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REVIEW

Monogenic autoinflammatory diseases: Concept and clinical manifestations

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Abstract The objective of this review is to describe the clinical manifestations of the growing spectrum of monogenic autoinflammatory diseases including recently described syndromes. The autoinflammatory diseases can be grouped based on clinical findings: 1. the three classic hereditary "periodic fever syndromes", familial Mediterranean Fever (FMF); TNF receptor associated periodic syndrome (TRAPS); and mevalonate kinase deficiency/hyperimmunoglobulinemia D and periodic fever syndrome (HIDS); 2. the cryopyrin associated periodic syndromes (CAPS), comprising familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID) or CINCA, and; 3. pediatric granulomatous arthritis (PGA); 4. disorders presenting with skin pustules, including deficiency of interleukin 1 receptor antagonist (DIRA); Majeed syndrome; pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome; deficiency of interleukin 36 receptor antagonist (DITRA); *CARD14* mediated psoriasis (CAMPS), and early-onset inflammatory bowel diseases (EO-IBD); 5. inflammatory disorders caused by mutations in proteasome components, the proteasome associated autoinflammatory syndromes (PRAAS) and 6. very rare conditions presenting with autoinflammation and immunodeficiency.
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Contents

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1. Introduction

The history of "autoinflammatory diseases" dates back to the identification of the genetic causes of the two most prevalent monogenic autoinflammatory diseases worldwide. Mutations in *MEFV* as the cause of familial Mediterranean fever (FMF) and mutations in *TNFRSF1A* as the cause of TNF receptor associated periodic syndrome (TRAPS) were identified in 1997 and 1999 respectively [1–3]. These discoveries have marked the beginning of an exciting journey that led not only to the molecular understanding of previously clinically defined entities, but also to the characterization of novel diseases that were not previously clinically described.

The discovery that gain of function mutations in *NLRP3*, a component of an IL-1β processing complex, the NLRP3 inflammasome, can cause the spectrum of clinical disorders now called cryopyrinopathies, including familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID) also called chronic infantile neurological and articular syndrome (CINCA) led to the hypothesis that the proinflammatory cytokine IL-1β may play an important role in the pathogenesis of these disorders [4]. Early proof of concept studies with the IL-1 blocking agent anakinra (Kineret®) surprisingly showed impressive clinical responses in the patients treated. These studies not only validated the role of IL-1 blockade in these disorders, but also led to the FDA approval of now three IL-1 blocking agents for the treatment of these disorders, the long acting IL-1 blocking agents, rilonacept (Arcalyst®) and canakinumab (Ilaris®) approved in 2008 and 2009, respectively, and the short acting IL-1 inhibitor anakinra (Kineret®) in 2012.