The Th1-Th2 model—what relevance to inflammatory arthritis?

Just over a decade ago Mosmann and colleagues reported that murine T helper (Th) cell clones could be distinguished by distinct cytokine secretion patterns. Since then the concept of Th1 and Th2 subsets has become increasingly popular and the Th1-Th2 model represents one of the most important developments in our understanding of immunological processes in health and disease.

The model encompasses two concepts derived from in vitro observations of long-lived murine T cell clones: (1) CD4⁺ T cells may be classified into Th1 and Th2 subsets, based on the production of two functionally distinct profiles of cytokines. Th1 cells produce interferon γ (IFNγ), interleukin 2 (IL2), and tumour necrosis factor β (TNFβ), and in broad terms induce cell mediated immunity. Th2 cells secrete interleukins 4 (IL4), 5 (IL5), 6 (IL6), 10 (IL10), and 13 (IL13) and induce humoral and parasitic immunity. (2) Factors that stimulate the actions of one subset reciprocally inhibit the other subset, leading to a state of mutual antagonism. Thus IFNγ and interleukin 12 (IL12) stimulate Th1 cells and inhibit Th2 cells whereas IL4 stimulates Th2 cells and inhibits Th1 cells.

More recently the original clear cut concept that the Th1-Th2 split may be applied to individual Th cells has evolved. Early observations from T cell clones demonstrated that single Th cells secrete either a pure Th1 or Th2 profile of cytokines. However, freshly isolated Th cells from antigen stimulated animals express a range of Th1 and Th2 cytokines (mRNA and protein) in a random distribution. This pattern has not been found to develop in individual cells in culture into the exclusive Th1 or Th2 pattern observed in clonal cells. Instead, the Th1 or Th2 characteristics of an in vivo immune response seems to be determined by a net shift in the secretion profile of a population of Th cells towards a Th1 or Th2-like response, in which each individual cell retains a mixed picture to a greater or lesser extent.

There is no doubt that the distinct Th1 and Th2 cytokine profiles observed in vitro have critical biological outcomes in some in vivo situations, most notably infections. For example Leishmania major infection in mice results in a protective response in some strains (C57B6) characterised by a Th1 cytokine pattern, or a susceptible response in other strains (BALB/c) characterised by a Th2 cytokine pattern. Treatment with neutralising antibodies to IL4 or IFNγ changes survival, demonstrating a critical role in the Th1-Th2 balance in determining the outcome to infection. This is also seen in humans where the sequelae of infection with Mycobacterium leprae seem to be dependent on the Th1-Th2 split, as the dominant response in tuberculous disease is of the Th1 type and the dominant response in lepromatous disease is of the Th2 type.

In humans the interpretation of the contribution of Th cells and their cytokines to the pathogenesis of autoimmune disease is complex and problematic. Firstly, Th secretary responses in humans are not identical to the mouse; IL2, IL6, IL10, and IL13 are produced by both Th1 and Th2 cells in humans, but only by Th1 (IL2) or Th2 (IL6, 10, and 13) cells in the mouse. This undermines the wisdom of applying conclusions concerning the Th1-Th2 split in animal models of disease directly to humans.

Secondly, Th cytokines are not exclusively secreted by Th cells. Mast cells and basophils, for example, produce IL4 whereas natural killer (NK) cells and murine macrophages produce IFNγ. B cells and monocytes produce IL10 and macrophages, fibroblasts, chondrocytes and endothelial cells produce IL6. CD8 T cells also contribute to the same cytokine environment, for example in the rat the expression of IL4, 5, 10 and IFNγ mRNA is twofold to fivefold higher in stimulated splenic CD8 T cells compared with CD4 (Th) cells. This introduces the confusion that while Th1 and Th2 cells are defined by the pattern of cytokines that they secrete the same pattern of cytokines at an inflammatory site does not necessarily imply an involvement of Th1 or Th2 cells. To date no distinguishing Th1 or Th2 surface markers have been described to solve this problem.

A huge volume of work has been devoted to categorising the pathogenesis of inflammatory arthritis in terms of the Th1-Th2 split, driven quite reasonably by the near universal T cell dependence of animal models and a strong body of evidence supporting a role for T cells in human arthritis. Evidence from a number of experimental autoimmune diseases has led to the broad conclusion that the function of Th1 cells is pro-inflammatory and that of Th2 cells is anti-inflammatory. In some animal models of arthritis this paradigm seems to hold true. For example in pristane induced arthritis (PIA) in mice arthritogenic T cells secrete IFNγ and IL2 whereas T cells from protected animals secrete IL4 and IL5, suggesting that the response in susceptible animals is of the Th1 type and in protected animals of the Th2 type. Similarly in murine aggrecan induced arthritis the cytokine profile from arthritogenic T cell hybridomas is of the Th1 type, and in rat streptococcal cell wall induced arthritis (SCWA) IL4 has an anti-inflammatory effect in ameliorating the chronic phase of arthritis.

The picture becomes increasingly complex in collagen induced arthritis (CIA), probably the most widely studied model of all. In some circumstances CIA seems to be a Th1 driven disease, as seen in PIA, SCWA, and aggregan arthritis. Thus CIA induced with complete Freund’s adjuvant (CIA/CFA) is exacerbated after treatment with low concentration IFNγ injected intramuscularly or locally into the footpad, and when induced with incomplete Freund’s adjuvant (CIA/IFA) is exacerbated by IL12 (an enhancer of Th1 responses). Similarly a Th1 process is suggested by the report that selective inhibition of Th1 responses or treatment with either anti-IFNγ or IL4 or IL13 is protective. In contrast, however, IL12 treatment has been reported to ameliorate CIA/CFA as has treatment with high concentrations of IFNγ injected systemically. In keeping with these observations that Th1 responses might have an anti-inflammatory role in some circumstances, treatment with anti-IFNγ is also reported to increase disease severity in CIA/CFA and in IFNγ knock out mice CIA/CFA is more severe. Furthermore in two lines of Biozzi mice analysis of Th cytokine responses indicates that the Th1 phenotype characterises resistance and the Th2 phenotype characterises susceptibility to CIA/CFA. Finally DonCarlos et al report that collagen specific Th cells change in phenotype from a Th1 to a Th2 pattern during the induction of CIA/CFA. These observations in CIA undermine the general concept that...
Th1 responses are arthrogenic and Th2 responses protective—and they are not unique to this model. In chronic murine arthritis intra-articular anti-IL4 is protective whereas IL2 and IL4 are synergistic in the potentiation of antigen induced arthritis flares.25 Lastly in the mercuric chloride model of autoimmunity Brown Norway rats develop a severe inflammatory arthritis that is T cell dependent and arises in the context of a Th2 dominated immune response.23

The conclusion from these extensive studies in animals is that there is no stereotyped role for the Th1-Th2 model in the pathogenesis of inflammatory arthritis, with both Th1 and Th2 cytokines apparently acting in pro or anti-inflammatory capacities in different circumstances. In human experimental techniques to probe mechanisms of disease are constrained; none the less attempts to interpret arthrogenic mechanisms in terms of the Th1-Th2 model have been made.

In rheumatoid arthritis (RA) synovial tissue the cytokine profile reflects the large volume of activated macrophages, making an interpretation of the role of T cell subsets on the basis of particular cytokines virtually impossible. Both IFNγ and IL2 are present in small quantities, and IL4 is seemingly absent. However, the relevance of this observation to the Th1-Th2 model is unclear as IL2 is not restricted to either subset in humans, and IFNγ may also be secreted by CD8 and NK cells, and macrophages in mice. Chomarat et al24 have isolated synovial fluid w/β and γ/δ T cell clones from several RA patients and found that most of the clones produce IFNγ, but a substantial proportion also produce IL4. The relative IFNγ/IL4 production by these clones indicates a Th1-like bias in the majority, however the secretion profile is clearly of the Th2 type in a minority. The apparent Th1 bias in the rheumatoid joint has led to the broad conclusion that RA is a Th1 mediated disease.25 In contrast a number of trials have reported the effect of IFNγ treatment in RA, based on the observation that IFNγ may antagonise the actions of the macrophage cytokines TNFα and IL1. Interestingly the data show either a weak protective effect or no difference compared with placebo,25 rather than an exacerbation in disease activity as might be predicted if RA were a Th1 driven disease.

In reactive arthritis (ReA) and Lyme arthritis (LyA) antigen specific stimulation of synovial fluid mononuclear cells (SFMC) reveals IFNγ, IL10, and TNFα secretion and little, if any, IL4.26 27 The production of IFNγ and the demonstration that antigen induced SFMC proliferation is enhanced by IL2, and abolished by IL10, suggests a Th1-like response to antigen in these two diseases.

An anti-inflammatory role for the Th2 cytokine IL4 has been demonstrated when added to RA synovioum in vitro.28 However, the detection of this cytokine in vanishingly small concentrations in RA, ReA, and LyA29 30 raises doubt as to whether it has a significant role in the control of joint inflammation. In contrast, in RA, ReA, and LyA joints IL10 is present in significantly greater concentrations than IL4 and seems to have a greater anti-inflammatory effect. For example IL10 has a pronounced inhibitory effect on TNFα secretion in RA, ReA, and LyA synovial cultures, whereas IL4 (and IL13 in RA) has not been found to have a significant effect.29 30 31 The demonstration of a significant anti-inflammatory role for IL10 in vivo cannot be taken as evidence for Th2 involvement. IL10 is secreted by Th cells and monocytes in synovial membranes, and has recently been reported to be secreted in high concentration by a separate subset of antigen specific T “regulatory” cells, so called Tr1 cells.32 Until the principal cellular source of IL10 in the inflamed joint is known, an anti-inflammatory role, if any, for Th2 cells through IL10 production remains unproved.

In conclusion the revolution in our understanding of T cell cytokology on the basis of the Th1-Th2 model does not provide a dogmatic interpretation of the pathogenesis of inflammatory arthritis, either in animals or in humans. Some of the data support the general concept that inflammatory processes in the joint may be promoted by Th1 cytokines, but the evidence that Th2 cells play a critical part in counteracting this is weak. Furthermore the realisation that so called Th2 cytokines may play a pro-inflammatory part in some circumstances cannot be overlooked and is an example of an important principle: joint inflammation may result from a multitude of different mechanisms. Attractive as it may be, the Th1-Th2 model does not seem to be a basic pathogenic template for inflammatory arthritis; it may therefore be unwise to treat it as a foundation upon which to devise new therapeutic strategies.