T FOLLICULAR HELPER–LIKE CELLS IN THE RHEUMATOID ARTHRITIS SYNOVIIUM ARE SELECTIVELY ASSOCIATED WITH INTERLEUKIN-21 PRODUCTION AND ECTOPIC LYMPHOID STRUCTURES

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Background: A subset of RA patients are characterized by the presence of ectopic lymphoid structures (ELSs) in the synovium. Synovial ELSs display germinal centres with the in situ selection of ACPA-producing autoreactive B cells. T follicular helper (Tfh) cells play a critical role in germinal centre reactions in secondary lymphoid organs via expression of co-stimulatory molecules (e.g. ICOS) and the release of IL-21, a potent B cellactivator. Increased levels of IL-21 have been found in various autoimmune diseases and IL-21 is considered a potential therapeutic target in RA. The aim of this study was to characterize Tfh-like and IL-21-producing T cells in the RA synovium in the presence or absence of ELSs.

Methods: RA synovial tissue was evaluated for the presence of Tfh-like cells (defined by co-expression of PD-1 and ICOS) by immuno-fluorescence microscopy. SF mononuclear cells were either directly stained for surface marker expression or stimulated for 4 h with leucocyte activation cocktail in the presence of brefeldin A to evaluate cytokine expression by flow cytometry. IL-21 receptor (IL-21R) expression on fibroblast-like synoviocytes (FLSs) was analysed by flow cytometry.

Results: The numbers of PD-1+ICOS+ cells were significantly higher in ELS-positive than ELS-negative synovial tissue [median 18.50 (s.e.m. 9.6) vs 0.0 (1.4), P = 0.009]. Consistent with the histological findings, increased percentages of CD4+PD-1+ICOS+ cells [63.63% (s.d. 17.21) vs 9.0 (1.8)] and IL-21-producing CD4+ T cells were found in the SF of arthritis patients when compared with peripheral blood of healthy donors [median 19.53% (s.e.m. 5.6) vs 5.43 (1.3)]. Furthermore, a sizeable subset of FLSs [65.85% (s.d. 16.90)] expressed IL-21R, and IL-21R mRNA expression in FLSs could be significantly upregulated by Toll-like receptor stimulation.

Conclusion: Tfh-like cells are significantly more represented in ELS-positive than ELS-negative synovium. IL-21-producing CD4+ T cells in SF might have a direct pro-inflammatory effect on FLSs via IL-21/IL-21R signaling.

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