A172 T CELL LESSONS FROM THE RA SYNOVIUM SCID MOUSE MODEL: SYNOVIAL TISSUE RICH IN CD3 T CELLS LACKS RESPONSE TO CTLA4-IG, BUT IS SUCCESSFULLY TREATED WITH ANTI-IL-17 ANTIBODIES

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Background Target discovery and drug development is a very time consuming and expensive process, which is partly due to the fact that preclinical findings from animal models cannot always be translated to the clinical situation. To provide an intermediate step between classical arthritis models and clinical trials, the rheumatoid arthritis (RA) synovium severe combined immunodeficiency (SCID) mouse model is a valuable tool during preclinical research.

Objective First, the validity of this humanised mouse model was studied using anti-tumour necrosis factor (TNF) and anti-interleukin 1 (anti-IL-1) treatment. In addition, the direct effect of T and B cell-related therapies on the transplanted RA synovial tissue was investigated.

Methods SCID-CB17 mice were engrafted with two standardised pieces of human RA synovial tissue subcutaneously on the back. After an engraftment period of 7 days, mice were systemically treated with anti-TNF, anti-IL-1, anti-IL-17,

cytotoxic T lymphocyte antigen 4 (CTLA4)-Ig, anti-CD20 or isotype controls. As readout, serum levels of human cytokines and chemokines were analysed, and synovial grafts were isolated for histological analysis.

Results Validation of the model with anti-TNF treatment significantly reduced serum levels of hIL-6 and hIL-8, and histological analysis demonstrated a clear reduction in inflammation and suppressed local expression of TNF and IL-1 in the synovium. As could be expected from the outcome of clinical trials, anti-IL-1 therapy did not show any effect on the RA synovial grafts.

The potential of this RA SCID model for B and T cell-related therapies was investigated using anti-CD20, anti-IL-17 and CTLA4-Ig. In mice engrafted with B cell-rich synovial tissue, anti-CD20 treatment significantly reduced serum cytokine levels and histological scores. Also for anti-IL-17 treatment great therapeutic potential was observed, but only when CD3 T cells were abundantly present in the RA synovial tissue.

Surprisingly, CTLA4-Ig treatment did not show any effects in this transplantation model, even despite prescreening of the synovial tissue for the presence of CD3 T cells and the co-stimulatory molecules CD80/86. This finding suggests that to reach clinical effects CTLA4-Ig predominantly acts systemically on the immune system, and not directly on the local T cell activation in the arthritic joint.

Conclusion This human RA synovium SCID mouse model enabled them to show that CTLA4-Ig lacks direct effects on T cell activation processes in the synovial tissue. Further evidence was obtained that IL-17 might indeed be an interesting therapeutic target in RA patients with CD3-rich synovial tissue. Further characterisation of the RA patients' individual synovial profile is of great importance to achieve tailor-made therapy.