IgNS Immunoglobulin National Society

CLINICAL UPDATE

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Beyond Infection: The Realities of Primary Immunodeficiency

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Autoinflammatory Disorders

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OBJECTIVES

1. **Define autoinflammatory disorders**
2. **Appreciate the role of phenotyping and family history in the diagnosis of autoinflammatory disease**
3. **Describe the basis of inflammasome-mediated inflammation**
4. **Describe the role of cytokine-targeting biologics as therapy for these disorders**

Introduction: Genotype-phenotype correlation and rare diseases

Patients with immunologic diseases have provided clues that have led to a better understanding of immunology, often through the discovery of single gene mutations that have redefined the extremes of immunity.[1] Patients with primary immunodeficiency, for example, have defects in the immune defenses that protect the host. Often presenting in the first few years of life with severe infections, these genetically-defined disorders include severe combined immunodeficiency (SCID), phagocytic disorders such as chronic granulomatous disease and Mendelian susceptibility to mycobacterial disease (MSMD), and humoral defects such as X-linked agammaglobulinemia.[2,3] Other patients with syndromes such as autoimmune lymphoproliferative syndrome and syndrome of autoimmune polyglandular endocrinopathy with candidiasis and ectodermal dysplasia (APECED) have disease that is attributed to mutations in a single gene, yet have laboratory findings consistent with autoimmunity including high-titer autoantibodies, and antigen specific T cells (reviewed in Davidson and Diamond, 2001[4]). However, rare patients with episodic or chronic inflammation, in the absence of autoimmunity, and without evidence of infection, challenge this classic paradigm.[5] With symptoms driven by innate immune dysregulation, these patients have ultimately been labelled as having disorders of autoinflammation.[6]

Innate immunity and dysregulation

Traditionally considered "non-specific," it is now well-accepted that the innate immune system recognizes nearly 1000 conserved protein and nucleic acid patterns, leading to rapid immune responses against pathogens and metabolites. Pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide and peptidoglycan, are biochemically distinct from host proteins, and are identified by germline-encoded pattern recognition receptors, such as the toll-like receptors, RIG-like receptors, NOD-like receptors, and C-type lectin receptors (reviewed in Netea et al., 2011[7]). Similarly, damage-associated molecular patterns (DAMPs), such as ATP and uric acid, are upregulated in response to cell activation and cell death. This immune response is carefully coordinated for a rapid response to PAMP and DAMP danger signals.[7] A failure at any checkpoint in the system may lead to perpetuation of the innate immune response that could be damaging or even lethal to the host.

Three main principles underlie our understanding of immune dysregulation in autoinflammatory disease. First, an inborn error occurs in a component of the immune system. This leads to secretion of a predominant inflammatory mediator, and ultimately to disease presentation.[5,8] A number of different types of these inborn errors have been identified including those in intracellular sensors that lead to increased pattern recognition receptor function, errors in the cellular stress response that increase molecules that mediate intracellular stress, errors in negative regulator proteins that prevent inhibitor circuits, and those that enhance the signaling of innate immune cells.[8] Each of these pathways leads to an enhancement of the innate immune system inflammatory response, the auto-amplification loop known as autoinflammation.[6,8] The cases below serve to emphasize how the presentation of inflammatory symptoms can lead to a suspicion of these rare autoinflammatory disorders.

Case 1. Urticaria in infancy

The patient was a female infant who was the product of a di-zygotic twin pregnancy with no known complications.[9] The perinatal period was uneventful. The baby was in a normal state of health until 3 months of age, when she developed a raised, erythematous rash diagnosed as dermatographism. The rash resolved without medical intervention, but recurred at age 9 months, for which she was treated with antihistamines, as needed, for idiopathic urticaria. There were no known exposures, and intermittent therapy with antihistamines was successful. At 14 months of age, the patient developed an acute episode with prominent urticarial-like rash, 8 days of fever to a maximum temperature of 104.1°C, conjunctival infection, and irritability. She was admitted to a tertiary care children's hospital with a presumptive diagnosis of Kawasaki disease. Physical exam on admission was notable for a well-developed, well-nourished child with tachycardia, scattered lymphadenopathy, hepatosplenomegaly, and multiple erythematous, blanchable macules, and patches of an urticarial nature, mostly involving the face, torso, and extremities with relative sparing of the palms and soles. Clinical laboratory evaluation revealed elevated inflammatory markers, leukocytosis with neutrophilia, and thrombocytosis. Her infectious workup was negative and multiple echocardiograms were normal. Her fever and rash did not improve, despite high dose intravenous immunoglobulin (IVIG). A skin biopsy was performed which demonstrated a mixed perivascular inflammatory infiltrate comprised of lymphocytes, neutrophils, and rare eosinophils, without evidence for vasculitis, suggesting a diagnosis of cryopyrin-associated periodic syndrome (CAPS).[10]

Cryopyrin-associated periodic syndromes (CAPS)

Cryopyrin-associated periodic syndromes include a spectrum of autoinflammatory diseases caused by autosomal dominant mutations in *NLRP3* which encodes the NLRP3 protein.[11] Mutations in *NLRP3* lead to increased activity of the cryopyrin protein with over-production of the inflammatory mediator IL-1b.[12,13] The CAPS spectrum consists of familial cold autoinflammatory syndrome (FCAS) on the mild end,[10] Muckle-Wells syndrome as moderate disease,[14] and neonatal-onset multisystem inflammatory disease (NOMID) on the severe end.[15] Common symptoms include an urticaria-like rash, intermittent fevers, conjunctivitis, arthralgia, headache, and fatigue but certain

phenotypic features may suggest mild vs. moderate vs. severe disease.[16] Patients with the milder FCAS, tend to have 12-24 hour attacks, with urticaria-like rash, polyarthralgia, and conjunctivitis, often triggered by cold temperatures. The moderate Muckle-Wells syndrome episodes tend to be longer in duration (2-3 days) and have the addition of sensorineural deafness, often presenting in the second decade of life.[14] Finally, NOMID, also known as chronic infantile neurologic cutaneous articular (CINCA) syndrome, is characterized by continuous symptoms of fever, urticaria-like rash, uveitis with vision loss, sensorineural deafness, chronic aseptic meningitis, and epiphysial overgrowth. Despite the differences in severity, all result in activation of the NLRP3 sensor and release of IL-1b which drives the autoinflammatory loop.[16] Three different biologic therapies are currently available to treat patients with CAPS: a recombinant IL-1 receptor antagonist (anakinra [Kineret]), a fusion protein of IL-1 receptor and IL-1 receptor accessory protein (rilonacept [Arcalyst]), and a humanized monoclonal antibody to IL-1b (canakinumab [Ilaris]). For patients with CAPS, IL-1 blockade has consistently led to a reduction of symptomatic periods and inflammatory markers (reviewed in Booshehri and Hoffman, 2019[16]). In addition, early diagnosis and initiation of anti–IL-1 therapy has often shown substantial improvement in progressive and long-term complications of CAPS, including hearing loss and renal disease, as well as improvement in quality of life measures.[17,18]

Inflammasomes and the molecular mechanisms behind CAPS

NLRP3 is part of the NOD-like receptor (NLR) family of innate immune receptors. These proteins have a similar domain structure consisting of an effector, switch, and sensor domain.[19,20] Together, they act as intracellular sensors of pathogens and danger signals. In a two-signal process, cells respond to PAMPs or endogenous cytokines to increase transcription of pro-cytokine forms of IL-1b and IL-18, as well as the molecules of the inflammasome. The second signal, mediated by extracellular ATP, pore-forming toxins, or crystals (including urate, silica, asbestos, or cholesterol), leads to oligomerization of the NLRP3 sensor with an adaptor protein (ASC) and an enzyme effector (caspase-1) to form a multimeric cytosolic protein. This process ultimately leads to cleavage of caspase-1 which acts to cleave pro-cytokines to their mature, active forms.[12,13] In CAPS, a mutation in *NLRP3* results in inflammasome activation in the absence of the second signal.[21,22] However, the varied nature of the stimuli leading to activation of the NLRP3 inflammasome has led to implications for its involvement in numerous more chronic diseases including gout, pseudogout, asbestosis, silicosis, atherosclerosis, and type 2 diabetes (reviewed in Broderick et al., 2015[23]).

Since the identification of the NLRP3 inflammasome, several additional sensor proteins, including NLRP1, NLRC4, AIM2, and pyrin, and their associated inflammasomes, have been identified that respond to other innate immune pathways, though their triggers seem to be less varied than those for NLRP3. The NLRP1 inflammasome is activated by anthrax toxin. NLRC4 is triggered by type III/IV bacterial secretion systems and flagellin.[24,25] AIM2 senses cytoplasmic double-stranded DNA (of either host or microbial origin),[26] and the pyrin sensor detects Rho-GTPase modifications of host proteins mediated by bacterial toxins including *Clostridioides difficile*.[27] Subsequently, monogenic diseases have been linked to mutations in the genes for these sensors. NLRP1 variants have been linked to NLRP1-associated autoinflammation arthritis and dyskeratosis.[28] NLCR4 mutations are associated with macrophage activation syndrome and enterocolitis, as well as a CAPS-like disease,[24,25] and mutations in pyrin cause familial Mediterranean fever[29,30] and pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND).[31] A monogenic disease linked to variants in AIM2 has yet to be identified.

Case 2. Infant with prolonged fever

The patient was a 7-month-old female, ex-32-week di-zygotic twin admitted to a tertiary care children's hospital for 7 days of fever, diarrhea, emesis, and an erythematous papular rash on the torso, with no known ill contacts or travel.[32] Clinical laboratory evaluation was notable for elevated inflammatory markers, leukocytosis with neutrophilia, microcytic anemia, and thrombocytosis. Her infectious workup was negative. She was diagnosed with atypical Kawasaki disease as multiple echocardiograms demonstrated persistent borderline dilation of multiple coronary arteries despite treatment with high-dose IVIG and infliximab (Remicade, Inflectra, others).[33] During the course of her hospitalization, her fever curve was noted to be bimodal with persistent signs of systemic inflammation. Further inquiry into the family history revealed that her mother and maternal uncle had similar recurrent episodes of fever, arthritis, rash, serositis, and conjunctivitis since infancy, and were diagnosed with systemic juvenile arthritis. For them, several treatments were partially successful including etanercept (Enbrel) and anakinra, though infliximab caused severe disease flares in the mother. This new history was suggestive of an autosomal dominant autoinflammatory disease, most consistent with TNF-receptor associated periodic syndrome (TRAPS).[34,35]

In contrast to the inflammasomopathies, TRAPS is due to an accumulation of intracellular stressors which trigger pattern-recognition receptors. In TRAPS, autosomal dominant mutations in *TNFRSF1A* negatively affect the three-dimensional structure of the receptor. In the wild-type state, binding of TNF-α to the TNF receptor leads to inflammatory, apoptotic, and cellular regulation pathways. In TRAPS, the mutated protein has been proposed to result in decreased levels of circulating inhibitor soluble TNFR1, constitutive activation of the receptor, decreased TNF-mediated apoptosis, and intracellular oxidative stress due to misfolding of the receptor in the endoplasmic reticulum.[36-39] Resulting autoinflammatory flares may last from 5 days to several weeks, and may occur spontaneously or be triggered by a minor illness. Symptoms during acute attacks include fever, migrating myalgia, arthralgia or arthritis, centrifugal or urticaria-like rash, and serous membrane inflammation that manifests as chest and abdominal pain. Periorbital edema is also common and can be associated with uveitis or conjunctivitis.[34,35] The most severe complication of TRAPS is secondary AA amyloidosis with morbidity and mortality associated with nephrotic syndrome and renal failure, though other organ systems can be affected.[35,40] Treatment options include IL-1 blockade, such as anakinra, or canakinumab, as first-line therapy, though short-term glucocorticoids, with or without nonsteroidal anti-inflammatory drugs, or anti-TNF therapy with etanercept, have also been attempted.[18]

Summary

Studies in single patients, such as the cases highlighted above, have paved the way for the establishment of a causal relationship between genotype and phenotype in autoinflammatory disease.[1] Since the identification of *MEFV* and *NLRP3* in the late 1990s, more than 30 genes have been discovered as the underlying etiology behind autoinflammatory disorders, with significant benefit from increasing access to next-generation sequencing. These disorders cover all aspects of genetics from dominant to recessive inheritance, X-linked, and somatic mosaicism.[41] Understanding of the molecular pathways underlying these diseases has allowed for the creation of sub-categories of autoinflammatory disease including IL-1-mediated autoinflammatory diseases, interferon-mediated autoinflammatory diseases, autoinflammatory diseases caused by increased NF-κB signaling, and autoinflammatory diseases caused by persistent macrophage activation.[5,8] Still, a substantial portion of patients remain unclassified.[42,43] The cases above illustrate how careful clinical phenotyping and molecular genetic evaluations can guide the clinician towards an autoinflammatory diagnosis and targeted therapy.

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