



# **Horror Autoinflammaticus: The Molecular Pathophysiology of Autoinflammatory Disease (Annual Review of Immunology Book 27)**

*Seth L. Masters, Ivona Aksentijevich, Daniel L. Kastner*

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The autoinflammatory diseases are characterized by seemingly unprovoked episodes of inflammation, without high-titer autoantibodies or antigen-specific T cells. The concept was proposed ten years ago with the identification of the genes underlying hereditary periodic fever syndromes. This nosology has taken root because of the dramatic advances in our knowledge of the genetic basis of both mendelian and complex autoinflammatory diseases, and with the recognition that these illnesses derive from genetic variants of the innate immune system. Herein we propose an updated classification scheme based on the molecular insights garnered over the past decade, supplanting a clinical classification that has served well but is opaque to the genetic, immunologic, and therapeutic interrelationships now before us. We define six categories of autoinflammatory disease: IL-1 $\beta$  activation disorders (inflammasomopathies), NF- $\kappa$ B activation syndromes, protein misfolding disorders, complement regulatory diseases, disturbances in cytokine signaling, and macrophage activation syndromes. A system based on molecular pathophysiology will bring greater clarity to our discourse while catalyzing new hypotheses both at the bench and at the bedside.

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