Gene therapy for rheumatoid arthritis?

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In the wake of Jesse Gelsinger’s tragic death in a gene therapy trial, there has been much soul searching and investigation to evaluate whether the attractive basic concepts of gene therapy had been rushed too quickly into the clinic, and had contributed to this incident. As an unfortunate by-product, gene therapy trials, even for cancer patients with poor prognosis, have all but ceased. So it is a pleasure to read that research in this field, in the context of inflammatory diseases, continues. Two recent articles in the JCI report interesting progress in gene therapeutic approaches to type II collagen-induced arthritis, a well-validated model of rheumatoid arthritis.

Fathman and his colleagues, long-time researchers on the role of antigen-specific T cells in autoimmunity, have shown that collagen type II–specific T cells can be used as a vehicle to deliver an inhibitor, the IL-12 p40 dimer (1). The authors show that these cells accumulate in the synovium, consistent with a local inhibition of IL-12 signaling in this target tissue, but not ruling out other mechanisms. While large numbers of T lymphocytes accumulate in the inflamed synovium in human rheumatoid arthritis, very few T cells are found in the synovium in collagen-induced arthritis. For this reason, at least in the model studied, it is possible that another important target of IL-12 blockade is in lymphoid tissue, where IL-12 promotes the formation of CD4+ T cells with a Th1 phenotype. Regardless of where the effect takes place, Nakajima et al. demonstrated a significant reduction in the Th1/Th2 ratio, consistent with the anticipated mechanism of their treatment. The local delivery of an inhibitor would diminish the risk of infection due to systemic immune suppression.

Fox and his colleagues (2) demonstrate that another immune cell type, the immature dendritic cell, can also be used to deliver immunoregulatory molecules in a specific and effective manner. They used IL-4, which inhibits both Th1 induction and macrophage activation, effects that would be anticipated to be beneficial. Indeed, Morita et al. show a clear-cut benefit of adoptive transfer with these modified cells in the collagen-induced model of rheumatoid disease. Interestingly, the route of administration of the dendritic cells strongly affected the success of the therapy, with intraperitoneal being better than intravenous, which was better than subcutaneous. In contrast, for inducing immune responses, subcutaneous has been reported to be better than intravenous administration. The authors also tested IL-4-transduced T cells and fibroblasts and showed that these cells were not effective against arthritic symptoms. However, these T cells, unlike the ones successfully used by Nakajima et al. (1), were not selected for their specificity to joint antigens. Thus, the results are not inconsistent but, together, suggest that synovial targeting is important and that there are multiple ways of targeting the local inflammatory site.

Both of these strategies tell us that there are prospects for the gene therapy of rheumatoid arthritis. But how far are we from human trials? I think we are still rather a long way to trials that are beyond proof of principle (3). Both approaches used in the human context are individual-specific therapies and would need to use the patient’s own cells, after prolonged culture and manipulation. So there are hurdles to overcome, such as inconvenience and, most importantly, cost, which would limit the applicability of this therapy. Even the existing effective antirheumatoid therapies, such as the anti-TNF-α drugs etanercept (Enbrel®) and infliximab (Remicade®) (4), are now rationed by their cost, most obviously in Europe but also in the US.

Nevertheless, the principle that has been revealed by these two papers (1, 2), that either antigen-specific T cells or dendritic cells can deliver inhibitors and ameliorate arthritic symptoms, is likely to promote progress in this field. The current therapies for rheumatoid arthritis are principally anti-inflammatory, and these two papers clearly show that inhibiting the immune response would be useful clinically, most likely in combination with existing therapy. It may be that a key role of gene therapy at present is for mechanistic proof-of-principle studies, but the hope has to be that the specificity of gene regulation, and hence its targeting to the site of the disease, will enable gene therapy to emerge as a safe and effective therapeutic mode.

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