Nature Reviews Rheumatology **7**, 498 (2011); published online 16 August 2011; doi:10.1038/nrrheum.2011.114

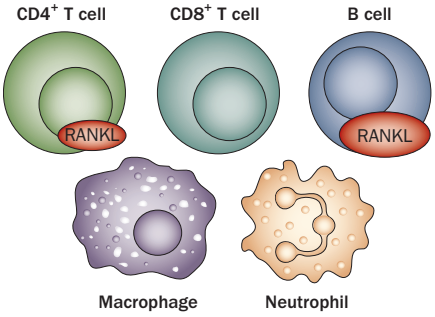
RHEUMATOID ARTHRITIS

Which cells produce which cytokines?

"The traditional approach to the investigation of cytokine production by inflammatory cells in rheumatoid arthritis [RA]," says Dagmar Scheel-Toellner, "is to focus on one particular cell type and a small group of cytokines, which rather limits the possibility of making new and unexpected observations." Now, Scheel-Toellner and colleagues have used a 'non-biased' experimental strategy to evade such limitations, as they report in *Annals of the Rheumatic Diseases*. "Among many interesting observations, one of the most striking was the unexpectedly high expression of RANKL in synovial fluid B cells," states Scheel-Toellner, "a population of cells not previously known to produce this factor in rheumatoid disease."

To enable this discovery, the researchers isolated the five main inflammatory cell populations from synovial fluid and peripheral blood of 12 patients with RA, and assessed the expression of 41 cytokines simultaneously by real-time quantitative PCR. Importantly, the cells were not stimulated *in vitro*, and thus the *in vivo* situation was preserved as faithfully as possible. "Using this approach we have generated a 'map', delineating which cell populations express mRNA for the cytokines investigated in this study," continues Scheel-Toellner. Cytokines characteristic for T cells and myeloid cells were found in the expected places (including comparatively low levels of RANKL mRNA in $CD4^+$ T cells), validating the method. The B-cell expression of RANKL was also demonstrated at the protein level.

RANKL (or TNF ligand superfamily member 11) binds receptor activator of nuclear factor κB, is required for osteoclast development, and mediates bone destruction. "A few years ago, investigators on the REFLEX trial showed that targeting B cells with rituximab limited the progression of bone erosion," says Scheel-Toellner. "Our finding provides a plausible mechanism for this observation, and we are currently investigating the impact of rituximab therapy on RANKL expression by synovial B cells."



RANKL is expressed by a subset of memory B cells that reside in epithelial niches; its expression in synovial fluid B cells might relate to the development of ectopic lymphoid structures. "Targeting B-cell populations that actively damage the joint may allow us to further refine cell depletion therapies and improve patient outcomes," concludes Scheel-Toellner.

Emma Leah

Original article Yeo, L. *et al*. Cytokine mRNA profiling identifies B cells as major source of RANKL in rheumatoid arthritis. *Ann. Rheum. Dis*. doi:10.1136/ard.2011.153312