Clinical reviews in allergy and immunology

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The role of the inflammasome in patients with autoinflammatory diseases

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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Activity Objectives:

1. To recognize the distinguishing features of autoinflammatory disorders.
2. To be able to address available therapies that target the inflammasome pathway.
3. To become familiar with the components and function of the inflammasome.

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Autoinflammatory diseases are disorders of the innate immune system, characterized by systemic inflammation often driven by inflammasomes, and independent of infection and autoreactive antibodies or antigen-specific T cells. These diseases are increasingly recognized as disorders of immune dysregulation, presenting with a constellation of fevers, rashes, and mucosal symptoms in many cases, which suggests that the allergist/immunologist is the appropriate specialist for these patients. However, many practicing physicians are unaware of these disorders in their pediatric and adult patient populations, leading to substantial delays in diagnosis. Recognizing autoinflammatory disease symptom patterns, performing appropriate diagnostic tests, and instituting early effective therapy are essential to reduce morbidity and mortality in these patients. This review will focus on understanding the molecular basis of inflammasomes, recognizing the distinguishing features of the classic autoinflammatory disorders, and appreciating the treatment modalities available. (J Allergy Clin Immunol 2016;138:3-14.)

Key words: *Autoinflammation, inflammasome, innate immunity*

The traditional classification of immunologic diseases cleanly divides immunodeficiency and allergy or autoimmunity. However, this classification scheme has blurred edges because there is evidence of autoimmunity and allergy in patients with classic immunodeficiency disorders, such as common variable immune deficiency and Wiskott-Aldrich syndrome. Elucidation of the

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Abbreviations used

ASC: Apoptosis associated Speck like protein containing a CARD
CAPS: Cryopyrin-associated periodic syndromes
CARD: Caspase activation and recruitment domain
CNS: Central nervous system
DAMP: Damage-associated molecular pattern
DIRA: Deficiency of the IL-1 receptor antagonist
FCAS: Familial cold autoinflammatory syndrome
FMF: Familial Mediterranean fever
HIDS: Hyper-IgD syndrome
IL-1RA: IL-1 receptor antagonist
MWS: Muckle-Wells syndrome
NLR: Nucleotide binding domain, leucine rich repeat or Nod-like receptor
NOMID: Neonatal-onset multisystem inflammatory disease
PAMP: Pathogen-associated molecular pattern
PAPA: Pyogenic arthritis, pyoderma gangrenosum, and acne
TRAPS: TNF receptor–associated periodic syndrome

disease mechanisms has introduced the term immune dysregulation in diseases such as immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome and, more recently, phospholipase C–associated antibody deficiency immune dysregulation syndromes.[1] The concept of unclassified immune dysregulation is not novel in that there are common inflammatory diseases that do not fit into any of the traditional classifications, including disorders of host-microbiome symbiosis, such as inflammatory bowel disease,[2] or crystal-induced diseases, such as gout or pseudogout. However, it was the rare hereditary recurrent fever disorders that prompted the development of a completely new and continually expanding immune disease classification now known as autoinflammatory disorders.[3]

AUTOINFLAMMATION

The term autoinflammatory disease was first coined by Galon et al[4] after discovery of the gene for TNF receptor–associated periodic syndrome (TRAPS)[5] to differentiate the hereditary recurrent fever disorders from other diseases with similar clinical features but somewhat distinct immune pathobiology. Patients with autoinflammatory diseases can display clinical and laboratory features observed in infectious and autoimmune diseases, including fever, rash, joint pain, neutrophilia, and increased inflammatory markers, as well as typical features of allergic diseases, such as responses to external stimuli (cold exposure). In contrast, patients with autoinflammatory disorders demonstrate no evidence of pathogenic infection and no indication of self-directed autoantibody or antigen-specific T-cell or IgE-mediated inflammation. Although each of these immune disorders relies at least in part on the adaptive immune response, autoinflammatory diseases are primarily innate immune-driven diseases with predominance of neutrophil-, macrophage-, or monocyte-mediated inflammation and the presence of inappropriate cytokine-mediated pathology. Autoinflammatory disorders are characterized by systemic inflammation with specific tissue involvement, including the skin, joints, conjunctiva, and serosal tissues (abdomen and pleura). The rarity of these disorders, combined with the recurrent intermittent nature of symptoms, presents a challenge for medical professionals and frustration for patients and families. To encourage physicians and patients to think about autoinflammatory diseases, we have proposed a list of 5 characteristic signs of autoinflammation so that physicians and patients will consider these disorders in the search for a possible diagnosis (Table I).

TABLE I. Five signs of autoinflammation*

- Recurrent unexplained noninfectious episodes (>3) of fever (>101°F)
- Each episode has a predictable pattern or characteristic course
- Episodes characterized by specific symptoms, including nonitchy rash, extremity/joint pain, severe abdominal pain, and/or conjunctivitis and absence of upper respiratory tract symptoms
- Episodes that can be triggered by specific stimuli (cold exposure or vaccines)
- Family history of autoinflammatory disease or amyloidosis

*Two or more signs might suggest an autoinflammatory disease.

GENETICS: DISCOVERY AND COMPLEXITIES

The hereditary fever disorders are some of the best examples of translational research made possible by the timely combination of motivated large families with clear heritable phenotypes and the rapid advances in human genetics and molecular genetics technology at the end of the last century. This led to recognition of the genetic basis of these classically Mendelian-inherited diseases beginning in 1997 with the discovery of *MEFV* as the gene for familial Mediterranean fever (FMF)[6,7] and followed by the identification of nucleotide binding domain, leucine rich repeat, pyrin 3 *(NLRP3)* as the gene for a continuum of disorders now known as cryopyrin-associated periodic syndromes (CAPS).[8,9] Investigations of the immune pathways underlying these unique inflammatory disorders have not only revealed novel innate immune mechanisms, namely inflammasomes, but also had a practical and significant effect on the treatment of patients with these diseases in the form of targeted biologic therapies.

Although it was the "simple" Mendelian inheritance that led to identification of the first genes responsible for autoinflammatory disorders, further analysis has revealed numerous complexities to disease expression. FMF is inherited in a classic autosomal recessive fashion, but there are patients with a complete or mild FMF phenotype who possess only 1 detectable *MEFV* mutation, challenging the loss-of-function model and introducing the possibility of complex genetic mechanisms. Recently, evidence in FMF knock-in mice suggested a gain-of-function model that could explain the findings in these patients.[10] CAPS-associated *NLPR3* mutations appear to be gain-of-function mutations consistent with autosomal dominant inheritance.[11] The search for the underlying disease etiology of patients with a classic clinical presentation of CAPS without detectable *NLRP3* mutations by means of traditional Sanger sequencing has resulted in identification of patients with somatic mosaicism. In some cases mutant allele frequency is as low as 4% in whole blood, indicating that a small fraction of affected cells were sufficient to cause systemic symptoms.[12,13] There are also cases of myeloid-restricted somatic mosaicism with disease onset in adulthood.[14] In both patients with FMF and those with CAPS, there are well-documented examples of low-penetrance mutations associated with a range of phenotypes from typical clinical presentation, mild or atypical disease, to complete absence of signs or symptoms.[15,16] Although these new genetic findings are intriguing for understanding disease pathophysiology, they similarly introduce new diagnostic dilemmas for the