RHEUMATOID ARTHRITIS

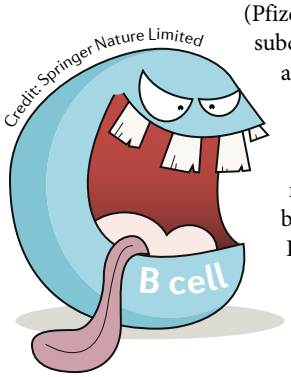
Pathogenic bone marrow B cells

Rheumatoid arthritis (RA) is characterized by progressive joint destruction that is mediated by excessive bone erosion relative to new bone formation. This defect in bone turnover has mostly been attributed to osteoclast dysfunction, although some studies also indicate a defect in osteoblast function. A new study implicates subchondral bone marrow (SBM) B cells in controlling osteoblast dysfunction in RA.

"In prior work, we demonstrated that B cells from patients with RA are abnormal as they produce the cytokine RANKL in excess and promote osteoclast activation and bone erosion," says corresponding author Jennifer Anolik.

In the new study, the researchers detected clusters of SBM B cells in close proximity to osteoblasts and areas of bone loss in TNF-transgenic mice and collagen-induced arthritis (CIA) models of RA. These B cells were phenotypically distinct from other bone marrow B cells, being mostly mature $IgD^{+}IgM^{+}$ cells expressing high levels of the osteoblast inhibitor TNF, the transcription factor DKK-3 and the chemokine CCL3.

> a critical function of TNF and CCL3



The researchers also performed ectopic bone formation experiments by mixing mesenchymal progenitor cells (which can differentiate into osteoblasts) and SBM B cells and embedding them into Gelfoam (Pfizer), which was then implanted subcutaneously into SCID mice to assess bone formation in vivo. Compared with B cells from wild-type mice, B cells from TNF-transgenic mice mediated a decrease in bone volume in these assays. Importantly, this bone-loss phenotype was reversed when using SBM B cells from TNF-transgenic CCL3-knockout mice or from TNF-transgenic TNF-knockout mice, further supporting a critical function of TNF and CCL3 in SBM B cell inhibition of osteoblast function.

Providing evidence that these results are of human relevance, the researchers also detected synovial aggregates of B cells with high expression of CCL3 and TNF in patients with RA, and that these cells can inhibit osteoblast differentiation in culture.

Anolik and colleagues are now looking to extend this research to understand why these SBM B cells are pathogenic in RA. "Our next questions include how the joint microenvironment affects local B cell activation and dysfunction," she concludes.

Nicholas J. Bernard

ORIGINAL ARTICLE Sun, W. et al. B cells inhibit bone formation in rheumatoid arthritis by suppressing osteoblast differentiation. *Nat. Commun.* **9**, 5127 (2018)

EXPERIMENTAL ARTHRITIS

Extracellular matrix in the crosshairs

Crosstalk between cells and the extracellular matrix (ECM) is an important factor during the development of rheumatoid arthritis (RA). In particular, the ECM molecule tenascin-C is expressed at high levels in the synovium in response to stress and injury and is thought to be involved in the pathogenesis of RA. However, attempts to study tenascin-C as a potential therapeutic target have been hampered by a lack of specific antagonists.

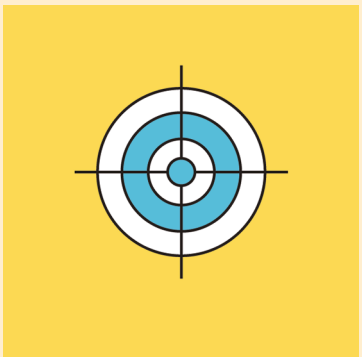
In a new study, researchers used phage display technology to generate antibodies that are specific for the fibrinogen-like globe (FBG) domain of tenascin-C, which binds to Toll-like receptor 4 (TLR4) and is essential for it to trigger pro-inflammatory signalling pathways. "We screened these antibodies to find those that were effective in neutralizing FBG binding to and activation of TLR4, but that did not affect activation of TLR4 by pathogenic stimuli such as bacterial lipopolysaccharide (LPS)," explains corresponding author Kim Midwood.

> attempts to study tenascin-C as a therapeutic target have been hampered by a lack of specific antagonists

In cells isolated from the synovium of patients with RA, the new antibodies blocked the release of cytokines upon stimulation with the FBG domain of tenascin-C but did not affect the release of cytokines upon stimulation with LPS, indicating specificity for targeting 'sterile' inflammation in synovial cells. "Using our antibodies, we could also see that tenascin-C expression is elevated very early in the development of RA, even before disease diagnosis," says Midwood.

When administered at the induction of disease in rats with collagen-induced arthritis, the new antibodies did not prevent the development of disease but did reduce the progression and severity of disease, indicating a role for tenascin-C in the persistence of inflammation.

"We think that targeting disease-specific signals from the RA joint microenvironment that drive the chronicity of inflammation could provide an effective way to reduce pathological inflammation while leaving intact physiological host defence mechanisms against infection," says Midwood. "This selective approach might offer a safer treatment alternative to global immune suppression for people with RA," she concludes.



Credit: Jagrutiben Patel/iStock/Getty Images Plus

Joanna Collison

ORIGINAL ARTICLE Aungier, S. R. et al. Targeting early changes in the synovial microenvironment: a new class of immunomodulatory therapy? *Ann. Rheum. Dis.* https://doi.org/10.1136/annrheumdis-2018-214294 (2018)