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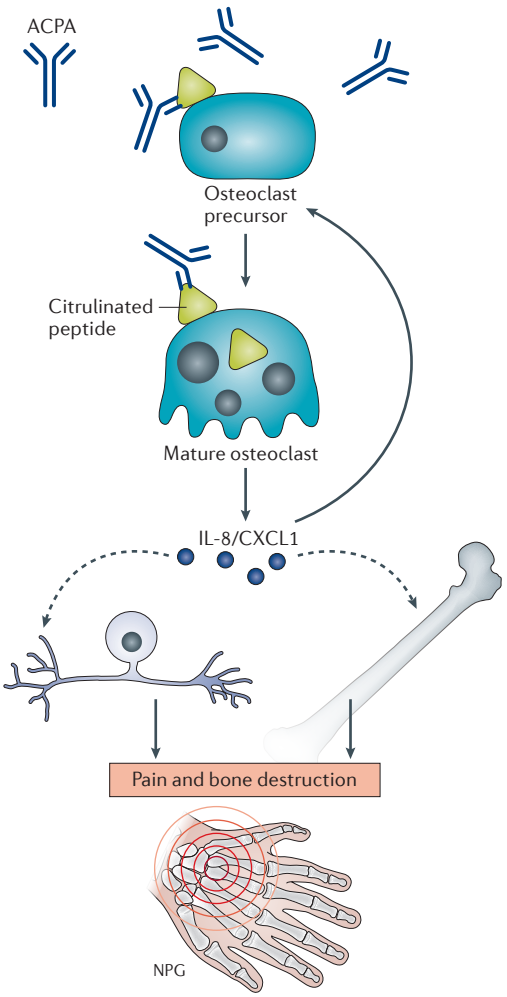
RHEUMATOID ARTHRITIS

Osteoclasts and ACPAs — the joint link

Two new studies published in the *Annals of the Rheumatic Diseases* describe previously unrecognized effects of anti-citrullinated-protein antibodies (ACPAs) — induction of pain and bone loss — mediated by osteoclasts and chemokine signalling. These findings have important implications for our understanding of pathogenetic mechanisms in rheumatoid arthritis (RA).

In assessing whether ACPAs could drive pain signalling independently of the inflammatory process, one of the studies showed that treatment of mice with affinity-purified ACPAs, but not with the IgG$^+$ flow-through fraction, isolated from plasma of patients with RA induced pain-like behaviour without signs of inflammation. No evidence that ACPAs could mediate neuronal excitability was found in a set of *in vitro* tests. The mechanical and thermal hypersensitivity induced by intravenous ACPA injection in mice was prevented by reparixin, an antagonist of C–X–C chemokine receptor type 1 (CXCR1) and CXCR2, the receptors for C–X–C motif chemokine 1 (CXCL1), a mouse analogue of human IL-8 that can be produced by osteoclasts. "It has been reported by others that mouse analogues of IL-8 increase neuronal excitability via IL-8 receptors (CXCR1/2) expressed by neurons," explains Camilla Svensson, the corresponding author on this report, providing a possible explanation for how CXCL1/IL-8 could induce pain. Altogether, these observations "provide an attractive explanation as to why joint pain often precedes the onset of arthritis in autoantibody-positive individuals, and perhaps [...] why joint pain often persists after inflammation has been successfully treated."

> "... new mechanisms of ACPA-induced pain and bone destruction help clarify the pathogenetic role of ACPAs in RA..."



The other study focused on how ACPAs affect osteoclast differentiation and subsequent bone destruction. Here, the researchers found that peptidylarginine deiminases (PADs), the enzymes that catalyze protein citrullination, are necessary for *in vitro* differentiation of osteoclasts from peripheral blood macrophages and for ACPA-induced osteoclast activation. Human osteoclasts produced high levels of IL-8 when stimulated with ACPAs, and IL-8 neutralization blocked osteoclast maturation induced by macrophage colony-stimulating factor 1 and receptor activator of nuclear factor κB ligand. Consistently with the ACPA-mediated increase in osteoclast activity, administration of ACPAs to mice led to a decrease in trabecular bone density, trabecular number and bone volume fraction, an effect; these changes were reversed by treatment with reparixin, implicating CXCR1/2 signalling in ACPA-mediated bone destruction. According to Anca Catrina, the corresponding author on this study, "[This] novel mechanism (IL-8 and PAD-dependent) might explain early pathogenic events that we believe are different from inflammatory mechanisms that take over once RA is fully developed."

These new mechanisms of ACPA-induced pain and bone destruction help clarify the pathogenetic role of ACPAs in RA, and both studies suggest a role for IL-8/CXCL1 and osteoclasts in these processes. "Mapping the nociceptive and osteoclast-activating effects of ACPAs will be important in order to understand the molecular mechanisms by which ACPAs induce pain," Svensson concludes. Furthermore, Catrina adds that "Our findings enable us to start planning for novel interventional strategies to specifically address the problems present in individuals not yet having RA but experiencing pain and already showing signs of bone loss."

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ORIGINAL ARTICLES Wigerblad, G. *et al.* Autoantibodies to citrullinated proteins induce joint pain independent of inflammation via a chemokine-dependent mechanism. *Ann. Rheum. Dis.* http://dx.doi.org/10.1136/annrheumdis-2015-208094 | Krishnamurthy, A. *et al.* Identification of a novel chemokine-dependent molecular mechanism underlying rheumatoid arthritis-associated autoantibody-mediated bone loss. *Ann. Rheum. Dis.* http://dx.doi.org/10.1136/annrheumdis-2015-208093