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THE T CELL RECEPTOR REPERTOIRE IN SYNOVIAL TISSUE OF PATIENTS WITH EARLY RHEUMATOID ARTHRITIS (RA) IS DOMINATED BY HIGHLY EXPANDED CLONES, WHICH IS NOT THE CASE IN ESTABLISHED RA

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Background Several lines of evidence support a role for the T cell receptor (TCR) in the pathogenesis of RA. Previously

we demonstrated that many T cell clones are specifically present in the synovial tissue (ST) of patients with established RA (ESRA) suggesting TCR-driven involvement of T cells. To further unravel TCR-involvement in the development of RA we investigated the earliest stages of synovial inflammation, as defined clinically. We hypothesised that the synovial inflammation in RA leads to epitope spreading, reflected by accumulation of new clonal T cell expansions. Therefore, ST in early RA (ERA) should yield less, but more expanded T cell clones.

Objective To compare the presence of T cell clones in ST and peripheral blood (PB) between patients with ERA and ESRA, using a new high-throughput sequencing protocol.

Material and methods Three DMARD-naïve ERA patients (disease duration < 1 year) and three ESRA patients (disease duration > 2 years) were included. All fulfilled the American College of Rheumatology 1987 criteria for RA. mRNA was isolated from paired ST and PB samples. A linear amplification with primers for all V(α)-genes of the T cell receptor β-chain was performed. The amplified products contain the CDR3s of all T cells. Samples were processed using a Genome Sequencer (454) analysing up to 15 000 receptors per sample. The frequency of each clone was determined by its CDR3 frequency (% of all CDR3s analysed). Clones with a CDR3 frequency of > 1% were arbitrarily considered as highly expanded clones (HECs).

Results T cell clones were found with a frequency of up to 10–20% in the ST of ERA patients while this was only 1–3% in ESRA patients (samples had equal numbers of T cells). Only a minority of the HECs could also be identified in PB, and always in low frequencies.

Surprisingly, we identified twice as many HECs in ERA-ST compared to ESRA-ST (39.5 clones ($\pm$ 5.8) (SEM) vs 18.8 ($\pm$ 3.6)). However, the impact of the HECs in ERA was far higher in ERA-ST. In ESRA only 17.3% ($\pm$ 5.0) of the T cells analysed belonged to the HECs, whereas this was 77% ($\pm$ 8.0) for the ERA samples.

Conclusion The TCR-repertoire in ST of ERA patients appears to be dominated by a few HECs (oligoclonal), in contrast to observations in ESRA (polyclonal). This is consistent with the notion of epitope spreading. Further research should therefore focus on the earliest phases of RA to unravel the role of T cells in the initiation of RA.