EXPERIMENTAL ARTHRITIS

Targeted anti-C5 drug neutralizes complement in the joint

Complement component C5—activation of which produces the proinflammatory peptide C5a and the proinflammatory and cytolytic complex C5b-9—can be neutralized in the inflamed joint without modulating the circulating complement system. A humanized anti-C5 antibody fused to a peptide that targets inflamed synovia was able to prevent and treat antigen-induced arthritis (AIA) in rats, and treat collagen antibody-induced arthritis in mice. If translated to humans, the work by Francesco Tedesco and colleagues, published in *Arthritis & Rheumatism*, could lead to control of chronic inflammation in patients with rheumatoid arthritis (RA) without creating an excess risk of infection.

“Our group has been working for over three decades on the involvement of the complement system in the pathogenesis of immune-mediated diseases including RA,” explains Tedesco. “We have developed human recombinant antibodies neutralizing C5 that have proven effective in controlling different models of

complement mediated-diseases, including AIA, thrombus formation and fetal loss in APS, ischemia reperfusion and others,” continues Tedesco, adding that intra-articular injection of these antibodies is effective in treating experimental arthritis. “Our major effort over the past few years has been to find ways to deliver these antibodies to tissue targets in order to avoid problems related to the depletion of circulating C5.”

“...targeted anti-C5 treatment should be considered as an adjunct to other therapies...”

To achieve this goal in the setting of arthritis, the investigators fused anti-C5 antibodies to a peptide previously shown to selectively target inflamed synovial tissue. The team used optical imaging to track *in vivo* distribution of the molecule (which was fluorescently labeled) and confirmed that it bound inflamed, but not normal, synovia, and did not bind to

other inflamed tissues. The compound could be observed in the inflamed joint in rats with AIA within 5 h of intravenous injection, with levels peaking at 3–4 days and remaining detectable at day 30. Such longevity could be important in the treatment of patients with chronic autoimmune diseases such as RA.

“We believe that the complement system has not received adequate attention as a therapeutic target in RA, and [targeted anti-C5 treatment] should be considered as an adjunct to other therapies that are currently used.” Such a drug would be cost-effective in the clinic, the researchers add, because reasonably low doses are required to control established inflammation in rats and mice.

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Original article Macor, P. *et al.* Treatment of arthritis models by targeting synovial endothelium with a neutralizing recombinant antibody to C5. *Arthritis Rheum.* doi:10.1002/art.34430