Introduction to Autoinflammatory Syndromes and Diseases

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KEYWORDS

• Autoinflammation • Inflammasome • Interleukins • Recurrent fever • Familial Mediterranean fever

KEY POINTS

- Autoinflammatory syndromes and diseases are an expanding, usually poorly understood, and difficult to treat group of conditions.
- They underlining pathophysiology revolves around the overactivation or underregulation of the inflammatory process resulting in multisystemic tissue damage.
- New insights into the molecular mechanisms of inflammation and genetic profiling have led to the development and use of anticytokine therapies with a level a success not previously achieved.

Autoinflammatory syndromes and diseases are a group of disorders of innate immunity that are often inherited, sometimes acquired, characterized by febrile episodes, recurrent, of variable duration, seemingly unprovoked, and with multidistrict inflammation of variable severity.[1,2] Unlike the classic autoimmune diseases in which the immunopathogenesis occurs primarily in lymphoid organs, that of the autoinflammatory disorders develops and occurs in the affected tissues, implying that tissue-specific factors in the target organs contribute to disease expression. A direct association between defective immune responses to bacterial components and these diseases has not been clearly established.[3] Excessive or protracted signaling, or both, by cell surface or intracellular innate immune receptors is central to their pathogenesis.

Most classic autoinflammatory syndromes are generally dependent on germline or de novo gene mutations that cause or facilitate the assembly of a protein complex called inflammasome, capable of detecting cellular danger signals generated by infectious agents or metabolic stressors. Consequent production of proinflammatory cytokines, principally interleukin (IL)-1β, leads to the creation of autoamplifying feedback loops that explain their chronicity.[4] These diseases and syndromes were initially cataloged as periodic fever syndromes.[5–7]

Clinical classification of autoinflammatory diseases and syndromes is presented in **Table 1**. A classification based on molecular insights garnered over the past decade was recently proposed; it is intended to supplant the classification shown in **Table 1**, which is opaque to the genetic, immunologic, and therapeutic interrelationships that have become evident of late. Intrinsic inflammasomopathies represent molecular lesions in the constituent proteins of the inflammasome; extrinsic inflammasomopathies denote disorders of various upstream or downstream regulatory elements (**Table 2**).[8]

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Table 1
Clinical classification of the autoinflammatory syndromes and diseases

Hereditary recurrent fevers	Familial Mediterranean fever (FMF) Mevalonate kinase deficiency syndrome (MKDS) Tumor necrosis factor receptor-associated periodic syndrome (TRAPS) Cryopyrin-associated periodic syndromes (CAPS) Familial cold-associated syndrome (FCAS) Muckle-Wells syndrome (MWS) Neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous articular syndrome (CINCA)
Idiopathic febrile syndromes	Systemic-onset juvenile idiopathic arthritis (SJIA) Periodic fever, aphthous stomatitis, pharyngitis and adenitis or periodic fever, aphthous pharyngitis and cervical adenopathy syndrome (PFAPA) Pyoderma gangrenosum, acne, and suppurative hidradenitis syndrome (PASH) Behçet disease Nakajo-Nishimura syndrome Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome
Pyogenic disorders	Pyogenic arthritis, pyoderma gangrenosum (PG), and acne syndrome (PAPA) Chronic recurrent multifocal osteomyelitis (CRMO) syndrome Majeed syndrome Deficiency of IL-1 receptor antagonist (DIRA) Deficiency of IL-36 receptor antagonist (DITRA) CARD14-mediated pustular psoriasis (CAMPS)
Immune-mediated granulomatous diseases	Blau syndrome Crohn disease
Autoinflammatory diseases of the bones	Cherubism
Complement disorders	Atypical hemolytic uremic syndrome (aHUS) Age-related macular degeneration (AMD)
Hemophagocytic and vasculitic syndromes	Familial hemophagocytic lymphohistiocytosis (FHLH) Secondary hemophagocytic lymphohistiocytosis
Miscellaneous	Atopic dermatitis Psoriasis Vitiligo Alopecia Rosacea Atherosclerosis Multiple sclerosis Diabetes

Data from Masters SL, Simon A, Aksentijevich I, et al. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol 2009;27:621–68.

CLINICAL CLASSIFICATION OF THE AUTOINFLAMMATORY SYNDROMES AND DISEASES

IL-1β Activation Disorders and Other Inflammasomopathies

IL-1β secretion has emerged as a central mechanism in the pathogenesis of many inflammatory diseases. Genetically defined syndromes such as cryopyrin-associated periodic syndromes (CAPS) and Familial Mediterranean fever (FMF), as well as diseases associated with NLRP3 activation by danger signals such as gout, pseudogout, Alzheimer disease, or diabetes mellitus, are included in this group. Drugs directed against IL-1 activity contribute to the identification and treatment of a

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