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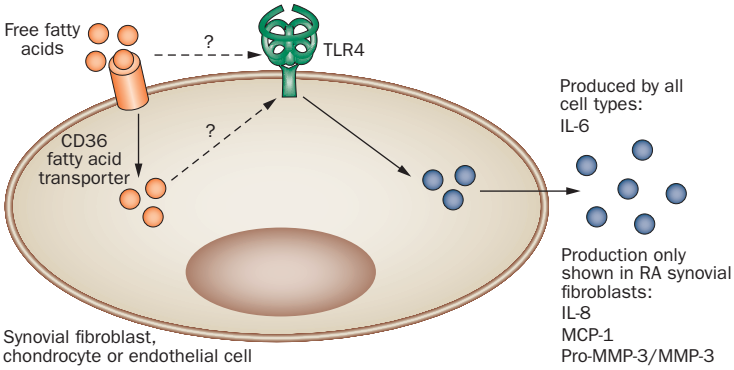
INFLAMMATION

Synovitis—are fats in the fire?



Obesity is a known risk factor for rheumatic diseases, including osteoarthritis (OA) and rheumatoid arthritis (RA), owing at least in part to the effects of adipokines produced by adipose cells. Now, new data implicate free fatty acids (FFAs), which can also be released from adipose tissue, as proinflammatory factors relevant to rheumatic diseases.

Klaus Frommer *et al*. examined the effects of a range of FFAs on key articular cell types *in vitro*. Their studies revealed that FFAs stimulated RA synovial fibroblasts (SFs) to release increased levels of key factors involved in joint injury, specifically IL-6, IL-8, monocyte chemoattractant protein 1 (MCP-1) and matrix metalloproteinase 3 (MMP-3); in particular, IL-6 secretion was typically induced over 10-fold above baseline levels. Furthermore, IL-6 production by SFs from patients with OA and psoriatic arthritis was also increased by FFAs. Interestingly, SF responsiveness varied between donors, irrespective of disease, which the authors hypothesized could reflect differential expression of FFA receptors or interaction partners; however, this theory was not tested.

Regarding IL-6 production, "RASFs showed a comparatively strong response to all FFAs tested, independent of their type," explains Frommer. "On the other hand, differences in the response to various FFAs could be observed for chondrocytes and endothelial cells." The chondrocytes and endothelial cells used were not derived from patients with rheumatic disease; thus, whether cells from such individuals would demonstrate different responsiveness remains unclear.

Inhibitor studies revealed that the fatty acid transporter CD36 was essential for palmitic-acid-induced IL-6 secretion by RASFs, suggesting that FFAs must be internalized to promote IL-6 production. However, both extracellular and intracellular Toll-like receptor 4 (TLR4) inhibitors blocked IL-6 induction in RASFs. This finding is in keeping with controversy surrounding the mechanism of TLR4-dependent FFA signalling, and highlights the crucial role of this protein in the proinflammatory actions of FFAs.

"If our findings are also valid *in vivo*, then anything that leads to chronically elevated levels of FFAs should be avoided by patients with rheumatic diseases," says Frommer. "Alternatively, targeting proteins involved in FFA signalling (such as TLR4) or the use of drugs that lower FFA levels might be an option." Although these results are interesting, the role of FFAs in rheumatic diseases needs to be clarified before such approaches can be considered.

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Original article Frommer, K. W. *et al*. Free fatty acids: potential proinflammatory mediators in rheumatic diseases. *Ann. Rheum. Dis*. doi:10.1136/annrheumdis-2013-203755