

Editorial

Immunocytokines: the long awaited therapeutic magic bullet in rheumatoid arthritis?

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See related research by Schwager *et al.*, <http://arthritis-research.com/content/11/5/R142>

Abstract

Modulatory cytokines such as IL-4 and IL-10 looked promising biologicals, but suffered from poor exposure at the inflamed joints when administered via the patient-friendly subcutaneous route. Immunocytokines have now been engineered with tissue targeting potential and are a possible solution to this problem, although challenges still exist. Local inflammatory processes cause destruction of extracellular matrix (ECM) components, leading to neo-epitopes, and/or elicit the synthesis of new ECM components. This makes ECM elements interesting targets for antibody-mediated recognition and retention, to achieve higher levels of immunocytokines at the site of therapeutic interference. The study presented by Schwager and colleagues shows that targeted delivery of IL-10 is more efficacious in experimental arthritis. Clinical studies are warranted to show whether this strategy works for all rheumatoid arthritis patients or is better for subgroups with a defined ECM phenotype. In principle, the scFv-targeting system is plastic enough to allow for personalized strategies.

Immunocytokines

The successful introduction of biologicals such as neutralizing anti-TNF-antibodies in the treatment of rheumatoid arthritis has paved the way for using immunocytokines in non-lethal diseases. The study of Kathrin Schwager and colleagues [1] in a recent issue of *Arthritis Research & Therapy* reports impressive preclinical results using F8-IL-10 (DEKAVIL), a fully human fusion protein of the single-chain Fv (scFv) antibody F8, which specifically recognizes the extra-domain A (EDA) of fibronectin, with the anti-inflammatory cytokine IL-10. They showed the accumulation of this fusion protein at the site of inflammation, good therapeutic efficacy and a safety profile that provides the basis for the first clinical trial of antibody-based pharmacodelivery of DEKAVIL in rheumatoid arthritis (RA) patients

In general, immunocytokines are scFv fragments of a monoclonal antibody directed against a specific target fused to a cytokine, thus retaining the functions of both the antibody and the cytokine. In cancer, the use of single-chain antibody fragments for targeting and *in vivo* imaging of tumors is a new weapon in the oncologist's armamentarium [2]. These scFvs show good tumor targeting and biodistribution properties with a tumor-to-background ratio of more than 10% ID/g.

Extracellular matrix components for retention of immunocytokines

The therapeutic potential of recombinant cytokines is often limited by severe toxicities due to the high dosages needed as cytokines often have poor pharmacokinetics and dynamics. A straightforward strategy is the fusion of cytokines with the Fc tail of antibodies or liposomal encapsulation to increase their half-life in the circulation, although this will not improve the local accumulation [3,4]. Schwager and colleagues [1] showed that cytokines can be targeted to the site of interest by using scFv antibody fragments recognizing extracellular matrix (ECM) components present in the joint. The first question they addressed is which ECM protein is the best targetable candidate in the inflamed joint. Their approach was a side-by-side comparison of immunohistochemical staining of synovial tissue of several antibodies directed against different ECM antigens, and identified EDA, a splice variant of fibronectin, as the best candidate. They showed a therapeutic effect of F8-IL-10 that was better than an IL-10 fusion protein directed against an irrelevant protein antigen.

Concomitant neutralization of signaling?

Unfortunately, they did not include in their studies the therapeutic impact of the targeting antibody alone, without

ECM = extracellular matrix; EDA = extra-domain A; IL = interleukin; RA = rheumatoid arthritis; scFv = single-chain Fv antibody fragment; TLR = Toll-like receptor; TNF = tumor necrosis factor.

IL-10, or coupled to an inactive protein. It is now well accepted that EDA is an endogenous Toll-like receptor 4 (TLR4) ligand [5], and the F8 scFv antibody fragment possibly interferes with EDA-induced TLR4 signaling by blocking or steric hindrance. We recently demonstrated an important role for TLR4 in experimental arthritis. Blocking TLR4 using Bartonella lipopolysaccharide, a naturally occurring TLR4 antagonist, clearly ameliorates murine collagen-induced arthritis [6]. This potential double hit may add another layer of activity to the immunocytokines. The possibilities are unlimited as recombinant antibody fragments can be engineered to assemble into stable multimeric oligomers of high binding avidity and specificity to a wide range of target antigens and haptens [7]. Multi-specific Fv modules can be designed as cross-linking reagents for local accumulation of cytokine action through attachment to the ECM and by targeting carrier cells or proteins for trafficking to the joint. Furthermore, it is possible to select human svFc monoclonal autoantibodies for ECM proteins from B-cell phage-display libraries derived from RA patients that are more specific (recognizing RA-specific neo-epitopes as citrullinated antigens) and have higher affinities [8]. As well as the ECM, other proteins that are extremely upregulated and pro-arthritis in the inflamed joint (for example, S100 alarmins) are candidate targets for scFv antibody-based immunocytokines [9].

Local delivery versus local accumulation?

Intra-articular therapy is attractive in RA patients to enhance efficacy of a drug and reduce side-effects associated with systemic immunosuppression. Rheumatologists are familiar with local injections - for example, to extinguish the inflammation in affected joints with corticosteroids. Results from local delivery of anti-TNF biologicals are encouraging, and although a plausible form of therapy, larger studies are warranted to address the safety issues associated with repeated and prolonged antibody delivery in the joint [10]. The gene-therapy field has acknowledged this strategy and used recombinant vectors to transduce the synovium and produce biologicals locally. However, even using local gene delivery, effects on ipsilateral and contralateral joints were reported, although it remains debatable whether this reflected spill-over of biologicals to the system [11]. Combining the best of both strategies - local synthesis and retention using scFv antibodies against ECM components - can be envisioned.

Perspective

The successful introduction of immunocytokines as a magic bullet in the treatment of RA will depend on the spontaneous generation of autoantibodies against the svFc part of the molecule. The presence of anti-idiotypic antibodies has been identified in sera of RA patients, and these antibodies may impair the accumulation of immunocytokines, neutralize the cytokine activity and prohibit repeated injection. So far, autoantibodies against fully humanized anti-TNF antibodies have not been a major problem and we are hopeful that

immunocytokines will become a therapeutic reality in RA patients in the near future.

Competing interests

The authors declare that they have no competing interests.

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