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Review: Mechanisms of Autoimmune Disease Induction: The Role of the Immune Response to Microbial Pathogens
[Special Article]

Behar, Samuel M.; Porcelli, Steven A.

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Samuel M. Behar, MD, PhD, Steven A. Porcelli, MD: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Address reprint requests to Steven A. Porcelli, MD, Department of Rheumatology and Immunology, Room 508 Seeley G. Mudd Building, 250 Longwood Avenue, Boston, MA 02115.

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Outline

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Persistent antigens and persistent pathogens: the merging of infectious and autoimmune disease

The mechanisms discussed above consider the introduction of an infectious agent and the immune response to its antigens as a trigger for autoimmune diseases. However, also implicit in this model is the elimination of the infectious agent in the setting of continuing inflammatory disease. Thus, in true autoimmune disease, it is believed that the immune response is actually directed against self components, and that the continuing recognition of these self antigens accounts for the chronic phase of these diseases. However, a substantial number of situations have now been brought to light in which inflammatory disease believed to be autoimmune in nature may actually be caused by an immune response directed against nonviable but persistent microbial antigens present in the target tissues, or even against occult viable infectious organisms. Such situations blur the distinction between autoimmune and infectious diseases, and raise the possibility that some syndromes now classified as autoimmune diseases may be more correctly viewed as chronic infections.

Persistent microbial antigens. Persistence or repeated deposition of microbial antigens is a potential mechanism by which pathogenic organisms could cause chronic inflammatory disease. A possible example of this mechanism is the joint inflammation that is sometimes observed following nonarticular infections, and which has traditionally been classified as either postinfectious or reactive arthritis.

Postinfectious arthritis, which occurs during the acute phase of an infectious illness, is a noninfectious synovitis believed to be mediated primarily by deposition of foreign antigens in the form of immune complexes. Examples include the arthritis associated with acute hepatitis B ([25]), and the sterile joint effusions sometimes seen during acute disseminated infections with meningococci ([26]) or gonococci ([27]). In contrast, reactive arthritis occurs in a subset of patients several weeks after acute bacterial diarrhea (postenteric arthritis) ([28]) or urogenital infection with *Chlamydia trachomatis* (sexually acquired arthritis) ([29,30]). This is generally thought to occur after the clearance of infectious agents and their products, and is presumed to arise from an autoimmune mechanism such as molecular mimicry. However, recent improvements in our ability to detect the presence of microbes and their products have begun to erode the traditional distinction between postinfectious and reactive arthritis by suggesting that the latter may also result from the persistence of microbial products in the inflamed tissues.

The role of persistent microbial antigens in reactive arthritis has been extensively studied in a well-defined population of patients who developed articular symptoms following enteric infection by *Yersinia enterocolitica* ([31,32]). In two-thirds of these patients, *Yersinia* antigens are detected in 1–10% of synovial fluid (SF) cells (mostly neutrophils and some mononuclear cells) by immunofluorescence staining using a *Yersinia*-specific rabbit antiserum or a monoclonal antibody specific for a polysaccharide antigen of *Yersinia*, and these results are further supported by Western blot analysis ([31]). These studies have been confirmed by a second group of investigators who, using immunofluorescence, detected particles that were thought to represent *Yersinia*-derived antigens in the synovial membrane of 4 HLA-B27+ patients with *Yersinia*-triggered reactive arthritis ([32]). The antigens appear to be localized in the cytoplasm of large mononuclear cells, although the precise cell type has not been identified. Some of the biopsy specimens used in these studies were obtained long after the onset of arthritis (5 months to 17 years), indicating that these bacterial antigens can persist for extended periods of time ([31,32]). Although less well studied, similar findings have been reported in patients with reactive arthritis associated with other infectious agents. For example, *Salmonella* antigens have been detected in 10–50% of the SF cells from 8 HLA-B27+ patients with *Salmonella*-triggered reactive arthritis, in studies using rabbit antisera specific for *Salmonella* species and monoclonal antibodies specific for *Salmonella* lipopolysaccharide ([33]). *Chlamydia* antigens have also been detected in the SF and synovial tissue of patients with sexually acquired reactive arthritis and negative culture findings ([34,35]).

The detection of persistent *Yersinia* antigens in the synovium of patients with *Yersinia*-triggered reactive arthritis weeks, months, or even years after the sentinel enteric infection raises the possibility that a chronic infection by this organism has been established in the inflamed joints. This issue has been addressed in many of the above studies by performing cultures of SF or tissues, the results of which have proven to be uniformly negative. Furthermore, in studies using the polymerase chain reaction (PCR), bacterial DNA has been sought in SF and tissue as a surrogate marker for the presence of viable organisms. Although this method is exceedingly sensitive (DNA from as few as 10 bacteria per 10⁵ cells can be detected), no *Yersinia* DNA has been found in samples of SF or tissue, even when simultaneously performed immunofluorescence studies demonstrated *Yersinia* antigens in 1% of the SF cells ([36,37]). Similarly, despite the identification of immunoreactive antigens and particles thought to represent *Chlamydia*, PCR failed to detect chlamydial DNA in the SF of patients with sexually acquired reactive arthritis ([38]). Negative findings can never be viewed as conclusive, but the results of these experiments, together with the inability to culture the organisms, indicate that there may be persistent bacterial antigens within the joint in the absence of viable organisms.

The relevance of the detection of bacterial antigens in the joint to the development of chronic arthritis is unproven at this time. For example, it is not known if patients who recover from bacterial enteritis without developing arthritis also have bacterial antigens in their joints, or if the antigens that have been detected are present in a form that is recognized by the immune system. However, the possible significance of these findings has been highlighted recently by the isolation of T cell clones specific for *Yersinia* from the SF and tissue of patients with reactive arthritis. T cell clones from 1 patient recognized antigens from *Y. enterocolitica* and *Yersinia pseudotuberculosis*, but not other bacterial species ([39]). Such T cells presumably arose in vivo as a consequence of persistent stimulation by antigen in the joint. Interestingly, although the patient was HLA-B27+, these *Yersinia*-reactive T cells were CD4+ and restricted by HLA-DR4. More recently, CD8+ T cell clones have been derived from SF of several patients with *Yersinia*-triggered reactive arthritis. These T cells are restricted by HLA-B27 and lyse *Yersinia*-infected cells, but not cells that have been exposed to killed *Yersinia* organisms ([40]). This implies that active intracellular infection, and not simply phagocytosis of bacterial antigens, may be required for antigen presentation to HLA-B27-restricted T cells, as appears to be the case in general for T cells that recognize bacterial antigens in the context of class I MHC molecules ([41]).

Based on these preliminary findings, it can be speculated that HLA-B27 and other class I MHC molecules may be involved in the presentation of bacterial antigens to class I-restricted (i.e., predominantly CD8+) T cells during the initiation of reactive arthritis, when viable organisms are present within macrophages and possibly other types of cells. In contrast, during the chronic and relapsing phases of arthritis, which appear to be characterized by the presence of persistent bacterial antigens but no viable organisms, antigen presentation may be predominantly by class II MHC molecules with activation of CD4+ T cells. A true test of the validity of such a model awaits the detailed analysis of T cell clones isolated from the synovium of reactive arthritis patients at various times after the onset of their illness. This area of research could lead to new therapeutic strategies based on the elimination of either intracellular infections or persistent antigens, depending upon the stage of the disease ([42]). In this regard, differentiation between persistent antigens and chronic infections may be critical.

Persistent Pathogens: lessons from Lyme disease. Lyme arthritis provides an excellent example of how inflammatory arthritis with features suggesting an autoimmune pathogenesis can in fact be caused by an occult microbial pathogen. Many of the initial cases of Lyme disease were mistaken for juvenile rheumatoid arthritis before a series of landmark epidemiologic and laboratory investigations determined that the disease results from infection with the spirochete *Borrelia*

burgdorferi, which is transmitted by the bite of the deer tick *Ixodes dammini* (for review, see [43]). The many studies that have followed from this discovery have made Lyme disease perhaps the best example of a chronic arthritis with a known etiology. Arthritis occurs in approximately 60% of patients with untreated Lyme disease, and becomes chronic in 10% of cases, with erosions of cartilage and bone and synovial histopathologic features similar in many ways to those of RA ([44,45]).

In contrast to reactive arthritis, Lyme arthritis may be the result of an immune response in tissues that are persistently infected by viable, replicating microorganisms. Strong indirect evidence for this view is provided by the observation that treatment with antibiotics cures many cases of established Lyme arthritis, and prevents the development of this condition if given early after infection. More direct evidence for this hypothesis comes from silver staining of synovium from affected joints, which has revealed the presence of intact spirochetes ([46]). Antigens specific for *B burgdorferi* also have been detected in the synovium. In one report, synovial biopsy samples from 12 patients with chronic Lyme arthritis were investigated by immunohistochemistry ([45]). Monoclonal antibodies specific for the *B burgdorferi* 31-kd outer membrane polypeptide and the 41-kd flagellar antigen detected spirochetes and globular antigen deposits in and around blood vessels in areas of lymphocytic infiltration in 50% of biopsy specimens. Nevertheless, it has proven difficult to culture the organisms from synovial specimens, and relatively few instances of successful isolation of *B burgdorferi* have been reported ([47–49]).

Recent application of detection methods based on PCR now provides strong additional support for the presence of intact viable *B burgdorferi* in the joints during chronic Lyme arthritis. Using a nested PCR technique with which DNA can be detected from as few as 10 spirochetes in 1 ml of fluid ([50–53]), *B burgdorferi* DNA has been detected in most synovial specimens. In one of the largest reported series, PCR was performed on 92 SF samples from 88 patients with Lyme arthritis and 64 controls with other articular diseases, using primers specific for the plasmid-encoded *Osp A* gene and the genomic 16S ribosomal RNA gene of *B burgdorferi* ([52]). Seventy-five of the patients with Lyme arthritis had a positive PCR result, whereas all of the controls had negative results. Of the 73 patients who had not been treated or had received only short courses of oral antibiotics, 96% had a positive PCR reaction. In contrast, only 37% of the 19 patients who had received appropriate antispirochetal antibiotic treatment had a positive PCR reaction. Remarkably, DNA from *B burgdorferi* was detected by PCR in 12 untreated patients up to 7 years after the onset of arthritis.

The detection of pathogen-specific DNA sequences at the site of inflammation in chronic Lyme arthritis stands in marked contrast to the results reported for patients with reactive arthritis associated with *Yersinia* and *Chlamydia* species, as described above. Although it may be

an immune response to bacterial antigens that gives rise to chronic inflammation in all of these diseases, it appears that in the case of Lyme arthritis this process is usually sustained by the persistence of living microorganisms, and not by the failure to clear nonviable antigenic material from the synovium. However, it may also be that both of these mechanisms are operating in some cases. For example, of 10 patients who had chronic Lyme arthritis despite multiple courses of antibiotics, 7 had no *B burgdorferi* DNA detected by PCR in posttreatment synovial samples ([52]), indicating that chronic arthritis may continue even after the eradication of viable spirochetes. An immunogenetic basis for this is likely, since certain class II MHC alleles (HLA-DR2 or HLA-DR4) are found with increased frequency in patients with chronic Lyme arthritis compared with patients with Lyme arthritis of short duration ([54]). However, it is not yet known if these patients harbor persistent *B burgdorferi* antigens in their joints in the absence of viable spirochetes.

These studies of Lyme disease have increased the need to consider persistent infection by slow-growing or fastidious bacterial pathogens as an etiology for idiopathic diseases with autoimmune features. A variety of other conditions have already been suggested to belong in this category, although in few of these is the evidence for a bacterial etiology anywhere near as convincing as for Lyme disease ([55-61]). Nonetheless, this concept has obvious clinical importance since, if correct, it would mandate that treatment strategies shift away from the use of immunosuppressive agents and toward the development of long-term antibiotic treatments, vaccines, and immunotherapy,