Commentary

Joint-specific and systemic autoreactivity in the development of inflammatory arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory disease with a prevalence of approximately 1%. RA primarily affects peripheral joints, where an inflammatory synovitis may result in cartilage destruction, bone erosion, and ultimately joint deformity and loss of joint function. The aetiology of RA is unknown and the pathogenesis is only poorly understood [1]. What is known is that certain major histocompatibility complex (MHC) class II genes, in particular those encoding the β-chain of the DR1 and DR4 molecules, confer inherited susceptibility to RA [2]. The MHC association strongly suggest that RA is an autoimmune T-cell dependent disorder, in which the disease-associated MHC class II molecules present autoantigenic peptides to autoreactive T cells, that in turn mediate the inflammatory process. The identity of the MHC class II bound autoantigen(s) in RA is unknown, but collagen type II (CII) has been a candidate primarily because it is the major protein component of articular cartilage and because it can induce arthritis in nonhumanized and humanized animal models of RA [3]. The involvement of CII in RA has, however, had a rather chequered history. Although there is now general consensus that humoral immunity to CII is associated with RA, it has been much more difficult to establish a direct role for CII-reactive T cells in the pathogenesis of RA (for example, see [4,5]). Moreover, treatment of RA patients with oral CII has not been as successful as expected on the basis of results obtained from similar trials in collagen-induced arthritis in animals [6].

Reported in this issue of *Arthritis Research*, Berg *et al* [7] have now reinvestigated T-cell reactivity to CII in RA patients and in healthy control individuals, and have correlated their findings to human leucocyte antigen (HLA) class II type and anti-CII antibody levels in serum. To study the *in vitro* T-cell response to CII, Berg *et al* measured interferon-γ production rather than T-cell proliferation after CII stimulation of peripheral blood mononuclear cells. This choice was based on a recent animal study [8] in which it was suggested that CII is physiologically exposed to the immune system, but only induces incomplete tolerization and/or elimination of responding T cells because of its restricted tissue expression. As a result, CII-reactive T cells do not proliferate or proliferate only little, but secrete cytokines when they are stimulated *in vitro*.

Berg *et al* [7] found no difference in the interferon-γ response to CII between RA patients and the control group. In contrast, there was a clear difference between these two groups in their interferon-γ responses to two standard recall antigens (purified protein derivative and killed influenza virus). Although the control group responded well to the two antigens, the RA patients did not, which may indicate that the RA patients have a general T-cell hyporesponsiveness.

The basis of this apparently depressed T-cell function is unknown, but has also been noted in earlier studies. Berg *et al* speculated that it might further complicate the detection of a RA-associated T-cell response to CII, and re-evaluated their data after they had compensated for the low T-cell responsiveness by using the T-cell responses to the standard recall antigens as references. Interestingly, the compensated interferon-γ response to CII was significantly higher in the RA group than in the control group, and was highest in the group of patients carrying RA-associated HLA class II alleles. When the authors compared the serum levels of anti-CII antibodies with the interferon-γ response to CII they found an inverse correlation. This

CII = collagen type II; GPI = glucose-6-phosphate isomerase; HLA = human leucocyte antigen; MHC = major histocompatibility complex; RA = rheumatoid arthritis; TCR = T-cell receptor.

observation was unexplained, but has also been noted in a recent analogous study by Kim *et al* [9]. In that study, the T-cell proliferative response to CII in peripheral blood and synovial fluid was also analyzed. Even though the proliferative responses to CII were only modest, and thus underscoring the point made by Berg *et al*, they were found to be higher in RA patients than in osteoarthritis patients and healthy control individuals. In the RA patients, the T-cell responses to CII were higher and more frequent in synovial fluid cells than in peripheral blood cells and were also higher in early RA patients than in late RA patients. Kim *et al* [9] also found that the T-cell proliferative response to a CII-derived peptide corresponding to residues 255–274 was enhanced in RA patients and correlated well with that to CII. This information is important because it has been demonstrated, by using a humanized mouse model for RA, that the DR4-restricted immunodominant T-cell epitope in CII corresponds to amino acids 261–273 [10]. This is interesting because this epitope fits the motif for peptides binding RA-associated DR molecules [11]. Kim *et al* [9] thus established that this epitope is also relevant to RA.

Taken together, the studies by Berg *et al* [7] and Kim *et al* [9] demonstrate how difficult it is to study T-cell responses to CII, but also that it is possible. It should now be possible to analyze the T-cell response to CII and other candidate autoantigens in more detail. From a mouse model of RA, it is known that post-translational modifications, such as glycosylation, of CII is of importance in the development of collagen-induced arthritis [12]. Accordingly, it will be of interest to study whether autoantigens modified by various enzymes or proteases during synthesis or degradation also play a role in RA. Moreover, it will be of importance to characterize the T-cell response to CII and other potential autoantigens at various stages of the disease, in order to achieve a thorough understanding of potential intramolecular and intermolecular epitope spreading.

The studies by Berg *et al* [7] and Kim *et al* [9] support the general view that T-cell responses to joint-specific autoantigen(s) are of importance in the development of RA. This classical concept is being challenged, however, by three recent studies [13–15] from the laboratory of Mathis and Benoist. This group has developed a new mouse model that spontaneously develops an inflammatory joint disease that is the result of systemic self-reactivity. The new model is based on a transgene encoded T-cell receptor (TCR) that recognizes a self-component in the context of the mouse MHC class II molecule I-A^{g7} (formerly known as I-A^{NOD}). When the TCR transgenic line (KRN) is crossed with NOD mice that express I-A^{g7} molecules, 100% of the offspring expressing both the KRN TCR and I-A^{g7} molecules develop a severe inflammatory arthritis. The arthritis begins when the animals are young, 3–4 weeks of age, and progresses rapidly. The inflammatory process results in cartilage destruction, bone erosion and ultimately joint deformity. The joint histopathology has interesting similarities with both RA and experimental arthritis in a number of different animal models [16]. No other clinical manifestations or histological abnormalities have been noted in the mice. The arthritis is clearly dependent on and initiated by T-cell recognition of a ubiquitiously expressed antigen presented by I-A^{g7} molecules. Once initiated, though, the disease is caused by immunoglobulin G molecules. These molecules, however, do not recognize CII. The target antigen for the initiating T cells and the arthritogenic immunoglobulin G has now, surprisingly, been identified as glucose-6-phosphate isomerase (GPI), which is a glycolytic enzyme that is expressed in all tissues [15].

Because RA is a systemic disease, rather than a joint-specific disease, it seems likely that systemic self-reactivity may also be the basis for the arthritic manifestations in humans. It is unclear how reactivity to GPI in the animal model actually leads to arthritis, however, and why there are no additional extra-articular manifestations that are frequent in RA. Mathis and Benoist have experimental evidence that the basis for the joint disease is not simply cross-reactivity with a joint-specific antigen. Instead they suggest that leaky T-cell and B-cell tolerances to GPI, perhaps combined with special features of synovial GPI expression and/or unusual physiological features of the joints, lead to an accumulation of immune complexes in the joints and, in turn, arthritis, when a linked T-cell and B-cell response towards GPI is initiated by an environmental or stochastic genetic or physiological event. Why the arthritic animals do not develop any of the extra-articular manifestations seen in RA patients is an open question, but it is interesting that these manifestations in general occur in patients with high concentrations of autoantibodies against immunoglobulin G molecules (rheumatoid factors), which are absent in the arthritic mice. Relatively limited genetic heterogeneity in this animal model may also explain the homogenous clinical appearance, because it known from RA and other autoimmune diseases, including their respective animal models, that specific clinical phenotypes are determined by genetic effects [17].

Given the impressive results of antitumour necrosis factor-α therapy of patients with RA [18] and the new promising results of interleukin-4 treatment of mice with collagen-induced arthritis [19], one might wonder whether it is worthwhile to investigate the initiating event(s) and the target autoantigen(s) that are responsible for the initiation and perpetuation for the inflammatory process in RA. The answer is clearly 'yes', because only a detailed understanding of the disease process will provide the information that is needed to develop a new generation of anti-inflammatory drugs that act more specifically than the ones currently in use. Thus, anticytokine therapy is a treatment with potential serious side effects such as infections,

including sepsis, and potentially also development of tumours [20]. Therefore, the studies from Berg *et al* [7] and Kim *et al* [9] that give support to the general idea that immune responses against joint-specific antigens are of critical importance in RA and the studies of Mathis and Benoist [13–15] describing that joint-specific disease can result from systemic autoreactivity provide an important and challenging basis for the further unravelling of the pathogenesis of RA.

To begin with, it will be interesting to study T-cell and B-cell reactivity to GPI in RA patients at different stages of disease and, if present, compare these parameters with anti-CII reactivity. By doing this, it might be possible to determine a potential temporal relationship between systemic and joint-specific autoreactivity. Alternatively, these two different forms of autoreactivity may either represent different pathways to the same clinical manifestations, or be associated with different clinical manifestations. It will also be important to define the molecular basis for how self-reactivity to GPI in the KRN TCR transgenic mice leads to arthritis, and in more general terms to define the rules for how systemic autoreactivity may lead to an autoimmune (organ specific) disease.

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