International Immunology, Vol. 30, No. 5, pp. 181–182
doi:10.1093/intimm/dxy022

Introduction: Autoinflammatory Syndromes Special Issue—hidden mysteries in the corners of autoinflammation

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Guest Editors

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FEATURED ARTICLE

This is the 18th year of ongoing research in 'autoinflammation'. Since the genetic and pathogenic characterization of the first autoinflammatory diseases—familial Mediterranean fever (FMF) and TNF-receptor associated periodic syndrome (TRAPS)—further genetic and clinical discoveries have advanced hand in hand with basic discoveries of innate-immune sensors and pathways that link danger-sensing to the production and release of key pro-inflammatory cytokines (1).

The findings of gain-of-function mutations in the genes for two intracellular sensors—the NOD-like receptor (NLR) gene *NLRP3* that causes the cryopyrin-associated periodic syndromes (CAPS) and more recently *MEFV* that forms an IL-1 activating inflammasome that causes FMF—coupled with groundbreaking insights into the biology of IL-1 activation, led to the successful use of treatments that target IL-1. Thus completing the cycle from bedside to bench and back to the bedside, the clinical responses to IL-1 inhibition justified the classification of these diseases as IL-1 mediated autoinflammatory diseases. Many of the IL-1 blocking treatments are now Food and Drugs Administration (FDA) approved and are considered first-line therapies for these conditions.

More recently, intracellular pathways that lead to production of type I interferons (IFN) have been identified to cause autoinflammatory phenotypes and are referred to as IFN-mediated autoinflammatory diseases (2). These conditions are a subset of a larger group of conditions of innate and adaptive immune dysregulation termed interferonopathies (3).

Together, these conditions link key innate-immune pathways that regulate the production of the cytokines IL-1 and type I IFN to the pathogenesis of 'autoinflammatory diseases' and suggest targeting these cytokines as effective treatment strategies. Many existing comprehensive reviews on the basic immunology and the clinical presentations of autoinflammatory diseases build upon these advances and are aimed at characterizing and categorizing the increasing number of genetically defined autoinflammatory diseases (1–4).

Up to this point, gain-of-function mutations in four inflammasome-assembling proteins (NLRP3, pyrin, NLRP1 and NLRC4) and the innate-immune sensor NOD2 have been associated with autoinflammatory phenotypes. The profound clinical responses to IL-1 inhibition as seen in the cryopyrinopathies (caused by mutations in the NLRP3 inflammasome), in FMF and in hyper-IgD syndrome (linked to activation of pyrin inflammasomes) hastened the need for early diagnosis that can be critical in obtaining access to IL-1-blocking therapies.

In this Special Issue of *International Immunology*, Sönmez and Özen (5) discuss how consensus-based methods that focus on clinical features seen in the context of activation of the pyrin inflammasome are useful in clinical practice.

We further highlight three emerging areas of autoinflammatory biology that have not been extensively researched and described. Overall, they focus on recent findings that link hyperferritinemic and granulomatous inflammation to the regulation of two NLRs—NLRC4 and NOD2, respectively.

Furthermore, macrophage activation syndrome (MAS) is not a common feature of the diseases caused by mutations regulating the NLRP3 and pyrin inflammasomes. In contrast, gain-of-function mutations in the NLRC4 (a.k.a. IPAF, CARD12 or CLAN) inflammasome are associated with the development of MAS in the context of very high levels of the other inflammasome-activated cytokine, IL-18. The high serum IL-18 levels in NLRC4-associated MAS result in chronic elevation of bioactive or 'free' IL-18 (6). Hence, Fusco and Duncan (7) discuss recent insights into the structural biology of the NLRC4 inflammasome: specific environmental signals (like cytosolic detection of bacterial products by NAIPs) that trigger its activation and reveal the NAIP/NLRC4 inflammasome as a sensor for a particularly pathogenic group of intracellular bacteria. Novel insights into the structure and function of the NLRC4 inflammasome reinvigorate the field of inflammasome activation by comparing the NLRP4 inflammasome to the NLRP3, pyrin and NLRP1 inflammasomes.

The link between activation of the NLRC4 inflammasome, elevated IL-18 levels and MAS may provide novel mechanisms that allow us to dissect the pathology of SIRS (systemic inflammatory response syndrome). Recent efforts to understand the different subsets of sepsis have identified that ~7% of patients have a hyperinflammatory phenotype, high mortality and present with features of MAS including highly elevated serum ferritin levels (hyperferritinemia) (8, 9). The resemblance of hyperinflammatory SIRS to patients with familial hemophagocytic lymphohistiocytosis (FHLH, caused

by mutations in genes necessary for cytotoxicity) or NLRC4-MAS is striking.

In that context, Schulert and Canna (10) dissect the pathogenic connections between the cytotoxic defects that cause FHLH and the constitutive NLRC4 activation that leads to high serum IL-18 levels, and the development of MAS. They debate the contributions of cytotoxic dysfunction (exemplified by loss-of-function mutations in patients with FHLH) and dysregulated signaling of IL-1 family members (particularly IL-18) in the development of hyperinflammation, hyperferritinemia and hemophagocytosis. Further focusing the debate on hyperferritinemia, Kernan and Carcillo (11) take on an area that is not well understood—the role of hyperferritinemia during systemic inflammation in patients with SIRS. Both reviews discuss the growing body of evidence that links autoinflammation and hyperinflammation with deadly hyperferritinemic disorders—MAS and FHLH.

Lastly, conditions with chronic granulomatous tissue inflammation indicate yet another form of macrophage dysfunction with no pathomechanism that can yet be therapeutically targeted. Non-infectious granulomas are seen in the context of autoinflammatory diseases caused by mutations in *NOD2*, *PLCG2* and *LACC1* that cause Blau syndrome, PLAID/APLAID (PLCG2 related antibody deficiency with immune dysregulation/autoinflammation PLCG2 related antibody deficiency with immune dysregulation) and a form of monogenic Still's disease with potentially granulomatous bowel inflammation, respectively. These diseases may provide models to study the development of autoinflammatory granulomatous disorders. Szymanski and Ombrello (12) examine these complex diseases in which granuloma formation and autoinflammation co-occur, and contrast these with conditions where granulomatous processes are thought to represent the attempt of macrophages to sequester infectious organisms including bacteria and fungi. Furthermore, they point to the interconnection of laccase and NOD2 in macrophage activation and a role for PLCG2 in B cell, mast cell and monocyte/macrophage activation. These conditions caused by mutations in *NOD2*, *PLCG2* and *LACC1* remain difficult to treat and examining the underlying pathogenesis may shed light on the perplexing intersection of granulomas and autoinflammation.

Like the landmark discoveries propelling this field, these reviews are meant to stimulate the integration of historically disparate inflammatory conditions, with the hope that the ideas and insights gained so far will inspire investigators in uncovering the mysteries that are hidden in these important new areas of autoinflammation.

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