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# On the TRAIL of an arthritis cure

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Neither as deadly as cancer nor as apocalyptic as AIDS, autoimmune diseases still visit abundant misery upon large numbers of people. Rheumatoid arthritis (RA) is one such disease. Despite recent improvements in therapy, this crippling and common condition remains incurable, costly and a target for gene therapists.[1,2] A recent publication in the *Journal of Clinical Investigation*[3] from John Mountz's laboratory at the University of Alabama describes an important strategic advance in the therapeutic use of genes for treating RA and other autoimmune diseases.

As the nomenclature indicates, autoimmune diseases result from the inappropriate immune recognition of self-antigens. For reasons that remain obscure, autoimmune reactions in RA are particularly severe in many, but not all, joints, leading to the inflammation, pain and characteristic deformities associated with this condition. According to most commentators, autoreactive T-lymphocytes are key drivers of the disease process. Their selective eradication is an attractive, but elusive, therapeutic strategy. In the experiments of *Liu et al*,[3] autoreactive T-lymphocytes were killed by *ex vivo* transfer of genetically modified, antigen primed, dendritic cells (DCs) expressing a killer gene, tumour necrosis factor-related, apoptosis-inducing ligand (TRAIL).

The logic behind this strategy is appealing. DCs are the body's most potent antigen-presenting cells (APCs). The process of antigen presentation requires them to interact specifically with T-lymphocytes. When the DCs express TRAIL, they induce apoptosis in the T-lymphocytes which they recognize. When the TRAIL$^+$ DCs are pulsed with autoantigen responsible for disease, they should selectively engage, and thus kill, only those T-lymphocytes that recognize the autoantigen. In this way, autoreactive, pathogenic T-lymphocytes are eliminated without causing generalized immunosuppression.

Mountz's group has previously demonstrated the promise of this approach with genetically modified macrophages,[4] an alternative type of APC, expressing Fas ligand which, like TRAIL, induces apoptosis in susceptible cells. The administration of FasL$^+$ macrophages to mice successfully treated collagen-induced arthritis, a common animal model of human RA. Despite demonstrating proof of principle, the prototype FasL$^+$ macrophage system had several flaws, the most inconvenient being Fas-mediated apoptosis of the genetically modified macrophages themselves. For this reason the investigators turned to TRAIL, a molecule whose tissue distribution is highly restricted. Of importance to the present study, it is expressed on T-lymphocytes, but not on mature DCs. TRAIL has been previously evaluated in the context of arthritis gene therapy as a means of destroying rheumatoid synovium[5] and genetically modified DCs expressing IL-4 have been used to induce immune deviation in animal models of RA.[6,7] However, the combination of DCs and TRAIL is novel and intriguing.

*Liu et al*[3] used recombinant, first-generation, type 5 adenovirus vectors to modify cultures of DCs recovered from syngeneic mice. The expression of TRAIL was controlled by a reverse tetracycline transactivator, enabling induction by doxycycline. Collagen-induced arthritis was initiated in four groups of mice, which received a series of four i.p. injections of $5 \times 10^6$ genetically modified DCs over a period of 2 weeks. Control groups of mice received TRAIL$^+$ DCs in the absence of doxycycline, or GFP$^+$ DCs in the presence of doxycycline. Two additional groups of mice received TRAIL$^+$ DCs and doxycycline; in one of these groups, the TRAIL$^+$ DCs were pulsed with type II collagen, the inciting autoantigen in this model of RA.

The results were impressive. Treatment with TRAIL$^+$, collagen-pulsed DCs dramatically reduced disease incidence and severity, as well as lowering the numbers of T-lymphocytes within the joint, the presence of type II collagen reactive T-lymphocytes in the spleen, and the production of IFN-$\gamma$ by splenic T-lymphocytes in response to type II collagen. Tracking studies identified the spleen, but not the liver or lymph nodes, as the primary site to which the genetically modified DCs migrated, and apoptotic T cells were detected in the spleens of arthritic mice treated with collagen-pulsed, TRAIL$^+$ DCs. The production of anti-type II collagen antibodies was also reduced in these mice.

Qualitatively similar, but weaker, responses occurred with TRAIL$^+$ DCs that had not been pulsed with type II collagen. This indicates advantages of selective, as opposed to unselective, T-lymphocyte depletion. Nevertheless, it also suggests that nonspecific T-lymphocyte apoptosis may be occurring, in which case the possibility of more widespread immunosuppression is of concern. Other unanswered questions include the longevity of the effect, and whether redosing is required to maintain it. Ideally a state of immune tolerance is achieved, under which conditions the treatment has become a cure.

Human application of this technology is constrained by several factors. For one, the autoantigen that drives human RA has not been identified, and there are likely to be several. They could vary between individuals and change at different times in the disease process. For these reasons, the strategy may find easier clinical application in human autoimmune diseases where autoantigens have been clearly characterized. Before this happens, the effects of DC-TRAIL therapy on normal immune function will need to be evaluated thoroughly. Arguably, enthusiasm may also be tempered by the lack of clinical success in trials involving T-lymphocyte depletion in human subjects with RA. Ultimately, however, the biggest barriers to clinical use could be economic. *Ex vivo* gene therapy using cultured

autologous cells is extremely expensive, a critical issue in today's health care environment. ■

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