Adaptive immunity (T cells and B cells) in rheumatic diseases

Background: Systemic Sclerosis (SSc) is a systemic autoimmune disease that carries the highest mortality burden among the rheumatic diseases. Disease risk and course are difficult to predict in individual patients, and anti-inflammatory and B-cell depletion therapies show varying results. >95% of SSc patients harbor autoantibodies. Among those, anti-topoisomerase antibodies (ATA) and anti-centromere antibodies (ACA) are most prevalent, mutually exclusive in individual patients and associate with distinct disease phenotypes. Despite these associations, the clinical value of both ATA and ACA for patient stratification within these phenotypes is limited. Here, we hypothesized that phenotypic and functional characteristics of the underlying autoreactive B cell responses could allow insights in differential "immunological disease activity" in individual patients, thereby providing indications as to potential drivers of these responses as well as granularity as to which patients may benefit from targeted interventions.

Objectives: To assess phenotypic and functional characteristics of anti-topoisomerase and anticientromere specific B cell responses in individual patients with SSc.

Methods: Peripheral blood mononuclear cells (PBMC) from ATA- and ACA-positive SSc patients were cultured with or without stimulation. PBMC were depleted of circulating plasmablasts by fluorescence activated cell sorting (FACS), and isolated plasmablasts were cultured separately. Furthermore, the presence of antigen-specific plasmablasts was confirmed by ELISPOT. Finally, the degree of spontaneous ATA secretion was correlated to the presence or absence of interstitial lung disease (ILD: based on high-resolution computed tomography). Healthy donors and patients with rheumatoid arthritis served as controls.

Results: We observed that individual ATA- and ACA-positive SSc patients harbored circulating B cells that secrete either ATA-IgG or ACA-IgA upon stimulation, depending on their serotype. In addition, we noted spontaneous secretion of ATA-IgG and, more remarkably, extensive secretion of ATA-IgA in ATA-positive patients. This degree of spontaneous, antigen-specific IgA secretion was specific for the ATA response, while spontaneous ACA-IgA secretion was undetectable in patients harboring ACA. FACS experiments and ELISPOT showed that the spontaneous ATA-IgA and -IgG secretion was attributable to circulating plasmablasts. Of note, the degree of spontaneous ATA-IgA secretion was remarkably higher in patients with ILD than in those without.

Conclusion: Our findings demonstrate that individual ATA-positive SSc patients harbor activated ATA-IgA and ATA-IgG B cell responses, as indicated by the spontaneous secretion of both ATA isotypes by circulating plasmablasts. Importantly, by taking the presence of plasmablasts as a proxy for recent B cell activation, our data suggest a link between the activity of the antigen-specific B cell response and the presence of ILD. In contrast, the ACA B cell response was far less active and lacked the active IgA component, which suggests a difference in the triggers driving these autoreactive B cell responses in patients. In fact, the remarkable ATA-IgA secretion points towards a potential mucosal trigger of the ATA response, which may be continuously active in individual patients.

Disclosure of Interests: None declared.

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RITUXIMAB THERAPY IN SYSTEMIC LUPUS EURYTHMATOUS – TRANSIENT EFFECTS ON AGE ASSOCIATED B-CELLS

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Background: Immune system abnormalities in SLE involve several subsets of the B-cell compartment, including double negative B-cells (DN) and CD11c+/CD21+ B cells (also referred to as ABC-age associated B cells), which are expanded in the disease. ABC cells are also known to interact with T helper cells, T follicular and peripheral helper cells (1). Rituximab, a chimeric anti-CD20 antibody, depleting B cells, is commonly used off-label as treatment for SLE patients, especially in lupus nephritis. Little is known on the impact of B-cell depletion on such B-cell subsets and on B-T cell interactions.

Objectives: To investigate the effects of rituximab (RTX) on the frequencies of double negative B-cell subsets and CD11c+CD21- ABC cells and as well as T follicular helper (Tfh) CXCR5+ PD-1+ and T peripheral helper (Tph) PD-1+ Tfh CD4+ T-cell subsets.

Methods: 15 SLE patients, starting RTX and followed longitudinally up to two years, were analyzed for lymphocyte subsets using multicolor flow cytometry. Cryopreserved PBMC were thawed and stained at the same time together with one buffy coat. Around 1 x 10^6 PBMC for each panel were labeled and further stained with fluorescent antibodies for B and T-cell markers. For the B-cell panel, PBMC were stained with anti-CD3, CD14, CD16, CD19, IgD, CD27, CD38, CD11c, CD21 and in some samples with anti-CXCR5 antibodies. For the T-cell panel, PBMC were labeled with anti-CD16, CD14, CD19 and CD3, CD4, CD8,