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RHEUMATOID ARTHRITIS

Linking ACPA to bone loss in rheumatoid arthritis

Autoantibodies that are found in two thirds of patients with rheumatoid arthritis (RA), and which are clinically associated with joint damage, have now been mechanistically linked with bone loss. The work in mice and with human cells, published in the *Journal of Clinical Investigation*, shows that anti-citrullinated protein antibodies (ACPA) that recognize citrullinated vimentin induce osteoclastogenesis and tip the balance of bone remodelling in favour of resorption.

"The link between ACPA and joint damage has been a consistent clinical observation by many groups, but the mechanism of it had been completely unclear," says Georg Schett, an author of the study, as he explains the rationale for the work. To investigate the effect of ACPA on bone metabolism, the investigators compared markers of bone turnover in serum from patients with RA with or without ACPA expression, and from healthy controls. Levels of markers of bone resorption correlated with ACPA titre in the samples, whereas bone formation was the same in patients with RA regardless of ACPA status.

> "...ACPA ... induce osteoclastogenesis and tip the balance of bone remodelling in favour of resorption"

Vimentin, one of the proteins whose citrullination—carried out by PAD enzymes—generates epitopes recognized by ACPA, is expressed by cells of the monocyte lineage and has important roles in macrophage biology. Schett and colleagues purified ACPA with specificity for citrullinated vimentin from human samples and showed that this epitope is not only expressed by osteoclasts, but also that it increases during their differentiation, particularly at advanced stages. Expression of one type of PAD, PAD2, also increased during osteoclastogenesis.

The researchers next showed that the purified ACPA increased osteoclastogenesis in cell culture, and increased resorption pit numbers without enhancing the resorptive capacity of individual osteoclasts. In lymphocyte-deficient mice, ACPA challenge increased trabecular bone loss, alongside enhancing the expression of TNF and increasing markers of bone resorption. Thus, says Schett, "this work links the major autoimmune feature (ACPA), the key clinical aspect (destruction) and the dominant cytokine (TNF) in RA".

The researchers will now investigate bone architecture in ACPA-positive people without RA, as they continue their efforts to define how susceptibility to RA is converted into active disease.

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Original article Harre, U. *et al*. Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin. *J. Clin. Invest*. doi:10.1172/JCI60975