ARTHRITIS AND INTERLEUKINS

The biochemical and functional properties of many cytokines are increasingly described. Essentially, cytokines are soluble peptides that affect cell growth, maturation or function. Interleukins, a subset of cytokines, are immunopeptides that satisfy three criteria: their production should be inducible in leucocytes; they should function during inflammatory responses; their primary sequence must be known [1]. It is important that any definition of an interleukin is not too restrictive since at this stage it is likely that our recognition and understanding of these proteins is very incomplete. Several other cytokines, e.g. interferons and tumour necrosis factors, fall within the definition of an interleukin given here but they were characterized before the interleukin nomenclature was widely accepted.

At present, six interleukins have been described [2]. Interleukin 1 (IL1) occurs in two forms produced by different genes [3, 4]. The mature forms of alpha and beta IL1 both have Mr of approximately 17kd and are cleaved from larger (31kd) precursor peptides [3, 4]. The biological properties of both are extremely similar and, indeed, they compete with equal affinity for receptor occupancy on target cells [5]. Mononuclear leucocytes, especially monocytes/macrophages but also B and T lymphocytes, can produce IL1. Additionally, all tissue macrophage-like cells tested so far can generate biologically-active IL1 after appropriate activation. Endothelial cells, vascular smooth-muscle cells, skin keratinocytes, contractile renal mesangial cells, fibroblasts, cartilage and bone cells are among an increasing list of nonmacrophage cells known to release IL1-like molecules [2]. These peptides are extremely potent biological agents, often producing responses from cells when present at concentrations as low as 10^{-15} molar. Their range of biological action is also impressive with activating or growth-inducing properties for T and B lymphocytes, phagocytic cells, endothelial cells, brain cells and, in cartilaginous, fibroblasts, chondrocytes and bone cells [2].

In tissue culture, IL1 induces resorption of bone and cartilage matrix [6, 7]. These in vitro effects reinforce the idea that IL1 might be important in the pathogenesis of inflammatory arthritis (the first report of IL1-like factors from synovial exudate cells long predates the recognition of its many biological effects [8]). Recently, more direct evidence of a role for IL1 in rheumatic diseases has accumulated. IL1 alpha and beta genes are activated in synovial cells during rheumatoid arthritis (RA) [9, 10] and significant levels of both IL1 beta and IL1 alpha protein are readily detectable in joint effusions [11]. Human synovial cells produce IL1 after exposure to agents relevant to arthritis (e.g. urate crystals) [12] and RA synovial fibroblasts proliferate in response to synovial cell crude IL1, highly purified natural IL1 and to human recombinant IL1 [12]. A single injection of human recombinant IL1 into a rabbit knee joint reproduced features of acute arthritis with proteoglycan breakdown and intra-articular leukocytosis [13].

In this issue, Soder and Madsen [14] report that guinea-pig peritoneal macrophages released a factor that stimulated thymidine incorporation in rat chondrocytes. Their original material also contained conventional LAF activity of IL1 on thymocytes and LAF activity co-eluted from a gel filtration column at 16—21k with one peak of the activity that stimulated chondrocyte DNA synthesis. Human recombinant IL1 alpha could also reproduce the signal for rat chondrocyte thymidine incorporation. These results, as the authors point out, do not exclude chondrocyte DNA synthesis being stimulated by other factors present in their crude material but do show that IL1 can act in this way and that at least some of the activity present in their starting material was probably mediated by IL1. It should be remembered, however, that a number of other cytokines (e.g. IL2, IL4, IL6 and even TNF) may be active in the thymocyte assay.

Cytokine regulation of mesenchymal cell proliferation and/or activation is far from being understood. Differences in assay conditions, purity of reagents, sources of cells and secondary effects such as PGE induction have produced highly variable results in studies on collagen synthesis and proliferation of fibroblasts [15]. The induction by IL1 (and TNF) of collagenase and PGE release from synovial cells and chondrocytes has, however, been well-documented [16, 17]. In cartilage, recombinant IL1 has also been reported to stimulate the synthesis...
of a secreted protease that could convert latent collagenase to the active enzyme [18]. The present report adds DNA synthesis to the list of effects that IL1 may have on chondrocytes.

As well as responding to IL1 in a number of ways, chondrocytes seem also to produce it. Human chondrocyte production of IL1 alpha and beta mRNA has been demonstrated and IL1-like activity occurred in supernatants of bovine articular cartilage [18, 19]. Thus there is evidence that autocrine control of extracellular matrix turnover based on chondrocyte production of IL1 and response to IL1 may occur.

In the immune system, perhaps the most important action of IL1 is to stimulate the production of the T cell growth factor interleukin 2 (IL2) and its receptor in the process of T cell activation [2]. Once produced, IL2 appears to stimulate any cells that display functional IL2 receptors. Human IL2 is a glycosylated peptide of approximately 15kd. The high-affinity IL2 receptor has at least two components: an alpha chain (also called Tac) of 55kd and a larger beta chain of approximately 70kd [20]. Human blood whole lymphocyte populations that do not react with Tac antibodies can still respond to IL2 by generating cytolytic activity. Recently it was noted that the beta chain is expressed on resting T cells and on large granular lymphocytes (LGL) and could act as a low affinity (Kd = 10nm) receptor for IL2. IL2 internalization by the beta receptor peptide on LGL led to the generation of natural killer activity, early-phase lymphokine activated killer (LAK) activity, lymphokine release and induction of expression of both the alpha and beta peptides of the receptor [20]. These two components together comprise a high affinity receptor (Kd = 10pm) that mediated IL2-driven proliferation and late-phase LAK cell generation. It is not yet clear whether analogous events take place in small circulating T cells.

IL2 is, however, known to stimulate resting T cells to produce interferon gamma (IFN gamma) in the absence of antigen and without a T cell proliferative response [21].

In RA, deficient cell-mediated immunity has been recognized for many years [22, 23]. This deficiency is also seen in terms of apparently subnormal IL2 production and responsiveness of T cells from patients with RA. It is known that high levels of mRNA for IL2 can be found in extracts of RA synovium [24] and it is possible that a defect in biosynthesis occurs after transcription or that IL2 protein is produced but not detected due to rapid removal or interference by other cell-derived factors in IL2 assays. The other cytokine paper in this issue of BJR is from Hasler and Dayer [25] and describes a defect in the production of IFN gamma by RA T cells stimulated with IL2. Previously, diminished IFN gamma production by RA T cells responding to autologous stimulation has been reported and was thought to result from production by adherent cells (macrophages) of an IL1 inhibitor [26]. Hasler and Dayer now show that resting blood T cells from healthy controls and patients with spondarthritis respond to IL2 by producing IFN gamma (sufficient to inhibit EBV-induced B cell proliferation). Similar cells from patients with RA failed to respond in this way. Since RA T cells have been reported to produce normal amounts of IFN gamma in response to allogeneic cells or monocyte-depleted autologous cells the authors conclude that responsiveness to IL2 rather than the synthetic capacity for IFN gamma is deficient in RA.

Thus, in addition to previous descriptions [27–29] of IL1 inhibitors published by these authors and others, further evidence for a reduced response to exogenous IL2 is given here. Whether this might follow from a low level of receptor expression, loss of receptor affinity, postreceptor failure, the presence of soluble IL2 'inhibitors' or a combination of several factors is not yet known. The recent finding that IL2 inhibition by synovial exudate fluids correlated with their content of soluble IL2 receptor [30] may be relevant.

In chronic inflammation, the importance of impaired T cell responses to interleukins is unclear. Reduced T cell sensitivity to potentiating factors could reasonably lead to failure of appropriate immune responses (e.g. eradication of foreign antigen). Equally, any T cell immunoregulatory function needed to stop self-reactivity (and cytokine release) might also suffer. Meanwhile, the disruption of articular tissues by cytokine-responsive mesenchymal cells continues unopposed?

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MARKERS AND SUBSETS—CLUE TO PATHOGENESIS IN SYSTEMIC LUPUS ERYTHEMATOSUS?

The discovery of first the LE cell and antinuclear antibodies and then more specific autoantibodies has turned a fascinating disease of protean clinical manifestations (systemic lupus erythematosus (SLE)) into an experiment of nature for clinical immunologists. One of the pressing current issues is the relationship of the various autoantibodies found in patients with SLE to the clinical manifestations of the disease. Based on animal models, broad general concepts of SLE would indicate that autoantibody production derives from an unrestrained general proliferation of B cells [1]. These cells can give rise to widely cross-reactive autoantibodies of low specificity and little pathogenic significance but also may produce autoantibodies of restricted specificity, usually of the IgG class, which can be associated with distinct and important disease manifestations.

In patients with SLE a number of these specific autoantibodies have been described. Historically, the association of anti-double-stranded-DNA antibodies with glomerulonephritis was described first and established by eluting these antibodies from the kidneys of patients with lupus nephritis. While the precise mechanism of tissue damage, whether by the deposition of circulating immune complexes or the formation of complexes in situ, is not certain, the presence of specific IgG antibodies of high affinity and high avidity appears to be related to tissue damage [2]. Since then, the relationship of anti-Ro antibodies to fetal heart block [3], of anticardiolipin antibodies to spontaneous abortions [4] and to the syndrome of thrombocytopenia, circulating anticoagulant and thromboses, of antiribosomal protein P antibodies to psychosis in cerebral lupus [5] and, in another but related disease, of anti-Jo-1 (anti histidyl-tRNA synthetase) antibodies to myositis [6] have all been described.

In this issue, the paper by Maddison and co-workers [7] describes a subgroup of patients with SLE identified by the autoantibody to La protein. This group of patients is older at onset of their disease, is less likely to have nephritis but more likely to have keratoconjunctivitis sicca and serologically to have a higher incidence of rheumatoid factor, a higher titre of antibodies to Ro antigen and perhaps a lower incidence of anti-DNA antibodies. There is a significant association of anti-La antibodies with the HLA-DR3 genotype. Can one discern a link between the presence of anti-La antibodies themselves and the characteristics of this subgroup of SLE? Not easily. The lower incidence of nephritis might be related to the lower incidence of anti-DNA antibodies or more likely to differences in the quantity and characteristics of the anti-DNA antibodies produced in the anti-La positive and negative subgroups, a subject that could be pursued further. The presence of keratoconjunctivitis sicca might also be related in part to the presence of rheumatoid factor and anti-Ro antibodies. What then is the value of defining this subgroup of patients with SLE on the basis of anti-La? One important finding is the further definition of the relationship of specific autoantibodies to HLA class II antigens. Maddison et al. [7] report a significant association between the HLA DR3 specificity and the presence of autoantibodies to Ro and a stronger association with the combined presence of autoantibodies to both of the physically related antigens Ro and La. As families of physically related antigens such as the Ro and the La antigens and the Sm and U1 snRNP antigens are defined [8], the relationship between autoantibodies to the related antigens and HLA class II molecules becomes clearer. This would be expected since the class II molecules presumably control the immune response by their ability to bind or not bind and