The prospect for cytokine based therapeutic strategies in rheumatoid arthritis

If the eighties was dominated by the T cell, then in the nineties the macrophage has moved perceptibly centre stage. There is a greatly increased understanding of the pro-inflammatory armamentarium of the macrophage and its role in chronic inflammation of the type found in the rheumatoid synovium. Advances in molecular biology have enabled the identification, sequencing, cloning and subsequent expression in transformed E coli cells of the macrophage derived cytokines, interleukin-1 (IL-1) and tumour necrosis factor (TNF), together with their soluble receptors. The availability of hybridoma technology has facilitated the development of monoclonal antibodies, both murine and increasingly humanised, that can specifically target cytokines and their receptors. A naturally occurring inhibitor of IL-1, initially identified in the urine of patients with monocytic leukaemia,\(^1\) and also found in supernatant of adherent monocyte cultures\(^2\) has been characterised as the IL-1 receptor antagonist (IL-1ra) which blocks the ligand binding to the receptor.\(^3\) This molecule has been purified, cloned and expressed as a recombinant human protein.\(^4\)

Regulation of cytokine activity may occur at the level of synthesis, secretion or target cell activation. The figure shows a schematic representation of proposed physiological and possible sites for the therapeutic inhibition of IL-1 and TNF. It is now clear that the response to an inflammatory stimulus is characterised just as much by the production of the antagonist, be it IL-1ra or soluble TNF receptor, as by the agonist.\(^5\) The importance of physiological regulation of IL-1 activity by IL-1ra is suggested by the high degree of conservation of this protein across species and by the evidence that the primordial IL-1 gene gave rise to the IL-1ra gene, before subsequent evolution of the IL-1a and IL-1b genes.\(^6\)

Much activity surrounds the investigation of the genetic regulation of cytokine expression. Recent work has identified the existence of genetic polymorphisms of the TNF, IL-1a, IL-1b and IL-1ra genes. Particular interest has focused on the TNF gene because of its situation in the short arm of chromosome 6 within the HLA region. Mice transgenic for the human TNF alpha gene consistently develop a polyarthritis at about three to four weeks of age in transgenic progeny.\(^7\) Patient studies have shown a relationship between a TNF gene promoter polymorphism and the autoimmune haplotype A1, B8, DR3\(^8\) as well as an association with systemic lupus erythematosus.\(^9\) The IL-1 gene family is situated on chromosome 2. An intriguing association has been described between a rarer allele of IL-1a and patients with juvenile chronic arthritis, especially those with iridocyclitis.\(^10\) Research is ongoing to determine whether these disease associated polymorphisms coincide with abnormal expression of the corresponding cytokine. Recently, the existence of an abnormal, high molecular weight TNF mRNA species has been demonstrated in murine macrophages and human monocytes infected with the influenza A virus.\(^11\) Further work is required to determine whether this abnormal mRNA codes for a biologically active product, and whether it is related to the observed prolongation of TNF mRNA stability seen in influenza A viral infection.

Much of the earlier work of the association of cytokines with disease has been confounded by the lability of cytokines and a failure to adhere to the strict sample handling procedures required for reproducible and accurate measurements. In addition, the fact that a substantial proportion of IL-1 binds to soluble factor(s) in serum may have frustrated attempts to measure the isolated cytokine. However, there is evidence that cytokine levels in body fluids may be related to clinical outcome. Serum levels of circulating IL-1 have been related to disease severity in rheumatoid arthritis\(^12\) and the ratio of IL-1ra to IL-1 in synovial fluid has been associated with time to recovery from Lyme arthritis.\(^13\)

Attempts to dissect the cytokine system have been frustrated by the overlapping activities of the various cytokines especially IL-1 and TNF. The traditional view is of a cytokine network with inherent redundancy. The inference is that specific intervention against single cytokines would not be a useful strategy in the treatment of inflammatory disease, since inhibition of the activity of one cytokine would be overcome by the actions of another. Results of clinical trials, however, suggest that single cytokine strategies may be useful in inflammatory disease and that it may be more appropriate to talk of a cytokine hierarchy. Sepsis is a severe systemic inflammatory condition with a mortality of about 40% at 28 days. A retrospective analysis in 893 patients with sepsis treated with the recombinant human interleukin receptor antagonist has shown a reduction in mortality of 23% in those with severe disease as defined by the presence of organ dysfunction.\(^14\) A similar trial in patients with shock treated with an anti-TNF monoclonal antibody displayed a 17% reduction in mortality.\(^15\)
Cytokine directed strategies in animal models of arthritis suggest that TNF and IL-1 may have overlapping yet distinct effects on the joint. Intra-articular injections of rTNF into rabbit joints produce less inflammation than seen with rIL-1 injection and no effect on proteoglycan loss. However, a synergistic effect on joint inflammation was seen when both cytokines were injected. In acute antigen-induced arthritis, the inhibition of IL-1 is without major effect on inflammation, contrasting with collagen-induced arthritis and streptococcal cell wall arthritis. A consistent finding in these models has been the lack of reversal of suppression of proteoglycan synthesis by anti-TNF antibodies, a feature characteristic of the action of anti-IL-1 antibodies or rhIL-1ra, and a phenomenon which may be uncoupled from the inflammatory process. The use of animal models to predict clinical efficacy is limited by unknown relevance of the pathophysiological processes operating and by the development of antibodies to recombinant human proteins, which limits the range of models that can be used. The clinical response seen in the recently reported small, open trial of anti TNFα monoclonal antibody looks promising—we must await the rigour of the controlled trial for more definitive information.

The promise of immunotherapy was embodied in terms, such as, ‘magic bullet’. The implication was specificity of action without appreciable side effects. Early hopes have given way to a feeling of disillusionment. The consequences of interfering with physiological proteins such as IL-1 and TNF have yet to be fully appreciated. Host resistance to infection is one obvious area that needs to be monitored closely. ‘Double-edged sword’ might be a more appropriate term than ‘magic bullet’. The problem is that advances in ability to modify the biological response has outstripped our understanding of the heterogeneity of the disease process in conditions such as rheumatoid arthritis. Clinical trials in sepsis have proved difficult, not so much because of inherent problems in developing therapies per se, but because of the extreme heterogeneity of disease and the learning curve involved in setting realistic targets for anti-sepsis therapies. The result is the realisation that in this dramatic inflammatory condition, biologics need to be targeted not only at particular receptors, but also at specific patient populations during a particular time in the evolution of the disease process. This window of opportunity needs to be defined.

A similar challenge confronts the development of new therapeutics in rheumatoid arthritis. In fact, what is
required is a revolution in clinical research of equal magnitude to that experienced in molecular biology.

The opportunity offered by specific anticytokine therapy is that patient targeting should be easier to achieve. This may occur in relation to the presence of certain cytokine gene polymorphisms or in relation to markers of IL-1 and TNF activity such as IL-6 levels, levels of IL-1ra, circulating soluble TNF receptors or inducible levels of cytokines in peripheral blood mononuclear cells. The disease process in rheumatoid arthritis is characterised by exacerbations and remissions. It would seem rational that therapy should also be phasic, perhaps with combinations of anti-cytokines during phases associated with active joint damage. Indeed should polymorphisms of cytokine genes prove important in disease susceptibility or severity in rheumatoid arthritis, then a population of patients may exist that would be expressly responsive to anti-cytokine strategies, and gene therapy could be an option. The challenge lies in a better understanding of the role of cytokines in the joint disease process and the availability of appropriate markers to monitor the effects of therapy in a dynamic fashion—and yes, preferably a large national database. In this way, the double-edged sword can start to make way for the magic bullet(s). Watch this space.

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