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EXPERIMENTAL ARTHRITIS

PATHOGENIC ROLE OF AUTOTAXIN AND LPA

A phospholipid signalling network that is a target in cancer drug development drives inflammation in rheumatoid arthritis (RA), according to data from animal models of the disease. Data published by Vassilis Aidinis and colleagues in the *Journal of Experimental Medicine* implicates autotaxin (also known as ENPP2) and its bioactive lipid product lysophosphatidic acid (LPA) in RA pathogenesis, and suggests that ongoing work to block this enzyme might eventually benefit patients with RA.

LPA signals through dedicated receptors to elicit responses including cell migration and proliferation, and is produced when autotaxin cleaves lysophosphatidylcholine. A polar lipid, LPA is soluble and found in bodily fluids including synovial fluid. Previous work showed that autotaxin mRNA is upregulated in synovial fibroblasts in mouse models of arthritis, but the importance of this expression was unclear.

Aidinis and colleagues used three animal models of arthritis as well as cells from patients with RA to confirm increased expression of autotaxin in arthritic synovial fibroblasts in comparison with healthy cells. In the mice, anti-TNF treatment attenuated overexpression of autotaxin, showing it to be downstream of exacerbated TNF signalling.

Next, the researchers bred *Enpp*$^{2-/-}$/*hTNF*$^{+/-}$/*Col1Cre*$^{+/-}$ mice—an inflammatory arthritis model modified to knock out autotaxin expression specifically in synovial fibroblasts. Inflammation and synovial hyperplasia were markedly decreased in these animals. "Conditional deletion of genes is, in our opinion, the ultimate experimental validation of a gene's function and involvement in pathogenic mechanisms," remarks Aidinis. Crossing *hTNF*$^{+/-}$ mice with other strains to produce either double or half the usual circulating level of autotaxin did not affect disease severity, indicating that local synovial expression is key to pathogenesis. *In vitro* experiments showed that autotaxin was signalling via LPA and its receptors.

"The next step is pharmaceutical targeting of autotaxin as well as LPA receptors," says Aidinis; "almost all major pharmas are developing an inhibitor". Finally, phospholipidomics will be the "ideal approach" to probe lipid signalling networks in arthritis, he adds.

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Original article Nikitopoulou, I. *et al.* Autotaxin expression from synovial fibroblasts is essential for the pathogenesis of modeled arthritis. *J. Exp. Med.* doi:10.1084/jem.20112012