Conclusion: Patient representatives of RMD patient organisations represent diverse profiles of health literacy strengths and weaknesses, but the most complex challenges in the original patient survey were not found. Differences may relate to how patients are selected and supported to become a representative, and how being a representative improves some aspects of health literacy. Patient organisations should take into account that their target population generally has more difficulty actively managing health and critically appraising information, and includes more people with diverse health literacy needs than their patient representatives may report.

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Single-cell omics in Rheumatic diseases

OP0185 IMMUNOPHENOTYPIC ABNORMALITIES REMINISCENT OF ESTABLISHED RHEUMATOID ARTHRITIS ARE PRESENT IN ACPA(+) AT-RISK INDIVIDUALS

Keywords: Rheumatoid arthritis, Biomarkers, -omics

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Background: RA-associated autoantibodies (RF, ACPA) are detectable before the onset of clinically-apparent inflammatory arthritis (IA) and classifiable RA (i.e. "Clinical RA"), defining a state known as 'At-Risk' for future RA. However, RA prevention trials in individuals in this At-Risk state have shown limited success in prevention. A challenge to developing more effective preventive interventions is that the immune phenotype of the At-Risk state remains incompletely understood.
Objectives: The purpose of this study was to (1) evaluate the hypothesis that ACPA(+) At-Risk individuals have immunopathologic features of Clinical RA, and (2) determine additional molecular features that define the At-Risk state. We propose that such features may help to identify biomarkers and causal pathophysiologic mechanisms that could be treatment or prevention targets. Furthermore, At-Risk immune features could improve prediction of future Clinical RA, as well as be used to monitor responses to therapeutic interventions.
Methods: Using a cross-sectional methodology, we analyzed ACPA(+) individuals without baseline IA (i.e. At-Risk) and age, sex and BMI matched ACPA(-) controls without IA (Table 1). We tested plasma proteomics, peripheral blood mononuclear cell (PBMC) composition by flow cytometry, and PBMC transcriptomes by single-cell RNA-sequencing (scRNA-seq). We further compared these findings to immunophenotypes reported in patients with Clinical RA. All studies were performed as part of a collaborative effort between the Allen Institute for Immunology, University of California San Diego, University of Colorado and Benaroya Research Institute.
Results: We observed significant differences in plasma levels of 138 proteins between ACPA(+) individuals vs. controls, including IL-6 (log2 fold change (FC) = 0.59-0.62, adjusted p value (padj) < 0.05), IL1B (log2 FC = 0.44, padj = 0.006), and CCL3 (log2 FC = 0.60, padj = 0.002). These changes also included additional elevated inflammatory chemokines and cytokines that have been reported in Clinical RA. B cell receptor signaling was one of the most significantly enriched protein pathways in ACPA(+) individuals. These proteomic alterations in ACPA(+) individuals were accompanied by numerous PBMC phenotypic changes, notably an increase in IgD- CD27- B cells (log2 FC = 0.814, padj = 0.002). Furthermore, compared to controls, scRNA-seq of IgD- CD27- B cells from ACPA(+) individuals expressed lower levels of genes previously shown to be increased in IgD- CD27- B cells or autoimmune processes, including SAMHD1 (log2 FC = -0.34, padj < 0.05), ARID3A (log2 FC = -0.32, padj < 0.05), and ZC3H12D (log2 FC = -0.30, padj < 0.05), suggesting dysregulation of this compartment at the preclinical stage.
Conclusion: ACPA(+) At-Risk individuals demonstrate numerous immune-related changes that are similar to changes in established Clinical RA, suggesting the ACPA(+) At-Risk state is on a continuum with Clinical RA. Highlighted are plasma proteomics demonstrating cytokine/chemokine elevations and B cell signaling pathways, and PBMC studies demonstrating specific B cell phenotypes and gene expression. These findings provide insights to potential immunopathologic mechanisms that may impact how we define the 'At-Risk' state, may improve prediction of future RA, and suggest targets for interventions or intermediate endpoints in trials for RA prevention.

Table 1. Cohort Information

Variable	ACPA(+) At-Risk	Control	p-value
Clinical Features			
Number	46	52	-
Age at sample draw, median	62	57	0.01
Sex at birth, %			
Female	78.26	78.85	1
Male	21.74	21.15	-
Race, %			
Caucasian	82.61	88.46	0.57
Black	8.70	0.00	0.05
Asian	2.17	7.69	0.37
Other	6.52	3.85	0.66
Ethnicity, %			
Non-hispanic	95.65	96.15	1
Hispanic/Latino	4.35	3.85	-
BMI	26.29	25.59	0.62
Serum Biomarkers			
Serum CCP3, median (IQR)	60 (42.5, 183)	0 (0,2)	< 1e-6
Serum RF IgA, median (IQR)	0.25 (0.25, 4.63)	0 (0,0)	< 1e-6
Serum RF IgM, median (IQR)	0.57 (0.25, 22.23)	0 (0,4.3)	2.5e-4

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OP0186 DISTINCT PERIPHERAL IMMUNOPHENOTYPING UNDERLINES HISTOPATHOLOGICAL FEATURES IN PATIENTS WITH LUPUS NEPHRITIS IN A LARGE MULTI-CENTER COHORT

Keywords: Kidneys, -Omics, Systemic lupus erythematosus

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Background: Lupus nephritis (LN) is a common and severe complication of systemic lupus erythematosus (SLE) requiring renal biopsy to guide treatment decisions. Despite standard-of-care therapy, a third of patients with LN class III, IV, or V show a progressive decline in kidney function, including those with improved proteinuria. Defining LN heterogeneity using a non-invasive approach is a pressing need to improve treatment.

Objectives: To determine circulating immune cell phenotypes characteristic of LN histology.

Methods: Mass cytometry using four 48-marker panels were applied to characterize peripheral blood mononuclear cells (PBMC) from 140 patients with biopsy-proven class III, IV, or V LN and 40 healthy controls included in the Accelerated Medicine Partnership RA/SLE Network Phase II study. After filtering for quality control and correcting for batch effects, we projected cells in a reduced dimensional space and identified cell neighborhoods and clusters using an unsupervised approach. We implemented covarying neighborhood analysis (CNA) to identify cell populations associated with clinical features.

Results: Compared to controls, LN patients displayed marked enrichment of cell neighborhoods that expressed interferon (IFN)-induced proteins including MX1 (p.adj < 0.001) and Siglec1 (p.adj < 0.001), reflecting a simple, cytometric detection of an IFN signature. Detailed immune cell subsetting using the B cell- (Figure 1A), T cell-, myeloid cell-, and NK cell-focused panels identified several alterations in LN patients compared to controls, including increased $CD27^{-}IgD^{-}$(DN) $CD11c^{+}Tbet^{+}$ B cells (OR 1.6, 95%CI 1.3-2.2, p.adj < 0.001) and T peripheral helper cells (OR 1.8, 95%CI 1.3-2.8, p.adj = 0.002), and decreased plasmacytoid dendritic cells (OR 0.6, 95%CI 0.4-0.8, p.adj < 0.001), adjusting for age, sex, ethnicity and race. LN patients with minimal immunosuppression (IS, n=14) displayed similar results. Comparing patients with proliferative LN (class III or IV +/- V, n=94) versus membranous LN (class V, n=46), we observed the most significant alterations within B cells, with enrichment of a naive B cell population characterized as $CD23^{-}$ and $CD21^{dim}$ (Figure 1B,C). The phenotype of this enriched naive B cell population was distinct from transitional and $CD11c^{+}$ 'activated naive' cells (Figure 1D). This B cell population was also associated with increased histologic NIH activity score (Figure 1B,C) even after adjusting for IS, and with positive anti-dsDNA antibody (p = 0.02). To further understand the LN heterogeneity, we clustered LN patients and controls based on proportions of all PBMC subsets using k-means clustering and projected subjects in a UMAP space. We identified two prominent clusters: cluster 1 included only LN patients, and cluster 2 included all controls and 26 LN patients. LN patients in cluster 2 (Control-like) had significantly lower clinical extrarenal activity (coef -1.1, 95%CI -2.1--0.1, p.adj = 0.03) and IFN-induced protein expression (coef -28.0, 95%CI -36.6—19.4, p.adj < 0.001), adjusting for IS. In addition, these patients had significantly higher histologic chronicity (coef 2.39, 95%CI 1.24-3.53, p.adj < 0.001). In line with these findings, we confirmed by CNA the association of increased histologic chronicity with fewer $MX1^{+}$ or $Siglec1^{+}$ IFN-responsive cells, adjusting for IS (p.adj = 0.002, FDR < 10%).

Conclusion: In addition to profoundly impaired circulating immunophenotype observed in LN patients, we identified a difference in naive B cell states in patients with proliferative LN compared to membranous LN. Based on circulating immunophenotype, we identified a subset of SLE patients with low extrarenal activity and increased histologic evidence of chronic kidney damage. These results nominate potential non-invasive biomarkers associated with LN heterogeneity and highlight altered naive B cell activation in proliferative LN.

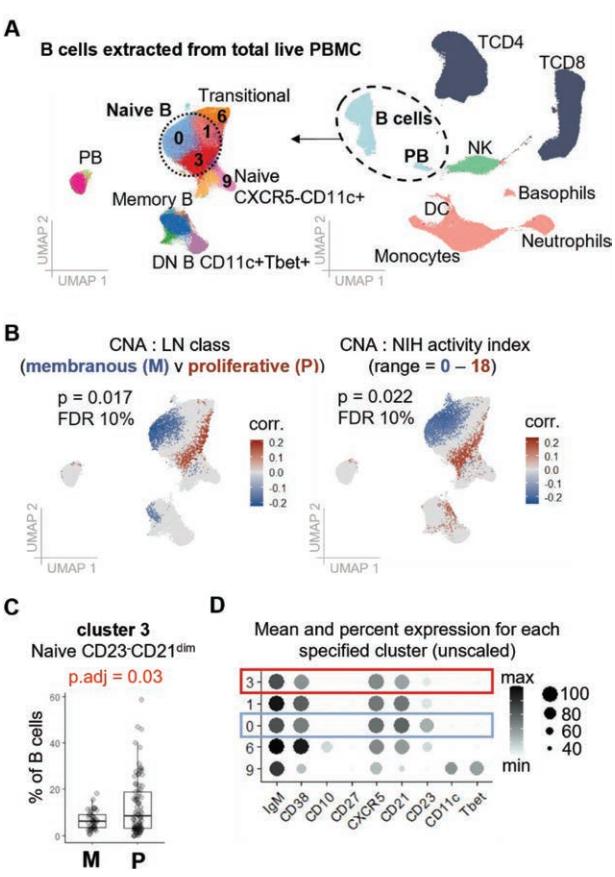

Figure 1.

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Spondyloarthritis across the ages

OP0187

REGIONAL DIFFERENCES IN CLINICAL PHENOTYPE OF AXIAL SPONDYLOARTHRITIS. RESULTS FROM THE INTERNATIONAL MAP OF AXIAL SPONDYLOARTHRITIS (IMAS)

Keywords: Spondyloarthritis, bDMARD, Geographical differences

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Background: Previous studies have suggested there could be regional differences in clinical phenotype of axial spondyloarthritis (axSpA).