Autoinflammation and autoimmunity in systemic juvenile idiopathic arthritis

Peter A. Nigrovic[a,b,1]

[a]*Division of Rheumatology, Immunology, and Allergy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115; and* [b]*Division of Immunology, Department of Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115*

Juvenile idiopathic arthritis (JIA) encompasses a range of phenotypes of joint inflammation that begin in childhood. The most distinctive and potentially most severe of these is systemic JIA (sJIA), an intensely inflammatory disease characterized by high spiking fevers and evanescent rashes that sometimes progresses to a devastating chronic polyarthritis. In PNAS, Ombrello et al. establish an unequivocal genetic association between sJIA and the major histocompatibility (MHC) region, in particular with the class II allele *HLA-DRB1*11* (1). This is a big deal. Let's consider why.

Autoinflammation and Autoimmunity

Over the last 15 y, it has become evident that there are multiple ways that the immune system can misfire to cause disease. The best recognized of these is termed "autoimmunity," wherein the immune system errantly targets self-antigens as though they were foreign. However, in some cases no autoantigen is involved, and the immune system initiates an inflammatory response because of a defect in normal self-inhibitory mechanisms. This family of disorders is termed "autoinflammatory" and is exemplified by diseases such as familial Mediterranean fever. At a first approximation, autoimmune diseases can be thought of as errors of adaptive immunity (mistakes by antigen-specific T and B cells), whereas autoinflammatory diseases arise through defects in hard-wired pathways typically associated with innate immunity.

These two broad categories of immune-mediated disease exhibit characteristic hallmarks. Autoimmune diseases are usually more prevalent in females, feature circulating autoantibodies, and display genetic linkage to specific MHC I and II alleles required for antigen presentation. Fever, if it occurs, is rarely a dominant feature of the presentation. Autoimmunity in its usual polygenic forms is also rare in the first year of life. In contrast, autoinflammatory diseases typically exhibit an even ratio of males to females and are free of autoantibodies or MHC I/II associations because immune tolerance is intact. Fevers and rashes are common presenting features and the most severe forms present early in life, reflecting the fundamental impact of defective immune "brakes." In many autoinflammatory conditions, IL-1 antagonism results in dramatic improvement, whereas such treatment is at best modestly effective in autoimmune diseases.

So where does sJIA fit on this spectrum? Most rheumatologic diseases are more prevalent in females, but sJIA affects boys approximately as often as girls. Autoantibodies have not been identified. sJIA is the only form of childhood arthritis to occur with any frequency in the first year of life. Fevers and rashes are florid. Finally, sJIA can respond dramatically to blockade of IL-1 (and IL-6, which is both induced by and induces IL-1). In common with some autoinflammatory conditions, circulating levels of IL-18 can be extreme. It is therefore not surprising that sJIA is often grouped with the autoinflammatory diseases.

Ombrello et al. establish an unequivocal genetic association between sJIA and the major histocompatibility (MHC) region, in particular with the class II allele HLA-DRB1*11.

sJIA and the MHC

Enter Ombrello et al. (1). The association of sJIA with the MHC has been explored previously, but the small size of earlier series and the inconsistency of their results have left the impression that—like any self-respecting autoinflammatory disease—sJIA is free of MHC linkage. The present investigators demonstrate otherwise. Gathering together almost 1,000 cases and over 8,000 controls, and using strict criteria to avoid artifacts resulting from divergent genetic backgrounds, Ombrello et al. (1) show that sJIA is linked to a specific MHC II haplotype. In particular, the authors identify a strong association with two specific alleles of *HLA-DRB1*11* (odds ratio 2.3). Using an imputation strategy pioneered by Raychaudhuri et al. (2), Ombrello et al. (1) implicate a specific amino acid, glutamate 68 (glut68), as the most important carrier of risk, although they are unable to exclude a role for closely linked amino acids.

On its face, this finding throws a monkey wrench into the characterization of sJIA as an autoinflammatory disease. MHC linkage implies a role for T cells, because presenting antigen to $CD4^+$ T cells is after all what MHC II does for a living. What are we to make of the fact that sJIA looks in so many ways like an autoinflammatory disease, and yet is clearly linked to the MHC?

The answer is likely complicated, and it's safe to say that we don't know yet. Ombrello et al. (1) raise the interesting hypothesis that the MHC may act not as an antigen-presenting molecule but as a direct activator of macrophages, dendritic cells, and other MHC II-expressing lineages. This hypothesis preserves sJIA as a pure autoinflammatory disease, with no role for antigen-specific T cells. Indeed, it is intriguing that—unlike rheumatoid arthritis-associated MHC II amino acids—glut68 is situated outside the antigen binding groove. This localization should exclude glut68 from a direct role in antigen selection, although it could presumably still alter the spatial conformation of the groove or otherwise modulate the interaction between the MHC and the T-cell receptor. Furthermore, close linkage raises the possibility that amino acids in the antigen-presenting groove may still play key roles. However, as Ombrello et al. (1) point out, there is well-established precedent for

Author contributions: P.A.N. wrote the paper.

Conflict of interest statement: P.A.N. is supported by the Rheumatology Research Foundation, the National Institute of Arthritis, Musculoskeletal and Skin Disease (NIAMS), investigator-initiated research grants from Novartis, Inc., and Sobi, Inc., and the Fundación Bechara. He has received consulting fees from Alkermes, Genentech, Novartis, Novo Nordisk, and Sobi.

See companion article on page 15970.

[1]Email: pnigrovic@partners.org.

cell activation via the MHC, and MHC II-mediated cell activation by staphylococcal enterotoxins can exhibit allele specificity (3).

However, the more straightforward interpretation of an MHC II association runs through antigen presentation. This would seem especially likely here because *HLA-DRB1*11* is linked not only with sJIA but also two other forms of childhood arthritis, oligoarticular and seronegative polyarticular JIA (4, 5). The plausibility of the T-cell alternative is enhanced by several interesting aspects of the sJIA phenotype. First, familial sJIA is extraordinarily rare. Second, whereas sJIA occurs in infancy, it is exceptionally rare in early infancy (first 6 mo of life), unlike many other autoinflammatory syndromes. Third, as Ombrello et al. (1) note, T-cell skewing toward Th17 cells has been observed in sJIA patients, whereas blockade of T-cell costimulation is anecdotally of some therapeutic value. Fourth, unlike other autoinflammatory diseases, sJIA is often self-limited. Between one-third and one-half of patients experience what is termed "monophasic sJIA," defined as a single episode of sJIA that resolves within 24 mo (6), a phenotype that could potentially reflect restoration of immune tolerance. Finally, sJIA typically evolves in phases. In many patients, overt systemic features (fevers and rashes) fade over time, leaving behind a chronic and sometimes intractable arthritis. IL-1 blockade is remarkably effective in the acute phase, leading to complete remission in greater than 50% of patients, but treatment efficacy is much more modest in chronic arthritis (7–9).

A further wrinkle in the sJIA story arises through the interesting association of sJIA with episodes of explosive inflammation, termed macrophage activation syndrome (MAS). MAS affects 10–20% of patients with sJIA, typically early in the disease course. Clinical features of this "cytokine storm" include persistent fever, disseminated intravascular coagulation, and multisystem end-organ dysfunction; hemophagocytosis is often noted on bone marrow biopsy. MAS mimics the phenotype observed in patients with congenital defects in perforin/granzyme-mediated cell–cell killing, a group of diseases termed familial hemophagocytic lymphohistiocytosis (FHL). Many patients with sJIA and MAS exhibit mutations in FHL-associated genes, implicating impaired cytotoxicity—involved both in downregulating immune responses and in combating viral infections—in sJIA-associated MAS. Indeed, impaired natural killer cell function and "subclinical MAS" are very common in active sJIA, suggesting that related control defects represent a broad underlying theme of sJIA pathogenesis (10).

The Biphasic Hypothesis

How can we harmonize the findings of Ombrello et al. (1) with these clinical and mechanistic observations? One potential solution is that mechanisms of disease onset may be distinct from mechanisms driving disease chronicity (11). According to the so-called "biphasic hypothesis," sJIA begins as a syndrome of immune dysregulation manifesting as elevated levels of cytokines, such as IL-1. This autoinflammatory-like cytokine milieu skews the T-cell effector/regulatory balance, promoting development of a population of pathogenic lymphocytes responsible for chronic arthritis. This hypothesis is suggested by the surprisingly central role of T cells (including γδ cells) in arthritis resulting from IL-1 receptor agonist (IL-1ra) deficiency in mice (12, 13). Genetic or acquired impairment in cell–cell killing, perhaps exposed by intercurrent infection, could drive the initial inflammatory episode. Hypothetically, defective killing might also set the stage for disease chronicity by impairing elimination of autoreactive T cells. In this way, impaired cytotoxicity could give rise to episodes of uncontrolled inflammation and promote a T-cell–dependent chronic inflammatory disease (although this latter step is so far unsupported by clinical evidence and is not known to be required in IL-1ra$^{-/-}$ mice).

The biphasic hypothesis makes specific predictions. The most evident is that the MHC association should be stronger in sJIA patients who develop chronic arthritis than in those without, a possibility not tested in the present work. T-cell skewing and other features of autoimmunity (such as clonal expansion, and potentially even autoantibodies) should characterize chronic arthritis more than new-onset disease. Most importantly, early effective cytokine blockade should dramatically abrogate the development of chronic arthritis, a possibility suggested by observational series but not yet confirmed in clinical trials. It is important to note that many sJIA patients have no identified genetic defects in cell–cell killing, although functional impairment in cytotoxic cell function is common, at least in the acute phase. Some patients respond incompletely to IL-1 in early disease, whereas others exhibit excellent responses even years into the disease course. These differences may well reflect pathogenic heterogeneity, although the extent and importance of pathophysiological differences among sJIA patients remain to be defined (14, 15).

The findings of Ombrello et al. (1) are therefore a big deal because they force a reexamination of the increasingly prevalent assumption that sJIA is an autoinflammatory disease. More clues will likely emerge as further results from the authors' genome-wide association study become available.

More generally, the present study provides an occasion to reflect on immune-mediated pathology. The distinction between autoimmunity and autoinflammation is not black and white. For example, patients with familial Mediterranean fever show an enhanced prevalence and severity of many rheumatologic diseases, potentially reflecting amplification of inflammation originating with a slip in immune tolerance. Indeed, many inflammatory diseases are likely somewhere on the spectrum between purely autoimmune and purely autoinflammatory (16). The paper by Ombrello et al. (1) helps to situate sJIA in this continuum, and supports speculation that sJIA may exemplify a new mode of pathogenesis: an autoinflammatory process begetting an autoimmune disease.

1 Ombrello MJ, et al. (2015) *HLA-DRB1*11* and variants of the MHC class II locus are strong risk factors for systemic juvenile idiopathic arthritis. *Proc Natl Acad Sci USA* 112:15970–15975.
2 Raychaudhuri S, et al. (2012) Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. *Nat Genet* 44(3):291–296.
3 Scholl PR, et al. (1990) Effect of isotypes and allelic polymorphism on the binding of staphylococcal exotoxins to MHC class II molecules. *J Immunol* 144(1):226–230.
4 Thomson W, et al.; British Paediatric Rheumatology Study Group (2002) Juvenile idiopathic arthritis classified by the ILAR criteria: HLA associations in UK patients. *Rheumatology (Oxford)* 41(10): 1183–1189.
5 Hollenbach JA, et al. (2010) Juvenile idiopathic arthritis and HLA class I and class II interactions and age-at-onset effects. *Arthritis Rheum* 62(6):1781–1791.
6 Singh-Grewal D, Schneider R, Bayer N, Feldman BM (2006) Predictors of disease course and remission in systemic juvenile idiopathic arthritis: Significance of early clinical and laboratory features. *Arthritis Rheum* 54(5):1595–1601.
7 Nigrovic PA, et al. (2011) Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. *Arthritis Rheum* 63(2):545–555.
8 Vastert SJ, et al. (2014) Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: Results of a prospective cohort study. *Arthritis Rheumatol* 66(4):1034–1043.
9 Quartier P, et al. (2011) A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis* 70(5):747–754.
10 Mellins ED, Macaubas C, Grom AA (2011) Pathogenesis of systemic juvenile idiopathic arthritis: Some answers, more questions. *Nat Rev Rheumatol* 7(7):416–426.
11 Nigrovic PA (2014) Review: Is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? *Arthritis Rheumatol* 66(6):1405–1413.
12 Horai R, et al. (2004) TNF-alpha is crucial for the development of autoimmune arthritis in IL-1 receptor antagonist-deficient mice. *J Clin Invest* 114(11):1603–1611.
13 Akitsu A, et al. (2015) IL-1 receptor antagonist-deficient mice develop autoimmune arthritis due to intrinsic activation of IL-17-producing CCR2(+)Vγ6(+)γδ T cells. *Nat Commun* 6:7464.
14 Gattorno M, et al. (2008) The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum* 58(5): 1505–1515.
15 Shimizu M, Nakagishi Y, Yachie A (2013) Distinct subsets of patients with systemic juvenile idiopathic arthritis based on their cytokine profiles. *Cytokine* 61(2):345–348.
16 McGonagle D, McDermott MF (2006) A proposed classification of the immunological diseases. *PLoS Med* 3(8):e297.