition, AIF and AIM diseases can be triggered by physical agents and exposure to drugs and other chemical agents which can alter immune system homeostasis.

## EFFECTOR MECHANISMS

The sensors of innate immunity are named pattern recognition receptors (PRRs) and they bind pathogen-associated molecular patterns (PAMPs) or damaged cells (damage-associated molecular patterns, DAMPs). The effector cells are macrophages, dendritic cells, and other antigen-presenting cells. PRRs include three classes of receptors: TLRs, nucleotide-binding oligomerization domain-like receptors (NLRs), and retinoic acid-inducible gene-I-like receptors [5].

Activation of NLRP, i.e., NLRP1, NLRP3 (also known as NALP3 or cryopyrin) and NLR family CARD domain-containing protein 4 (NLRC4), leads to the formation of large protein complexes termed inflammasomes, which are critical for the defense against pathogens. Indeed, they mediate the activation of procaspase-1 and, consequently, the cleavage of the proforms of interleukin (IL)-1β and IL-18 to the active forms [5] [Figure 1].

Adaptive immunity acts through highly specific antigen receptors, the most important of which are T and B cell receptors. Patients affected with AIM diseases have autoreactive antigen-specific T cells and produce autoantibodies [1].

## CLINICAL FEATURES

Constitutional symptoms, such as recurrent fever, fatigue, flu-like symptoms, weight loss, myalgia, malaise, lymphadenopathy and splenomegaly, are frequent in both diseases. Skin, musculoskeletal and gastrointestinal symptoms are the most common in AIM diseases, while involvement of other organs, such as lung, eye, ear, hematopoietic and nervous system, is less common.

Notably, while signs and symptoms are often similar in AIF and AIM diseases, biological and bioptic investigations may reveal more specific features [1]. For instance, AIF and AIM patients complain very often of myalgia and asthenia. However, muscle weakness and fatigue are associated with increased creatinine phosphokinase (CK) serum levels in AIM diseases, especially in polymyositis/dermatomyositis (PM/DM), whereas CK serum levels are usually within the normal range in AIF diseases.

AIF and AIM patients have a higher morbidity and mortality risk due to disease complications. In particular, AA amyloidosis develops in patients with long-lasting inflam-

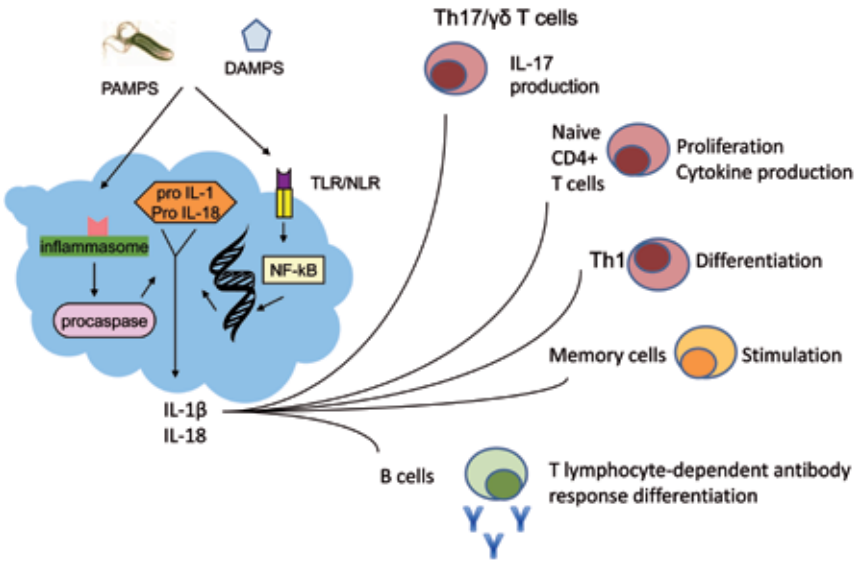


**Figure 1.** Effects of IL-1 and IL-18 on the adaptive immune system

PAMPS = pathogen-associated molecular patterns, DAMPS = damage-associated molecular pattern molecules, TLR = toll-like receptor, NLR = nucleotide-binding domain and leucine-rich repeat containing, IL = interleukin, Th = T helper

PAMPS and DAMPS stimulate TNF or a TLR exposed to the cell surface, resulting in the translocation of NF-κB into the nucleus where expression of the immature (pro-) forms of IL-1β and IL-18 are induced. On the other hand, PAMPs and DAMPs can enter cells, inducing the activation of inflammasome which, in turn, recruits and cleaves procaspase-1 to its active form, leading to the consequent activation of pro-IL1 and pro-IL18. The effects of IL-1β and IL-18 are not limited to the innate immune system but they play a role in the differentiation, activation and proliferation of distinct effector T and B lymphocyte subsets, thus promoting inflammatory phenotypes in autoimmune disorders (RA, diabetes, SLE, etc.)

matory conditions, whereas several autoimmune diseases are associated with premature atherosclerosis.

## BIOMARKERS

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) usually increase during a period of active disease. High ferritin serum levels typically arise in Still's disease. High immunoglobulin serum levels can be found in SLE, primary Sjögren syndrome, hyper-immunoglobulin D syndrome (HIDS), and familial Mediterranean fever (FMF). Serum amyloid A protein (SAA) is often increased in patients with AIF diseases, while low complement component 3 and 4 serum levels are more frequently observed in SLE.

Autoantibodies are diagnostic biomarkers in AIM diseases, some of them displaying a pathogenic role, i.e., anti-P ribosomal protein in neuropsychiatric SLE [6], others displaying a protective role, such as IgG anti-pentraxin 3 antibodies, again in SLE [7].

## THERAPY

Since the dysregulation of the immune system is the common pathogenic background of both autoinflammatory and autoimmune diseases, drugs such as NSAIDs (non-steroid anti-inflammatory drugs) and corticosteroids are used in both. Colchicine is useful for the majority of AIF diseases. Additionally, it is used to prevent the development of amyloidosis in most cases, ameliorating the disease in 95% of patients. Immunosuppressants are effectively used for the majority of severe manifestations in autoimmune patients, while their role in AIF diseases is less clear.

In recent years, specific anti-cytokine drugs have been developed. For instance, IL-1 antagonists are used in AIF diseases, anti-TNFα and anti-IL6 are used in rheumatoid arthritis as well as in spondyloarthropathies and irritable bowel syndrome, and anti-BLYS (B lymphocyte stimulator) is used in SLE.

## AUTOINFLAMMATION IN AUTOIMMUNE DISEASES

Over the past years it has become clear that AIF processes play a pathogenic role even in AIM diseases. For instance, it was recently demonstrated that neutrophil extracellular traps (NETs), an important defensive mechanism against microorganisms, are involved in the pathogenesis of some autoimmune and autoinflammatory diseases. Defects in clearance of NETs expose immunostimulatory molecules to plasmacytoid dendritic cells, thus stimulating the activation of inflammasomes and the release of IL-1β and IL-18. IL-18, in turn, stimulates NETosis in human neutrophils, thus enhancing the formation of NETs, which results in a feed-forward inflammatory loop that potentially leads to disease flares and/or organ damage [8].

A recent study in a southern Brazilian population supports the association between specific SNPs localized in the inflammasome gene *NLRP1* and SLE. Indeed, these SNPs were associated not only with an increased risk of developing SLE but also with the manifestation of specific pathologic features, such as rash and arthritis which are typically observed in AIF patients [6]. Thus, it might be that specific SNPs of inflammasomes affect the clinical and immunologic features of AIM diseases, favoring the development of some AIF-like manifestations and leading to an increase of some

inflammatory-related biomarkers, such as IL-1β and IL-18.

IL-1β can act on lymphocytes in several ways, favouring the expansion of autoreactive Th1 and Th17 lymphocytes [9,10], and the down-regulation of regulatory T cells [9]. Moreover, it yields the up-regulation of IL-2 receptor expression, prolonging survival of T cells [10]. All these mechanisms may induce and enhance the development of autoimmune diseases in genetically predisposed individuals [Figure 1].

Finally, the involvement of inflammation in autoimmunity was recently underlined by the positive effects of the administration of anakinra in autoimmune patients, leading to the amelioration of arthritis not only in rheumatoid arthritis, but also in SLE and in PM/DM patients. In addition, chloroquine, used widely in SLE, has been shown to decrease aberrant NLRP3 expression, a mechanism that might be related to its therapeutic effect.

## CONCLUSIONS

From a pathogenic point of view, autoinflammatory and autoimmune diseases share the chronic activation of the immune system, which eventually leads to tissue inflammation. The specific effectors of damage are different in the two groups of diseases. Nevertheless, in the past decade we began to understand the involvement of AIF processes in AIM disease. However, the effects of IL-1β and IL-18 on lymphocyte programming and function have not been extensively studied and require further research to expand our knowledge in this field and to hypothesize new therapeutic approaches in autoimmune diseases.

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