The role of T cells in rheumatoid arthritis

Sir: Dr Gaston presented a scholarly review of current publications on the role of T cells in chronic rheumatoid synovitis. We would like to comment briefly on a few aspects of his editorial. It is interesting to see how the view of T cells in the rheumatoid joint has evolved over the past decade. In the mid-1980s it was assumed that T cells churned out lymphokines like interferon and interleukin-2 in the joint, and that in situ expansion of antigen-specific T cells in synovium accounted for the plethora of T cells in synovial tissue. Only a few people would argue today with the fact that T cell products are, in fact, quite difficult to find in rheumatoid synovial samples. Our current understanding of T cell recruitment and retention through non-antigen related adhesion molecules like selectins and integrins also suggests that the accumulation of CD4+ memory T cells in rheumatoid synovium is not due to local proliferation but is a direct reflection of local cytokine action on vascular endothelial cells and other interstitial cells. The simple T cell model of the past decade has, however, inspired a far more complex paradigm that includes cytokine networks, activated mesenchymal cells, and possibly activated T cells responding to either an aetiological agent or perhaps a host of ‘irrelevant’ antigens. Hence, one of the major goals of the autocrine/paracrine model proposed in 1990 has been achieved—namely, to encourage people to think critically about the interpretation of data on soluble mediators in the joint.

As Dr Gaston points out, we have always maintained that T cells might have a critical role in the initiation of rheumatoid arthritis, though there has been to date no data to support this apart from major histocompatibility complex (MHC) associations. An alternative view of these findings could be that the specific MHC molecules associated with rheumatoid arthritis result in a ‘hole’ in the T cell repertoire as the MHC clearly has a major role in thymus selection of the T cell repertoire. In a retrovirus mediated disease it would not be difficult to envisage that susceptible subjects lack the appropriate T cells to respond adequately to the infecting agent, as opposed to the traditional view that the MHC contributes to the disease by permitting specific aetiological antigens to be presented to the appropriate T cells.

With regard to the relative lack of T cell cytokines in rheumatoid arthritis being consistent with other immune responses, we would be wary of that conclusion. It is probably true that relatively small numbers of activated lymphocytes and small amounts of lymphokines can orchestrate inflammation and exuberant mononuclear production. For instance, the insulin in NOD mice seems to be ameliorated by antibodies to interferon γ, even though very little interferon γ is produced by these cells. However, in many other cases T cells in antigen specific processes express cytokine genes, and their products are easy to detect. In our own laboratory we have shown that granulocyte-macrophage colony stimulating factor (GM-CSF) is a major product of airway T cells in allergen induced asthma but have been unable to show any GM-CSF production by synovial T cells.1 Interferon γ and mRNA are abundant in tuberculous pleurisy, a disease that all would agree has a significant T cell component.2 We would caution against assuming that low T cell lymphokine production is ‘typical’ of antigen mediated processes and continue to await more definitive proof of T cell activation in rheumatoid arthritis. Furthermore, it is not even established that T cell factors like interferon γ are detrimental in rheumatoid arthritis, and we have recently treated several patients with single or multiple intra-articular injections of recombinant interferon γ and have seen no evidence of flare (unpublished data).

Our current view of rheumatoid synovitis is more eclectic than the simple cytokine network proposed in 1990. Even though the data implicating T cells in chronic disease are mounting, this controversy is enhanced by a deeply rooted (almost religious) sense that T cells must be doing something in the joint because they are there in such abundance. Our more recent paradigm has suggested a three-axis network, involving macrophages, fibroblasts, and T cells, each of which is ‘talking’ to the others and contributing to the perpetuation of the disease. While we understand the language of the first two, we have not yet established how (or even if) the T cells communicate with their neighbours. While we would happily embrace significant new data that would help resolve this longstanding conundrum, we expect that this approach will have significant therapeutic impact, as already a variety of specific and potent anti-T cell strategies have had rather disappointing clinical results—for example, anti-CD4, -CD5, -CD7, or CAMPATH-1 antibodies, interleukin 2/deptheria toxin fusion proteins, and total nodal irradiation. Hence we encourage others to maintain a healthy measure of skepticism about the ‘religion’ of T cells until more data are available.

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Occurrence of arthritis in hyperimmunoglobulinemia D

Sir: We were interested by the brief report of Loeliger and colleagues on arthritis in hyperimmunoglobulinemia D.1 They report on four adult Dutch patients whose febrile attacks of the hyperimmunoglobulinemia D syndrome were accompanied by genuine arthritis. Their observation, however, indicates that arthritis should be incorporated within the clinical spectrum of the syndrome, is non-specific.

In 1983 Prieur and Griscelli described eight cases with juvenile onset of periodic fever and joint disease.2 All patients had lymphadenopathy, splenomegaly, skin lesions, and presented leukocytosis.1 Recent paradigms have suggested a three-axis network, involving macrophages, fibroblasts, and T cells, each of which is ‘talking’ to the others and contributing to the perpetuation of the disease. While we understand the language of the first two, we have not yet established how (or even if) the T cells communicate with their neighbours. While we would happily embrace significant new data that would help resolve this longstanding conundrum, we expect that this approach will have significant therapeutic impact, as already a variety of specific and potent anti-T cell strategies have had rather disappointing clinical results—for example, anti-CD4, -CD5, -CD7, or CAMPATH-1 antibodies, interleukin 2/diphtheria toxin fusion proteins, and total nodal irradiation. Hence we encourage others to maintain a healthy measure of skepticism about the ‘religion’ of T cells until more data are available.

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1 Loeliger et al. Multicentricity of the occurrence of arthritis as a symptom during febrile attacks of the hyperimmunoglobulinemia D syndrome.2 Their observations on the occurrence of these attacks, however, have been reported previously.

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