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HELPER AND CYTOTOXIC FOLLICULAR T-CELLS IN SJÖGREN'S SYNDROME

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Background: Follicular T-cells, characterized by the expression of CXCR5, secrete interleukin 21 (IL-21) and help B-cell differentiation in lymphoid follicles. They are also found in circulation and may play a key role in Sjögren's syndrome's (pSS) chronic autoimmune epithelitis.

Objectives: To characterize circulating follicular helper (Tfh) and cytotoxic (Tfc) T-cells in peripheral blood (PB) from pSS patients, Rheumatoid Arthritis (RA) patients and healthy controls (HC), and to investigate how they correlate with B-cell subsets. We also aimed to explore associations between the Tfh and Tfc cells and clinical and laboratory features of pSS.

Methods: PB from 57 pSS patients, 20 RA patients and 24 HC was analysed by flow cytometry to characterize T and B-cell subsets, with CXCR5 defining Tfh and Tfc within CD4 and CD8 T cells, respectively. A stimulation assay was used to assess the production of IL-21 by CD4⁺ and CD8⁺ T-cells.

Results: Compared to HC, pSS and RA patients presented significantly lower lymphocyte absolute counts (1615 and 1935 cells/ μ L respectively, compared to 2228 cells/ μ L in HC, $p < 0.001$ for HC vs pSS, $p = 0.018$ for HC vs RA), and percentages (29.9% in pSS, 24.0% in RA, and 35.4% in HC, $p = 0.022$ for HC vs pSS, and $p < 0.001$ for HC vs RA). B-cell and T-cell absolute counts were also lower in both groups of patients compared to HC (in HC vs pSS, $p = 0.011$ for B-cells and $p < 0.001$ for T-cells; in HC vs RA, $p < 0.001$ for B-cells and $p = 0.018$ for T-cells). B-cells absolute counts and percentages in pSS were higher than in RA (177 vs 132 cells/ μ L, $p = 0.013$; 9.7 vs 6.4%, $p < 0.001$). There were no differences in CD8 T-cells percentages between groups, but pSS had lower CD4 T-cell percentages compared to HC ($p = 0.004$).

pSS patients presented lower absolute counts of CXCR5⁺ Tfh compared to RA (134 vs 181 cells/ μ L, $p = 0.038$) and HC (134 vs 241 cells/ μ L, $p < 0.001$). No differences were found in Tfh percentages. RA patients had lower percentages of CXCR5⁺ Tfc compared to pSS (2.1 vs 2.6%, $p = 0.113$) and HC (2.1 vs 3.0%, $p = 0.046$).

pSS patients exhibited higher percentages of IL21⁺CD4 and IL21⁺CD8 T cells (IL21⁺CD4 T cells: 12.4% in pSS vs 9.0% in RA, $p = 0.046$; vs 9.7% in HC, $p = 0.028$; IL21⁺CD8 T cells: 4.1% in pSS vs 2.3% in RA, $p = 0.001$; vs 2.8% in HC, $p = 0.030$).

In pSS patients, CXCR5⁺ Tfh correlated positively with the percentages of plasmablasts ($r = 0.262$ for CD24⁺CD38⁺⁺ cells, and $r = 0.282$ for IgM⁺CD38⁺⁺ cells). IL21⁺CD8 T cells correlated positively with the Naïve/Memory B cells ratio ($r = 0.323$; $p = 0.014$) and negatively with Bm1 memory B cells ($r = -0.370$; $p = 0.005$). IL21⁺CD4 T cells behaved similarly, though without statistical significance.

Anti-SSA-positive patients ($n = 38$) presented higher CD4⁺IL21⁺ (13.3 vs 8.5%, $p = 0.025$) and CD8⁺IL21⁺ cells percentages (4.4 vs 4.0%, $p = 0.198$) than SSA-negative patients ($n = 19$). Although there were no differences between pSS patients with active ($n = 27$) and inactive disease ($n = 30$), a tendency for positive correlations was found between IL-21⁺CD4 and IL21⁺CD8 T-cells and the ESSDAI score ($r = 0.229$, $p = 0.086$ for CD4, $r = 0.223$, $p = 0.096$ for CD8). Moreover, ESSDAI correlated positively with the Tfh1/Tfh17 ratio.

Conclusion: pSS patients present a profile of circulating Tfh and Tfc distinct from RA and HC, both phenotypically and functionally. Moreover, our data support a crucial role for these cells in B cell development, as they correlate with B cells, in pSS patients, which are known to exhibit a typical circulating B cell compartment. Both Tfc and Tfh cells can be critical for disease pathophysiology and activity, as underlined by the correlations between these cells and ESSDAI scores.

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EBV SEROLOGICAL PROFILE AFFECTS CIRCULATING LYMPHOCYTES IN PSS

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Background: Genetic, hormonal, and environmental triggers have been related to the dysregulated autoimmune response observed in primary Sjögren Syndrome (pSS), but its aetiology is still unestablished. Epstein-Barr virus (EBV) is a strong candidate as a trigger for the autoimmune epithelitis in pSS.

Objectives: We aimed to evaluate the EBV serology in pSS patients, and to compare it with other autoimmune patients and healthy controls (HC). In parallel, we have characterized the immune profile of pSS patients, in order to assess if the viral background affects the circulating lymphocytes.

Methods: We have recruited 34 pSS patients (2002 AECG criteria), 20 Rheumatoid arthritis (RA) patients (ACR/EULAR classification criteria) and 20 HC. Immunoenzymatic assays were used to determine the serum levels of IgG, IgA and IgM antibodies against EBV Nuclear Antigen (EBNA), Early Antigen (EA) and Capside antigen (VCA). Flow cytometry was used for the characterization of T and B cells, including regulatory (Tregs) and follicular (Tfh) T cells, T helper and Bm1-Bm5 subsets. Significance was considered for $p < 0.05$.

Results: All sera were negative for VCA-IgM. Only 2 HC and 3 RA were positive for EA-IgA. For VCA-IgG and EBNA-IgG we found no differences in positive cases between groups (all participants, except 2 pSS were positive for VCA-IgG; 26/34 pSS, 16/20 RA and 13/20 HC were positive for EBNA-IgG). However, pSS patients evidenced more positive sera for EA-IgG than HC (32% vs 5%; $p = 0.0215$) and RA (32% vs 20%; $p = 0.2312$), suggesting a more prevalent state of late acute/chronic active infection in pSS.

Thus, according to the serologic pattern observed, we divided pSS patients in 3 groups: G1 ($n = 18$), past infection (EA-IgG⁻, EBNA IgG⁺); G2 ($n = 11$), late acute/chronic active infection (EA IgG⁺, EBNA IgG⁺), and G3 ($n = 5$), without serological evidence of active infection (EA IgG⁻, EBNA IgG⁻). Within the T cell compartment, G2 patients presented increased percentages Tregs compared to G1 pSS patients ($p = 0.031$). G1 and G2 patients presented increased CXCR3⁺ Th1 cells and CXCR3⁺ Tfh1 compared to G3 (Th1: G1vsG3, $p = 0.120$ and G2vsG3, $p = 0.008$; Tfh1: G1vsG3, $p = 0.003$ and G2vsG3, $p = 0.067$).

As for B cells, pSS patients are known to have increased percentages of transitional Bm2' cells in circulation, and in fact we found that these cells were also augmented in G2 patients compared to G1 ($p = 0.024$). Moreover, plasmablasts (Bm3+Bm4) were increased in G1 and G2 patients compared to G3 (%: G1vsG3, $p = 0.088$ and G2vsG3, $p = 0.003$; absolute counts, G1vsG3, $p = 0.020$ and G2vsG3, $p = 0.003$). Plasmablasts were also slightly augmented in G2 patients compared to G1 ($p = 0.099$).

Conclusion: Our study shows a higher prevalence of EA-IgG in pSS patients. Moreover, the distinct EBV serological profiles observed in pSS patients seem to affect circulating B and T cells. Particularly, pSS patients with serological evidence for late acute/chronic active infection show a more proinflammatory pattern, with increased Th1 cells, and elevated transitional B cells with increased plasmablast differentiation. Despite the low number of cases and the absence of other confirmatory methodologies, our study reveals for the first time the association of EBV with distinct immune profile in pSS patients.

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