90% of ACPA-IgGs harbour N-linked glycans in the antibody variable (V) domain. The corresponding N-glycosylation sites in the amino acid backbone of ACPA V-regions result from somatic hypermutation, a T cell-dependent process. Notably, both genetic evidence and data obtained from the analysis of serum ACPA indicate that T-cells drive the maturation of the ACPA-response prior to the onset of arthritis.

Objectives: We investigated whether ACPA-IgG carry V-domain N-glycans prior to the development of arthritis and whether the occurrence of such glycans predicts the transition from pre-disease autoimmunity to overt RA.

Methods: Two independent sets of serum samples were obtained from RA patients and from ACPA-positive first-degree relatives (FDR) of RA-patients (n=126) of an Indigenous North American (INA) population with high incidence rates of ACPA-positive RA. These samples comprised cross-sectional and longitudinal samples of individuals who did or did not transition to inflammatory arthritis. Serum ACPA-IgG were affinity-purified and subjected to enzymatic glycan release and UHPLC-based glycan analysis.

Results: ACPA-IgG V-domain glycosylation could be detected in RA patients and in FDR of RA patients. In both datasets, FDR-derived ACPA-IgG displayed markedly lower levels of V-domain glycans (<50%) compared to ACPA-IgG from RA-patients. Notably, FDRs that later developed RA showed extensive V-domain glycosylation before the onset of arthritis. Moreover, the degree of ACPA-IgG V-domain glycosylation in FDRs was strongly associated with future development of RA (HR: 6.07 [95% CI: 1.46-25.2]; p=0.013).

Conclusion: Glycosylation of the ACPA-IgG V-domain can be detected prior to the onset of disease. Extensive glycosylation is present in a subset of predisposed FDRs of INA RA patients. The presence of this feature substantially increases the risk of RA development. These observations fit well with a pivotal role for T cells in the selection and expansion of ACPA-expressing B cells, possibly by facilitating the introduction of N-glycosylation sites in ACPA-IgG V-domains. Moreover, glycosylation of the ACPA-IgG V-domain represents a predictive marker for RA development in ACPA-positive individuals and may serve to better time and target preventive therapeutic interventions.

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OP0296 COMPARISON OF TRANSCRIPTOMIC PROFILES BETWEEN PAIRED JOINT BIOPSIES FROM RHEUMATOID ARTHRITIS PATIENTS

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Background: Rheumatoid Arthritis (RA) is a chronic and heterogenous condition characterized by inflammatory involvement of the synovial membrane in multiple joints. Synovial biopsies are used in research setting in order to identify diagnostic and theranostic markers. Many studies have shown a high degree of heterogeneity in histological and transcriptomic profiles between patients.

Objectives: We wanted to explore histological and transcriptomic profile of synovial biopsies across pairs of joints in the same patients to assess heterogeneity at the individual level.

Methods: Synovial biopsies were performed simultaneously in one small and one large joint per patient using needle-arthroscopy for the knee and US-guided needle biopsy for the hand or foot. Synovium from individuals with osteoarthritis (OA) were used as control. Paraffine-embedded samples were stained for CD3, CD 20, CD 68 and CD138. Whole-tissue RNA was extracted and hybridized on GeneChip Human Genome U133 Plus 2.0 Array (Affymetrix). The samples were tested for RNA integrity by Bioanalyzer (Agilent). Normalization and statistical analyzes were performed on Genespring. Pathway analysis were performed using DAVID.

Results: 10 RA patients were included (females: 10/10, ACPA/RF positivity: 8/10, mean age (± SEM): 54.4 (± 4.4) years, mean disease duration (± SEM): 13.3 (± 3.7) years, mean DAS28CRP (± SEM): 5.01 (± 0,34), mean HAQ (± SEM): 1.7 (± 0.28)).

Quantification of histological markers did not show differences in population of macrophages, plasmocytes, T and B Cells, across pairs of joints.

After correction for multiple comparisons, no transcripts were differentially expressed between large and small joints. Similarly, we did not find any significant difference in the expression of transcripts involved in pathways (TCR-activation and cell-division) specifically overexpressed in RA compared to OA synovial tissue.

In order to increase our ability to observe pair-wise differences in gene expression profiles, we studied correlations between transcripts significantly overexpressed in RA compared to OA joints with a fold change > 2 (n = 581) and clinical or biological markers of disease activity (DAS28-CRP, CRP, Physician Global Assessment of disease activity). Similar patterns of correlations indicated that disease activity was not driven by different pathways in small versus large joints.

Conclusion: This study is an important methodological milestone in the field of synovial biopsies, as it indicates that cellular and molecular alterations occurring in RA synovitis are similar across small and large joints from the same patient. Hence, biopsy of a single joint is representative and can be used to explore pathogenic processes or potential biomarkers in RA.

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OP0297 ABERRANT ADENOSINE TO INOSINE RNA EDITING IN ACTIVE RHEUMATOID ARTHRITIS

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Background: Adenosine to inosine (A-to-I) RNA editing is a widespread post-transcriptional RNA modification mainly located in repetitive *Alu* elements and mediated by the enzyme adenosine deaminase acting on RNA-1 (ADAR1). A-to-I RNA editing controls various aspects of RNA metabolism, which may affect tissue-specific gene expression. Although deregulation of RNA editing has been previously reported in various human diseases including cardiovascular disease and cancer (Stellos et al., *Nat Med*, 2017; Liu et al., *Nat Med*, 2019 and Ishizuka et al., *Nature*, 2019), its role in autoimmune diseases and especially in rheumatoid arthritis (RA) remains unknown.

Objectives: To study whether A-to-I RNA editing is involved in the pathogenesis of RA and to determine the impact of anti-rheumatic treatment on RNA editing.

Methods: We first analysed the expression of ADAR1 in 185 RA synovial tissues versus 76 healthy/osteoarthritic synovia derived from 4 independent RNA-sequencing and microarray datasets. We validated the findings in peripheral blood mononuclear cells (PBMCs) derived from 19 patients with active RA vs 14 controls and performed an additional ADAR1-isoform analysis (ADAR1p110/ADAR1p150) by RT-qPCR. Further, we studied in single nucleotide level the A-to-I RNA editing levels of the pro-inflammatory gene cathepsin S (CTSS) 3'-untranslated region (3'UTR), a matrix degradation enzyme which is a well-established target of ADAR1, by *Alu* Sanger sequencing and RNA editing analysis. Last, we examined the effect of anti-rheumatic treatment on RNA editing.

Results: Expression of the RNA editor ADAR1 was significantly increased in RA synovium compared to healthy or osteoarthritic synovium. Similarly, a significant increase of ADAR1, mainly due to an increase of the interferon-inducible ADAR1p150 isoform, was observed in PBMCs from active RA. Next, we studied the RNA editing levels in PBMCs from active RA patients before and after 12-week treatment versus controls. RNA editing of CTSS 3'UTR *AluSx*$^{+}$ was increased in active RA (6-47% increase in editing rate of 8 individual adenosines, all P<0.05). Increased CTSS mRNA expression in RA PBMCs was associated with both ADAR1p150 expression (r=0.623, P=0.004) and RNA editing rate of 12 individual adenosines (r=range 0.45-0.72, P<0.05 for all) located within the CTSS 3' UTR *AluSx*$^{+}$. The correlation between CTSS and ADAR1 was also observed in synovial tissue. Notably, ADAR1p150 expression and RNA editing rate reached control levels after 12-week treatment with methotrexate ± corticosteroids and/or biologics in patients with good clinical response (EULAR responders) but remained unchanged in the EULAR moderate/non-responders.