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THERAPY

Hitting the target: delivering IL-10 to treat experimental arthritis

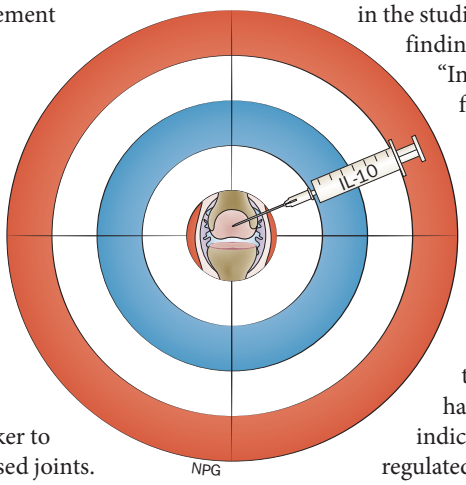
Targeting therapeutic agents specifically to the diseased joint during active disease has been an area of much research in recent years. Now, two new studies demonstrate that the anti-inflammatory cytokine IL-10 can be delivered as a therapeutic agent—either via local gene therapy or via a fusion protein with specific affinity to arthritic joints—and can effectively combat arthritis in experimental models.

In the first study, Vermeij *et al.* wanted to explore the concept of disease-regulated local gene therapy, by placing the gene for IL-10 under the control of inflammation-dependent promoters in the streptococcal cell wall mouse model of arthritis. "The goal was to fine-tune the supply of biologic agents in a 'supply-meets-demand' fashion, a disease-regulated local gene therapy for rheumatoid arthritis," says author Fons van de Loo.

Proximal promoters of six inflammation-associated genes—*S100a8*, *Cxcl1*, *Mmp13*, *Saa3*, *Il1b* and *Tsg6*—were assessed and, after analysis of the different activation kinetics of these promoters during the course of active arthritis in mice, two of them (*Saa3* and *Mmp13* promoters) were selected as candidates for use in disease-regulated gene therapy using the IL-10 transgene. Lentiviral vectors expressing a luciferase reporter gene and the IL-10 transgene under the control of either the *Saa3* or *Mmp13* promoter were then injected intra-articularly into mouse knee joints, with arthritis induced 4 days later.

Crucially, the researchers confirmed that IL-10 expression was upregulated by the *Saa3* and *Mmp13* promoters during arthritis. Moreover, disease-dependent IL-10 expression from these constructs led to decreased levels of synovitis and depletion of proteoglycan in mouse knee joints after induction of arthritis. "These unmodified endogenous promoters were reactive to disease and 'strong' enough to produce high enough levels of IL-10 locally to ameloriate disease," clarifies van de Loo.

The second study, by Hughes *et al.*, took a different approach for IL-10 therapy. Previous work had demonstrated that an antibody fragement specific to collagen type II that had been post-translationally modified by reactive oxidants, termed 1-11E, could be used to direct agents to inflamed arthritic joints. As such, viral IL-10 (vIL-10) was fused to 1-11E via a matrix metalloproteinase (MMP)-cleavable linker to deliver IL-10 to diseased joints.



Investigating cartilage samples from several mouse models of arthritis (antigen-induced arthritis, collagen-induced arthritis and the destabilization medial meniscus model of osteoarthritis) as well as from patients with osteoarthritis, the 1-11E–vIL-10 fusion was observed to bind specifically to damaged arthritic cartilage. *In vitro* assays confirmed that IL-10 activity only occurred after cleavage by MMP-1. When administered systemically in mouse models of arthritis, 1-11E–vIL-10 localized specifically to inflamed knee joints with active arthritis. Importantly, the fusion protein reduced inflammation in diseased joints, with similar features as healthy joints after treatment.

"We were able to demonstrate the increased efficacy of IL-10, which lacks therapeutic efficacy when delivered systemically, by targeting it to arthritic joints through an antibody fragment that binds to a diseased-tissue-specific biomarker," explains author Ahuva Nissim. "These fragments have the potential for targeting treatments such as inflammatory cytokine blockers, anti-inflammatory cytokines or cartilage regenerating factors," she adds.

Speaking to *Nature Reviews Rheumatology*, Christopher Evans (Mayo Clinic, USA), who was not involved in the studies, puts these new findings into context. "Intra-articular therapy for joint diseases is intuitively attractive, but surprisingly difficult," he says.

"The first study builds on previous work and has shown that IL-10 cDNA is an effective transgene ... and has provided data indicating the value of regulated gene expression," he notes, but concedes that moving gene therapy approaches to the clinic is complicated, arduous and expensive. For the second study, "the strategy has the potential to serve as the basis for novel therapeutics, because it can achieve what no existing drugs can do: localize specifically to inflamed joints, remain there and release its active payload in response to disease activity," he explains. However, how long the agent remains in the joint and indeed how sustainable the therapeutic effect is, as well as whether neutralizing immune responses are generated, remain to be determined. Further work on the feasibility of intra-articular therapy using IL-10, and indeed the delivery methods used, will be needed.

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Original articles Vermeij, E. A. *et al.* Disease-regulated local IL-10 gene therapy diminishes synovitis and cartilage proteoglycan depletion in experimental arthritis. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2014-205223 | Hughes, C. *et al.* Targeting of viral Interleukin-10 with an antibody fragment specific to damaged arthritic cartilage improves its therapeutic potency. *Arthritis Res. Ther.* **16**, R151 (2014)

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