Systemic Autoinflammatory Disorders: Autoinflammatory and autoimmune disorders

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The published article entitled “Systemic autoinflammatory disorders” reviewed the recent molecular mechanism, clinical manifestations, diagnostic approach with molecular genetic testing and treatment of systemic autoinflammatory disorders (SAIDs). And, this article introduced major categories of SAIDs according to their mechanism, including inflammasomopathies and other IL-1-related conditions, endoplasmic reticulum stress, mutations in endogenous antagonists, dysregulation of NFκB signaling, interferonopathies, and adult-onset SAIDs.

SAIDs are a group of rare monogenic disorders characterized by excessive activation of antigen-independent inflammatory pathways due to an imbalance in the innate immune system. Clinical manifestations of SAIDs include periodic fever, a multisystem inflammatory response, and immunodeficiency.

Autoinflammatory and autoimmune disorders are two main categories of the immune system disorders. Although these two inflammatory disorders have a lot in common, but each has unique characteristics. In most cases, dysfunctions of innate immunity represent autoinflammatory disorders that are caused by mutations in the genes, while dysfunctions of adaptive immunity reflect autoimmune disorders.

Discrimination between self and non-self is the fundamental properties of the immune system. Self tolerance is the process by which immune cells are made unresponsive to self-antigens to prevent damage to healthy tissues. Failure of self-tolerance results in immune responses against self-antigens. Such reactions are called autoimmunity and may give rise to autoimmune disorders.
In autoimmune disorders, lymphocytes are overactive, the release of cytokines lead to abnormal secretion of autoantibodies, resulting in inflammation and damage to tissues and organs. So far, there are more than 100 autoimmune diseases which are divided into systemic or organ specific. Systemic lupus erythematosus is the most representative systemic autoimmune disorders, and type 1 diabetes represents organ-specific autoimmune disorders.\(^5\)

Autoinflammatory disorders are characterized by inflammation due to hyperactivation of antigen independent immune pathways. Most autoinflammatory disorders are hereditary diseases, and they develop by dysregulation of innate immunity through various pathways, including inflammasomes, endoplasmic reticulum stress, NF-\(\kappa\)B dysregulation, and interferon production.\(^6\) Overactivation of proinflammatory cytokines mediates and participates in inflammation in autoinflammatory disorders.

There are more than 40 known autoinflammatory disorders which can be classified into several categories based on underlying genetic mutations and clinical findings.\(^7,8\) Monogenic autoinflammatory disorders include familial Mediterranean fever (FMF), tumor necrosis factor (TNF) receptor-associated periodic syndrome, and cryopyrin-associated periodic syndrome. Polygenic autoinflammatory diseases include systemic juvenile idiopathic arthritis and Behcet's disease.

FMF is an inflammasomopathy caused by mutations in the MEFV gene, and most other autoinflammatory disorders are caused by NF-\(\kappa\)B and/or aberrant TNF activity, interferon production and excessive interleukin-1 (IL-1) signaling.\(^8\)

However, autoinflammatory and autoimmune disorders affect each other, and in many diseases,
the two inflammatory reactions appear together (Fig-1).

In SAIDs, the immune system becomes overactive and produces excessive amounts of cytokines, resulting in various symptoms such as periodic fever, joint pain, skin rash, serositis and lymphadenopathy. The diagnosis of SAIDs is based on clinically suspicious findings, laboratory tests including inflammatory cytokines and genetic confirmation. As genetic sequencing technology and analysis improved and cost has decreased, more cases are being identified. By 2022, the US market offered over 429 genetic immune dysregulation panels designed to diagnose SAIDs. The goal of SAIDs treatment is to suppress the hyperinflammatory immune state, restore the function of multiple systems, and improve the quality of life. Conventional treatment approaches, such as nonsteroidal anti-inflammatory drugs, corticosteroids and colchicine, have been in use, while significant advances are being made in recent times, including biologic agents such as IL-1 blockers, TNF inhibitors, Janus kinase inhibitors and gene therapy.

In conclusion, SAIDs are a spectrum of innate immune disorders that induce multisystem inflammatory damage through excessive activation of inflammatory pathways. Early and accurate diagnosis is important for appropriate treatment and management of SAIDs. However, due to the rarity of SAIDs, studies their pathogenesis and treatment are limited, so currently SAIDs are difficult to manage. SAIDs will further increase due to advances in genetic research and biotechnology, leading to better understanding, diagnosis and treatment of these diseases.
References


Legends

Figure 1. The spectrum of immune-mediated inflammatory diseases

Footnotes

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Figure 1. The spectrum of immune-mediated inflammatory diseases

FMF, familial Mediterranean fever; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; PAPA, pyogenic arthritis, pyoderma gangrenosum and acne; HIDS, hyperimmunoglobulin D syndrome; IBD, inflammatory bowel disease; AS, ankylosing spondylitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; DM, dermatomyositis; PM, polymyositis; ALPS, autoimmune lymphoproliferative syndrome; IPEX, immune dysregulation, polyendocrinopathy, X-linked syndrome; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.
Inflammatory spectrum

Mechanism
- Autoinflammation
- Autoimmunity

Diagnosis
- Identification of candidate genes
- Presence of autoantibodies

Classification
- Monogenic autoimmune diseases
- Polygenic autoinflammatory diseases
- Mixed pattern diseases
- Polygenic autoimmune diseases
- Monogenic autoimmune diseases

Examples
- FMF, TRAPS, PAPA, HIDS...
- Gout, IBD, Sarcoidosis...
- Bechets disease, AS...
- RA, SLE, DM, PM...
- ALPS, IPEX, APECED...