Methods: We assessed the expression of cytotoxic effector molecules and transcription factors in CD4⁺ T cells in synovial fluid (n=21) and paired peripheral blood (n=16) from ACPA- and ACPA+ RA patients by multi-parameter flow cytometry. We performed single cell sequencing, in combination with 5' TCRab sequencing, on purified CD4⁺ T cells from the peripheral blood (PB) and synovial fluid (SF) of ACPA+ RA patients (n=7).

Results: Flow cytometry experiments show that Granzyme-B+ Perforin-1+ CD4⁺ CTL are significantly increased in the SF of ACPA+ RA patients as compared to ACPA- RA patients (p=0.0072). The presence of CD4⁺ CTL could be confirmed by single cell sequencing in SF of each ACPA+ RA patient tested (n=7). Moreover, we found that the adhesion G-protein coupled receptor GPR56 is selectively expressed on the recently described peripheral helper (T_{PH}) T-cell subset¹¹ and associates with the expression of tissue resident memory markers LAG-3, CXCR6 and CD69. In blood, we confirmed a previous report¹² showing that GPR56 delineates cytotoxic CD4⁺ T cells. Finally, expanded TCR clones expressing cytotoxic effector molecules were identified in synovial fluid of ACPA+ RA patients and, for some patients, in their corresponding peripheral blood.

Conclusion: We identified GPR56 as a marker of T_{PH} cells in SF of ACPA+ RA patients that associates with tissue residency receptors. The combination of single cell sequencing and multi-parameter flow cytometry highlights the importance of CD4⁺ CTL in ACPA+ RA and suggests a potential therapeutic target (Figure 1).

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Figure 1. Cytotoxic CD4⁺ T cells and GPR56+ peripheral helper CD4⁺ T cells are two T-cell subsets identified in SF of ACPA+ RA patients.

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OP0073

SINGLE-CELL TRANSCRIPTOMICS UNCOVERS DEFECTIVE BONE MARROW EARLY B CELL DEVELOPMENT IN A SUBSET OF LUPUS PATIENTS ASSOCIATED WITH AGGRAVATED INFLAMMATION

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Background: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that occurs when the body's immune system attacks own tissues and organs. B cells play a central role in SLE pathogenesis by producing autoantibodies as well as antibody-independent functions. Peripheral B cell abnormality is well known in lupus patients such as expansions of plasmablasts and atypical memory B cells, which are associated with active diseases. However, little is known about the B cell development in the bone marrow of lupus patients.

Objectives: We conduct this survey to explore the disorder of the B cell development in the bone marrow of lupus patients.

Methods: In this study, we have performed the scRNASeq to profile the bone marrow B cell compartment in lupus patients and healthy donors.

Results: We identified that in a subset of lupus patients, the early B cells (proB and preB cells) were strongly decreased, which were confirmed by flow cytometry in an expanded cohort. Furthermore, bone marrow B cells from these patients showed a strong proinflammatory signature revealed by pathway analysis. Interestingly, BCR repertoire analysis showed that the IGHV-4-34 was highly enriched in these patients, indicating an enhanced B cell tolerance defect. Finally, a panel of proinflammatory cytokines (TNF-α, IL-1α, IL-12p70, IFN-γ, et al.) were strongly increased in the bone marrow plasma of these patients compared with early B normal patients and healthy donors, confirming a localized proinflammatory microenvironment.

Conclusion: Altogether, the current study has revealed that a defective early B cell development in lupus patients is associated with a more severe B cell tolerance defect and aggravated inflammation, which may shed new light on developing novel therapies by targeting relevant pathways.

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Education

OP0074

A FRAMEWORK OF POTENTIAL INTERVENTIONS TO ACCELERATE GENDER-EQUITABLE CAREER ADVANCEMENT IN ACADEMIC RHEUMATOLOGY

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