

Correspondence

Response to Fionula Brennan's Commentary "A follow-up to 'Anti-cytokine therapy in chronic destructive arthritis' by Wim B van den Berg"

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In her commentary [1] on my recent review "Anti-cytokine therapy in chronic destructive arthritis" [2], Fionula Brennan raises a number of interesting discussion points. A first issue regards the critical question of whether animal models of arthritis resemble the human disease. Brennan recognises that models and cytokine transgenic mice have been a valuable tool to test hypotheses, but concludes that they can never fully substitute for human rheumatoid arthritis (RA). Although I have spent most of my recent research on exploring the role of cytokines in murine arthritis models, I fully agree with this statement.

Animal models can at best reflect elements of the human disease and should be used as such. Great care has to be taken with extrapolation of findings in a particular model to human RA. When consistent observations have been made in a whole range of arthritis models, however, it is more likely that similar elements might apply to RA. Apart from the consistent findings that anti-IL-1 treatment blocked the progression to chronic erosive arthritis in all models, the relevance of IL-1 as a crucial destructive mediator and propagator of joint inflammation is further underlined by the total lack of induction of chronic arthritis and joint erosions in IL-1 β -deficient mice, in whatever arthritis model studied so far. In clear contrast, arthritis and erosions were still found in most models when induced in tumour necrosis factor (TNF)-deficient mice.

The apparent limitations of the mice transgenic for human TNF, in which it was shown that the pathology is transmitted through the IL-1 receptor pathway [3], are well taken.

Indeed, the transgene is expressed in synovial fibroblasts [4], rather than in macrophages, which are the dominant TNF-producing cells in human RA. Although the cellular source of TNF differs in the transgenic synovial tissue, induction by TNF of downstream mediators in other (nearby) cells is of major importance, making the origin of the initial producer cells less critical.

The group of George Kollias has extended their work on TNF transgenics, with the elegant construction not only of transgenic mice that selectively overexpress a membrane-bound form of TNF (mTNF), but also of 'normal' mice that carry just the mTNF and selectively express this form after triggering. These mice show spontaneous [5] and induced arthritis (my personal observation) respectively, demonstrating that mTNF expression can be enough to drive the arthritic process. The importance of cell-cell interactions in the synovial tissue, with subsequent cytokine/enzyme production, are further underlined by the work of the group of Jean-Michel Dayer [6].

Some of the cartilage destruction occurs at sites of pannus overgrowth, where synoviocyte-chondrocyte interaction might occur. In animal models as well as in human RA, cartilage destruction is also seen away from pannus. In the latter situation, traffic of cytokines and susceptibility of chondrocytes to these cytokines are major determinants. The higher potency of IL-1, compared to TNF, as a catabolic factor for chondrocytes is not debated. Furthermore, as soluble TNF is a short-lived molecule, synovium-derived TNF is unlikely to reach the chondrocytes in

significant quantities. In this respect, IL-1 seems to be the major effector molecule.

Receptor expression on chondrocytes and local cytokine production are other determinants in the relative importance of TNF and IL-1. It becomes clear that TNF expression in arthritic cartilage can vary enormously, as recently shown in articular cartilage obtained from late stage osteoarthritis patients [7]. In fact, classification as high- or low-TNF responder groups was suggested. Whether similar subgroups can be identified in RA and whether the existence of subgroups has consequences for an erosive pathway driven more by TNF or by IL-1 remains to be seen.

In animal models, IL-1a is found in the inflamed joint only at acute stages, probably linked to substantial cell death. Neutralisation of IL-1a, in addition to IL-1b, is then needed. In advanced stages of arthritis, massive cell death is not a key event and IL-1b is the more abundant cytokine. In line with this, antibodies to IL-1b alone are very effective in treating established collagen arthritis [8], whereas ICE inhibitors (which block maturation of IL-1b) also caused significant suppression. IL-1b can be identified in increased quantities in macrophages in the synovial tissue of all RA patients, but the technology of immunostaining does not allow accurate statements on membrane-associated IL-1a to be made. Therapeutic studies with high-quality, neutralising antibodies to the IL-1 isoforms have to be awaited. Anyway, such studies are needed to prove the validity of IL-1b as a therapeutic target.

At present, clinical studies with novel ICE inhibitors are in progress. Such inhibitors will not only prevent IL-1 maturation, but will also inhibit the maturation of IL-18, an IL-1-like molecule with the ability to induce TNF and IL-1 [9]. It is expected that such inhibitors provide a dual hit. The selectivity for caspase-1 and the pharmacokinetics remain points of concern.

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