Commentary

Innate Immunity as a Hired Gun: But Is It Rheumatoid Arthritis?

Maripat Corr and Gary S. Firestein

Division of Rheumatology, Allergy, and Immunology, University of California, San Diego, La Jolla, CA 92093

Inflammatory forms of arthritis such as rheumatoid arthritis (RA) are chronic diseases that primarily affect peripheral synovial joints. The pathogenesis of RA is multifactorial, including genetic influences on susceptibility, postnatal events in immune maturation, environmental factors, and amplifying cytokine networks that perpetuate inflammation (1). Many elegant models of transgenic and gene disrupted mice provide insight into the pathogenic mechanisms of these diseases. Some of these models such as the K/BxN, TNFα transgenic, IL-1 receptor antagonist deficient, and human T lymphotropic virus type I (HTLV-I) tax transgenic mice develop spontaneous disease. Other models rely on the induction of disease by collagen inoculation in DBA/J or humanized HLA transgenic mice, direct intraarticular antigen or oligonucleotide administration, injection with bacterial cell walls, or by creating immune complexes. The panoply of pathogenic mechanisms illustrates the wide variety of initiating circumstances that can ultimately lead to joint damage. In each case, the final common pathway, i.e., synovial inflammation and joint destruction, resembles RA. However, RA is a complex, heterogeneous disease and the limitations of each animal model should be recognized.

Recently, one model has attracted particular interest, the K/BxN model, wherein spontaneous arthritis occurs in mice that express both the transgene encoded KRN T cell receptor and the IAg^7 MHC class II allele (2, 3). These transgenic T cells have specificity for a self-peptide derived from the glycolytic enzyme glucose-6-phosphate isomerase (G6PI) and are able to breach tolerance in the B cell compartment resulting in the production of autoantibodies to the same antigen (4, 5). Affinity-purified anti–G6PI Ig from these mice can transfer joint specific inflammation to healthy recipients (4). The mechanism for joint-specific disease arising from autoimmunity to a ubiquitous autoantigen has been puzzling. In a rapid succession of articles, including one in this issue, some of the mechanisms of this model are revealed. G6PI bound to the surface of cartilage might be the target for immunoglobulin binding and sub-

sequent complement–mediated damage (6). Antibodies of the IgG1 isotype are predominantly responsible for this disease, but monoclonal antibodies can only transfer disease in pairs that bind to separate epitopes (7). In further experiments, free Ig transferred paw swelling more efficiently than fractions of preformed immune complexes (6). However, the dependence of the arthritis on Fc receptors and the alternative complement pathway suggests that immune complexes either form on the cartilage surface as an array or in the circulation (8–10). Using various knockout mice, some of the genes required for induction of joint inflammation and destruction induced by anti-G6PI antibodies have been determined (Table I). In this model the inciting event is the expression of an autoreactive T cell receptor in the periphery; however, joint destruction is delegated by the adaptive response to innate immune mechanisms and can be transferred to animals that lack B and T cells (11). Hence, it is the reverse of the usual immune paradigm: adaptive immunity activates innate mechanisms rather than the reverse.

Now that the mechanisms of this model have been elegantly elaborated, it is important to ask how they relate to the uniquely human disease known as rheumatoid arthritis. Our scientific understanding of RA has evolved through many stages, beginning with the discovery of anti-Ig autoantibodies called rheumatoid factors over 50 yr ago. This led to the remarkable hypothesis in 1973 that RA represented an intraarticular immune complex disease mediated by complement activation (12). This notion subsequently fell into disfavor as antigen-specific T cell responses, both autoimmune and otherwise, held primacy. In 1990, we proposed that RA had a T cell–independent component based on its cytokine profile (13), and this hypothesis was recently updated and modified to incorporate the role of innate immunity, partial transformation of synovial fibroblasts, and antigen-independent T cell mechanisms (14). Although still controversial, this paradigm has been partially validated by the relative success of anti-cytokine approaches compared with anti-T cell therapy for RA.

The fortuitous discovery that K/BxN mice spontaneously develop arthritis after an initial T cell–dependent phase with a subsequent T cell–independent phase fits very well with this line of reasoning. As noted above, the pathogenesis of the model has been precisely defined and is due

Address correspondence to Maripat Corr, Division of Rheumatology, Allergy, and Immunology, University of California, San Diego, La Jolla, CA 92093-0663. Phone: 858-534-7817; Fax: 858-534-5399; E-mail: mcorr@ucsd.edu

Table I. *Responses in Mutant Mice to K/BxN Serum Transfer*

Disrupted gene	Disease severity	Reference
Rag-1	Similar to wild-type	(11)
CD40L	Similar to wild-type	(18)
TNFRp55/p75	Delayed disease onset	(18)
Inducible NO synthase 2	Similar to wild-type	(21)
gp91 (phox)	Similar to wild-type	(21)
TRANCE/RANKL	Protected from bone erosions	(22)
FCRγ	No inflammatory response	(9, 18)
FCγRI	Similar to wild-type	(9)
FCγRIIb	Similar to wild-type	(10)
FcγRIII	Weak inflammatory response	(9)
CLq or C4	Similar to wild-type	(8, 9)
C3 or factor B	Weak inflammatory response	(9)
C5 or C6	No inflammatory response	(9, 10)

to autoantibodies directed against a ubiquitous antigen that seems to be adherent to cartilage surfaces. The next question is "what does this have to do with rheumatoid arthritis"? The answer is not at all clear at this point.

While few would argue with the participation of immune complex–mediated inflammation in RA, it is quite relevant to question whether it is specific for the disease and whether it is a primary or a secondary phenomenon (15). Anti-G6PI antibodies are not necessarily specific for RA, and appear to be equally abundant in forms of arthritis with an entirely different pathogenesis, clinical course, and joint distribution like the spondyloarthropathies (16). The localization of G6PI protein in the rheumatoid joint is controversial, at times described in the synovial vasculature or on the surface of cartilage (6, 17). However, only a limited number of patients have been examined and we do not know if a similar distribution occurs in other inflammatory joint diseases. The lack of rheumatoid factors, a hallmark of RA, is also a major difference with the murine model (2).

Although no animal models are actually RA, they can help us understand normal inflammatory and immune responses or serve as vehicles to test therapeutic agents. It is not yet known whether the K/BxN model is superior, or even equivalent, to the ever-expanding universe of spontaneous and induced models (18, 19). As the basic mechanism of the K/BxN model appears to be immune complex formation on the surface of cartilage, it is very similar to collagen-induced arthritis (CIA). Indeed, passive CIA induced by a mixture of monoclonal antibodies that bind to the surface of cartilage and fix complement is readily induced and can, like the passive K/BxN model, be used to determine which genes play a critical role in joint destruction or inflammation (7, 20). Like anti-G6PI antibodies, anti-type II collagen antibodies can be detected in a subset of patients but are not specific for RA (15, 17). After years of study, most investigators believe that immune responses directed against type II collagen are a potential contributory factor to

the disease but not a primary mechanism. It remains to be seen if G6PI will merely join the growing list of autoantigens implicated in RA (e.g., other collagen types, gp39, proteoglycans, RA33, p205, and citrullinated proteins).

Perhaps the most interesting aspect of the K/BxN model is not the end stage involving relatively nonspecific mechanisms that may (or may not) be related to human disease; instead, the intriguing breakdown of tolerance that permits the formation of autoantibodies could be more relevant to RA as well as other autoimmune conditions. Of particular interest is how these adaptive immune responses, in turn, activate innate immunity as an effector mechanism that can inflame and damage target tissues. Careful dissection of this pathway, including the influence of the genetic background, can define mechanisms of proximal events rather than the undifferentiated final common pathway that is clinically defined as arthritis. Exploration of these mechanisms might provide important clues to etiology of self-directed adaptive responses.

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