Genomics, Biology, and Human Illness

Advances in the Monogenic Autoinflammatory Diseases

Hirotsugu Oda, MD, PhD[a,b,*], Daniel L. Kastner, MD, PhD[c]

KEYWORDS

- Haploinsufficiency of A20 (HA20) • Otulipenia • Deficiency of ADA2 (DADA2)
- Interferonopathy • CANDLE/PRAAS • SAVI • NLRC4 inflammasome
- Pyrin inflammasome

KEY POINTS

- Two deubiquitinase (DUB) deficiencies, haploinsufficiency of A20 (HA20) and otulipenia, derive from the impairment of the negative regulation in immune signaling.
- Deficiency of adenosine deaminase 2 (DADA2) results in clinical manifestations, including recurrent lacunar strokes, polyarteritis nodosa (PAN)-like vasculitis, hypogammaglobulinemia, Diamond-Blackfan anemia, and bone marrow failure.
- Stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) is characterized by severe dermatologic and pulmonary lesions.
- Clinical features of NLRC4-related autoinflammatory syndromes vary from cold-induced fever to chronic central nervous system inflammation or macrophage activation syndrome (MAS).
- RhoA GTPase suppresses the pyrin inflammasome by stimulating pyrin phosphorylation, which in turn favors the binding of inhibitory 14-3-3 proteins to pyrin. Certain bacterial toxins inactivate RhoA and thereby derepress the pyrin inflammasome. Mutations in *MEFV*, encoding pyrin, and *MVK*, encoding mevalonate kinase, predispose to autoinflammatory disease (AID) by decreasing 14-3-3 interaction with pyrin.

Disclosure Statement: This work is supported by the Intramural Research Program of the NHGRI, and Dr H. Oda is supported by JSPS Postdoctoral Fellowships for Research Abroad.
[a] Inflammatory Disease Section, Intramural Research Program, Metabolic, Cardiovascular and Inflammatory Disease Genomics Branch, National Human Genome Research Institute, National Institutes of Health, Building 10, Room B3-4129, Bethesda, MD 20892, USA; [b] Department of Pediatrics, Kitano Hospital, Tazuke Kofukai Medical Research Institute, 2-4-20, Ohgimachi, Kita-ku, Osaka 530-8480, Japan; [c] Inflammatory Disease Section, Intramural Research Program, Metabolic, Cardiovascular and Inflammatory Disease Genomics Branch, National Human Genome Research Institute, National Institutes of Health, Building 50, Room 5222, Bethesda, MD 20892, USA
* Corresponding author.
E-mail address: hirotsugu.oda@nih.gov

Rheum Dis Clin N Am 43 (2017) 327–345
http://dx.doi.org/10.1016/j.rdc.2017.04.011
0889-857X/17/Published by Elsevier Inc.
rheumatic.theclinics.com

INTRODUCTION

Autoinflammatory diseases (AID) are a group of disorders characterized by seemingly unprovoked inflammation that may be recurrent or sometimes nearly continuous. The term, *autoinflammatory*, first appeared in the literature in 1999 to describe 2 monogenic disorders with recurrent fevers and episodes of systemic inflammation without high-titer autoantibodies or antigen-specific T cells: familial Mediterranean fever (FMF) and the then newly described TNF receptor–associated periodic syndrome.[1] At present more than 20 monogenic AID have been reported. The clinical manifestations of AID are typically driven by genetically determined dysregulation of innate immunity, which results in overproduction of inflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-18, tumor necrosis factor (TNF), and type I interferon (IFN). Specific treatments targeting these cytokine signaling pathways have proved effective in many AID patients, highlighting the importance of accurate genetic diagnosis and detailed molecular pathophysiology.

This article reviews some of the recent advances in the field of AID over the past 3 years, including the discovery of several newly identified monogenic disorders (**Table 1**). It also focuses on recent insights into the pathogenesis of FMF to demonstrate how genetics and basic biology have synergized to demystify one important mechanism of host-pathogen interaction.

THE DEUBIQUITINASE DEFICIENCIES

NF-κB denotes a group of transcription factors that regulate the expression of genes involved in the cell cycle, immune response, differentiation, and DNA repair. This signaling pathway is in part regulated by ubiquitination, a protein post-transcriptional modification process.[2,3] The DUBs are a group of enzymes that specifically remove ubiquitin (Ub) moieties from target proteins, and their dysregulation has been reported to result in various human diseases.[4] Several DUBs, including A20, CYLD, OTULIN, and OTUD7B (Cezanne), act as negative regulators of NF-κB signaling.[2] Prior to 2016, CYLD was the only DUB for which germline mutations had been implicated in a Mendelian human disease.[5]

Haploinsufficiency of A20

A20 is a DUB that plays a key inhibitory role in the NF-κB proinflammatory pathway. The inhibitory function of A20 is coordinately effected by its N-terminal ovarian tumor (OTU) domain-mediated DUB activity and by its C-terminal zinc finger-mediated E3 Ub ligase activity. Thus, A20 removes lysine 63 (K63)-linked Ub chains from proinflammatory signaling complexes, leading to their disassembly, and then conjugates the constituent proteins with lysine 48 (K48)-linked Ub chains, marking them for proteasomal degradation. Hence, the net effect of A20 is anti-inflammatory and a deficiency of A20 is predicted to cause unchecked inflammation.

In 2016, Zhou and colleagues[6] reported 6 families with dominantly inherited truncating mutations in the *TNFAIP3* gene, which encodes A20. Clinical manifestations included early-onset fevers, arthralgia, oral and genital ulcers, and ocular inflammation, in some cases resembling Behçet disease. Five of the mutations were in the OTU domain, whereas 1 was in a zinc finger domain. Mutant A20 demonstrated no inhibitory effect on the NF-κB pathway, whereas a mixture of wild-type and mutant A20 had substantial inhibitory activity, suggesting that the mutant proteins are likely to act through haploinsufficiency rather than a dominant-negative effect. In vitro reconstitution experiments showed accumulation of K63-Ub on RIPK1, one of the A20 substrates, an effect that was also confirmed in patients' cells. Patients'