THERAPY

A role for TIARP in TNF-dependent arthritis

Tumor necrosis factor (TNF) agonists are widely used in the treatment of rheumatoid arthritis (RA), but the mechanisms of action of these agents remain poorly understood. New research suggests that TNF-alpha-induced adipose-related protein (TIARP) has an important role in inflammatory arthritis in both mice and humans through the regulation of proinflammatory cytokines.

Expression of the transmembrane protein TIARP in adipocytes has previously been shown to be regulated by both TNF and interleukin-6. To characterize the role of TIARP in inflammatory arthritis, the investigators studied mice with glucose-6-phosphate isomerase (GPI)-induced arthritis—a model of TNF-dependent arthritis. "We have recently demonstrated a clear therapeutic effect of anti-TNF monoclonal antibodies in mice with GPI-induced arthritis, and the therapeutic response correlated with the *in vitro* regulation of TNF production," says Isao Matsumoto, one of the study's researchers.

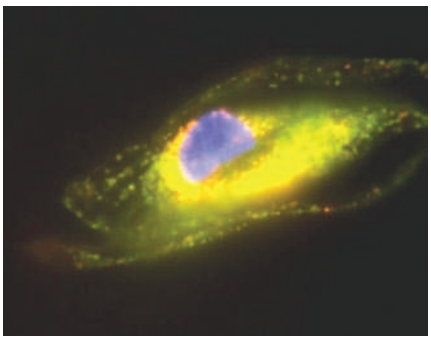

Figure 1 | TIARP (green) co-localizes with CD68 (red) in the RA synovium.

The study first demonstrated that expression of TIARP messenger RNA (mRNA) was strongly upregulated in GPI-immunized splenocytes to levels at least 20-fold higher than in control splenocytes. TIARP mRNA was also detected in the joints of mice with GPI-induced arthritis, where its expression correlated positively with the severity of joint swelling observed. Treatment with an anti-TNF monoclonal antibody ameliorated symptoms of arthritis and also significantly downregulated TIARP mRNA expression in the spleens of arthritic mice, although levels of TIARP mRNA in the arthritic joints were similar in mice treated with the antibody or control immunoglobulin.

Further investigation demonstrated that the induction of arthritis following GPI immunization was associated with the upregulation of TIARP mRNA in $CD11b^+$ splenocytes, particularly in the early phase of the disease. Within the joints of arthritic mice, staining with anti-TIARP antibodies revealed that the protein was mainly localized to the hyperplastic synovium. The authors point out, however, that this expression pattern indicates neither a constructive nor a destructive effect of TIARP on the synovium.

The researchers then evaluated the expression of the human ortholog of TIARP, metalloreductase STEAP4 (six-transmembrane epithelial antigen of prostate 4), in the joints of patients with RA and healthy controls. STEAP4 mRNA was found in peripheral blood mononuclear cells in only one of four RA patients, but it was highly expressed in the synovium of all four patients compared with controls. Immunostaining of the RA synovia revealed that STEAP4 co-localizes with CD68 (Figure 1), a protein expressed by macrophages.

"Our findings shed light on a new mechanism of action of TNF antagonists in autoimmune arthritis," says Matsumoto. The nature of that role, however, remains to be clearly defined. The investigators plan to further investigate the correlation between this TNF-induced protein and arthritis by use of TIARP-knockout mice, as well as large-scale studies of STEAP4 expression in the joints of patients with RA before and after anti-TNF treatment.

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