Editorial

Paradoxical effects of tumour necrosis factor-α in adjuvant-induced arthritis

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Abstract

Anti-tumour necrosis factor (TNF)α therapy is highly effective in rheumatoid arthritis and it is surprising, therefore, that a recent study showed that intraperitoneal administration of recombinant TNFα reduced the severity of adjuvant-induced arthritis and decreased IFNγ expression in cultured draining lymph node cells. Furthermore, in untreated arthritic rats, maximal TNFα expression in draining lymph node cells coincided with spontaneous disease remission, suggesting a role for endogenous TNFα in recovery from arthritis. If confirmed in further studies, these findings suggest that, in addition to its well-established pro-inflammatory properties, TNFα may also play a disease-limiting role in this model of rheumatoid arthritis by suppressing effector T cell responses.

A recent paper by Kim and colleagues [1] published in this journal reports that intraperitoneal administration of recombinant tumour necrosis factor (rTNF)α to rats with adjuvant-induced arthritis has a beneficial effect on disease outcome. This is surprising given the efficacy of anti-TNFα therapy in rheumatoid arthritis (RA) [2], with patients receiving not only immediate clinical benefit, but also reduced joint damage in the long-term [3]. How can we reconcile the fact that blockade of endogenous TNFα is beneficial in human RA, whereas administration of exogenous rTNFα reduces disease severity in an animal model of RA?

In response to this question, it is important to bear in mind that cytokines generally act within their local pericellular microenvironment. It is conceivable, therefore, that endogenous TNFα plays a pro-inflammatory role in the joints of arthritic rats whereas exogenous rTNFα triggers an anti-inflammatory response when injected into the peritoneal cavity. For example, injection of rTNFα could induce a neutralising antibody response against TNFα, or could induce the production of soluble TNF receptors, which could inhibit TNFα activity at the site of disease activity. However, the authors found no evidence of increased levels of anti-TNFα antibodies or soluble TNF receptor (TNFR) [1].

Another possibility is that administration of TNFα could induce the production of IL-10, resulting in suppression of TNFα expression in the joint. Alternatively, injection of rTNFα could result in activation of the hypothalamic-pituitary-adrenalin axis, leading to the production of immunosuppressive glucocorticoids. Although the authors did not rule out these possibilities, they did not find any evidence of generalised immunosuppression in control mice treated with rTNFα [1]. Another possibility considered by the authors was the induction of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase, which is known to inhibit effector T cell responses. Again, however, no evidence was found to support this [1].

It was also shown that the recovery phase of adjuvant-induced arthritis in Lewis rats coincided with the peak of TNFα expression in antigen-stimulated draining lymph node cells, suggesting an immunomodulatory role for endogenous TNFα in disease remission [1]. In contrast, TNFα expression was highest in Wistar-Kyoto rats (which are resistant to adjuvant-induced arthritis) in the immediate post-immunisation period. In the light of these findings, another possibility to consider is that the pathogenesis of adjuvant-induced arthritis is fundamentally different to that of RA, such that TNFα is anti-inflammatory in the former but pro-inflammatory in the latter. In this respect it is important to point out that in the study by Kim and colleagues, arthritis was induced by immunisation with heat-killed *Mycobacterium tuberculosis* plus mineral oil [1], both of which may induce arthritis independently. Hence, multiple arthritogenic factors contri-

EAE = experimental autoimmune encephalomyelitis; IFN = interferon; IL = interleukin; RA = rheumatoid arthritis; rTNF = recombinant TNF; TNF = tumour necrosis factor; TNFR = TNF receptor.

bute to disease induction and it is possible that TNFα plays different, and perhaps changing, roles in the overall pathogenesis of this form of arthritis.

In the light of the findings presented by Kim and colleagues [1], it is interesting that a small number of studies have shown exacerbation of specific autoimmune diseases by anti-TNFα therapy. For example, TNFα blockade was shown to increase both the rate and frequency of relapse in patients with existing multiple sclerosis [4]. Similarly, in experimental autoimmune encephalomyelitis (EAE), $TNF\alpha^{-/-}$ mice developed enhanced inflammation and demyelination, whereas treatment of susceptible mice with TNFα reduced disease severity [5]. In another study, EAE failed to resolve in $TNF\alpha^{-/-}$ or $TNFR^{-/-}$ mice, suggesting that TNFα plays an important role in resolution of inflammation [6]. In murine lupus it was shown that administration of rTNFα was protective [7] whereas TNFα deficiency was associated with increased production of anti-nuclear antibodies and accelerated onset of disease [8]. TNFα was also shown to have anti-inflammatory properties depending on the timing of TNFα expression in a murine model of autoimmune diabetes [9].

One possibility to consider is that TNFα acts on cells of the joint (for example, endothelial cells) to promote cellular infiltration but acts on cells of the adaptive immune system to suppress T cell responses, possibly as part of a negative feedback loop. This is supported by the observation by Kim and colleagues that administration of rTNFα suppressed IFNγ production by antigen-stimulated T cells. Furthermore, studies from the laboratory of Cope and colleagues have shown that prolonged exposure of T cells to TNFα in the context of RA leads to the induction of hyporesponsiveness to T cell receptor signalling [10]. However, the fact that Kim and colleagues did not observe reduced T cell responses in TNFα treated rats immunised with a control antigen (hen egg lysozyme) would argue against a generalised immunosuppressive effect [1]. Another possibility is that TNFα modulates antigen presenting cell function, leading to alterations in T cell activity. For example, two recent studies have shown that TNFα selectively inhibits expression of p40, the common subunit of IL-12 and IL-23, in human and mouse myeloid cells, respectively [11,12].

In summary, this paper raises intriguing questions about the diverse roles played by TNFα in adjuvant-induced arthritis although further studies will be required to establish their relevance to human disease.

Competing interests

The author declares that they have no competing interests.

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