



## RHEUMATOID ARTHRITIS

# New player in RA pathogenesis brought to light

A novel subset of T cells is responsible for driving autoantibody production by B cells in the synovium of patients with rheumatoid arthritis (RA), according to new research published in *Nature*. These cells, dubbed T 'peripheral helper' cells, are expanded in patients with seropositive RA and are thought to home to the inflamed synovium, where they fulfil a similar role to T follicular helper (T<sub>FH</sub>) cells. "Our strategy was to focus on T cells that express markers that indicate that they have been recently or chronically activated or might be homing into involved tissues," explains Michael Brenner, corresponding author of the study. "We hypothesized that these T cells would be the most informative in telling us about pathologic T cell functions that drive RA," he adds.

Autoantibody production is an important factor in driving seropositive RA. "T cells and B cells frequently form aggregates within the synovium in RA, yet which T cell population promotes B cell responses within the synovium has remained unclear," states Brenner. Within

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lymphoid organs, T<sub>FH</sub> cells interact with B cells, stimulating them to produce antibodies. "The T cells we identified in rheumatoid synovium also drive B cell responses, but do so within inflamed peripheral tissues, rather than within lymphoid tissue," explains Deepak Rao, first author on the study. "Using mass cytometry, RNA sequencing, and functional studies, we found that this T cell population has a unique phenotype that combines the ability to infiltrate inflamed tissues with the ability to drive B cell responses and antibody production," he continues, noting that, "this study provides the first detailed description of T cells with this unique combination of features."

The T peripheral helper cells identified by Rao and colleagues accounted for almost a quarter of all CD4<sup>+</sup> T cells in the synovium of patients with seropositive RA, but were not expanded in patients with seronegative RA, psoriatic arthritis or juvenile idiopathic arthritis. Importantly, the frequency of T peripheral helper cells fell over time in patients with seropositive

RA who responded to immunosuppressive therapy. "This remarkable disease-specific association with autoantibody-positive RA makes mechanistic sense because the expanded T peripheral helper cell population promotes B cell activation and antibody production," says Rao.

Phenotypically, T peripheral helper cells share some similarities with T<sub>FH</sub> cells, with both subsets producing IL-21 and expressing programmed cell death protein 1 (PD1) and inducible T-cell co-stimulator (ICOS). However, T peripheral helper cells do not express CXCR5, a key chemokine receptor expressed by T<sub>FH</sub> cells, but instead express a range of chemokine receptors known to direct cells towards inflamed tissue, including CCR2, CX3CR1 and CCR5. The differences continue at the transcriptional level, with T peripheral helper cells expressing only low levels of BCL6, a key T<sub>FH</sub> cell transcription factor, and high levels of BLIMP1, a transcription factor that is downregulated in T<sub>FH</sub> cells.

"When one thinks about the current targeted immunotherapies for autoimmune diseases like RA, one recognizes that they are 'blunt' instruments since they block major cytokines or cytokine receptors, deplete a whole cell type or globally block T cell activation or the homing of cells to major organs," says Brenner. "A next step that many investigators hope might be possible would be more 'specific' immunotherapies. Our discovery of a distinct T peripheral helper cell found only in patients with autoantibody positive RA raises the possibility that such T cell populations might be one of the first windows into the next level of specificity in targeting 'only the pathologic T cells,'" he concludes.

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