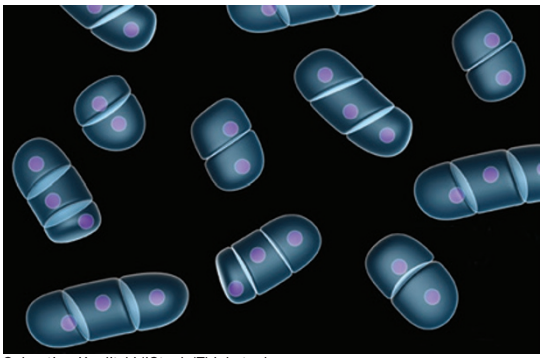
Nature Reviews Rheumatology **10**, 576 (2014); published online 2 September 2014; doi:10.1038/nrrheum.2014.148

OSTEOARTHRITIS

A role for CXCR2 signalling in cartilage homeostasis



Sebastian Kaulitzki/iStock/Thinkstock

ELR$^+$ (glutamic acid-leucine-arginine motif positive) CXC chemokines, which bind heparin and signal through the receptors CXCR1 and CXCR2 in humans and CXCR2 in mice, have a well-established role in the pathogenesis of arthritis, attributed to their capacity to attract inflammatory cells. New research, however, points to an unexpected role for CXCR1/2 signalling in maintaining chondrocyte phenotypic stability.

Sherwood *et al.* first showed that ELR$^+$ CXC chemokine receptors are expressed in early osteoarthritis (OA) and healthy human articular cartilage. Strikingly, healthy chondrocytes were found to produce high levels of the CXCR1/2 ligand CXCL6, which accumulated locally in the cartilage extracellular matrix (ECM), but CXLC6 was not detected in tissue from patients with more advanced OA. Similarly, expression of CXCL6 in mouse articular cartilage ECM was lost following surgery to induce experimental OA.

The researchers hypothesized that, in physiological conditions, binding of CXCL6 to heparan sulphate proteoglycans (HSPGs) confines its expression to the cartilage ECM and prevents this chemokine from attracting inflammatory cells. Accordingly, CXCL6 was detected in the supernatant of mouse cartilage explants incubated with heparitinase, but not from explants that did not undergo enzymatic degradation of HSPGs.

CXCR2$^{-/-}$ mice did not spontaneously develop arthritis, but after surgery to induce joint instability developed a more-severe OA phenotype and increased chondrocyte hypertrophy compared with wild-type mice, indicating that CXCR2 supports cartilage homeostasis *in vivo*.

In human chondrocytes *in vitro*, blockade of CXCR1 and CXCR2 resulted in reduced ECM production and expression of chondrocyte differentiation markers and increased chondrocyte apoptosis. Chondrocytes from CXCR2$^{-/-}$ mice had similar deficiencies in comparison with cells from wild-type mice. Notably, forced expression of constitutively active AKT rescued the decreased expression of phenotypic markers and apoptosis induced by disrupted CXCR2 signalling.

The authors suggest that cell-autonomous ELR$^+$ CXC chemokine signalling triggered by a local sequestered pool of ELR$^+$ CXC ligands supports chondrocyte phenotypic stability in physiological conditions, and the loss of this mechanism, through cartilage breakdown, is an important event in OA pathogenesis.

Sarah Onuora

Original article Sherwood, J. *et al.* A homeostatic function of CXCR2 signalling in articular cartilage. *Ann. Rheum. Dis.* doi:10.1136/annrheumdis-2014-205546