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SAT0005 DETECTION OF HIGHLY EXPANDED T CELL CLONES IN THE PERIPHERAL BLOOD OF AT RISK INDIVIDUALS FOR RHEUMATOID ARTHRITIS BEFORE THE CLINICAL ONSET OF THE DISEASE

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Background: Rheumatoid arthritis (RA) is an autoimmune disease with unknown etiopathogenesis. Systemic autoimmunity precedes clinical disease onset, and current evidence suggests that the immune onset of RA takes place outside of the joints several years before clinical manifestations. Expanded T cell clones can be found in the synovial tissue of established RA patients. The mechanisms by which systemic immune abnormalities progress to joint-specific autoimmunity are not yet understood.

Objectives: To examine if expanded T cell clone signatures can be detected in the peripheral blood before the development of clinical RA.

Methods: Next-generation sequencing of the T Cell Receptor β (TCRβ) CDR3 repertoire was performed on genomic DNA isolated from blood samples of individuals genetically at risk for RA, namely first-degree relatives of RA patients (RA-FDR) at different pre-clinical phases of disease development (SCREEN-RA cohort), and of matched RA patients used as a control group (SCQM cohort). All individuals were matched for age and sex, and categorized into four groups (n=20/group): **Group 1**: "healthy" asymptomatic RA-FDR without autoantibodies or symptoms associated with possible RA. **Group 2:** Asymptomatic RA-FDR with evidence of 'systemic autoimmunity associated with RA' defined by high levels of anti-citrullinated peptide antibodies (ACPA; 3x≥ ULN). **Group 3:** RA-FDR having presented undifferentiated arthritis (n=8) or having developed classifiable RA after inclusion (n=12). **Group 4:** patients with established RA of less than 3 years duration. T cell clones were identified by their unique TCRβ CDR3 sequence. Clones with a frequency over 0.5% were considered to be highly expanded clones (HEC). Both absolute number and frequency of productive T cell clones was compared between the 4 groups using mixed effect regression models to account for matching.

Results: As expected, the large majority of clones in the peripheral blood were detected at very low frequency (<0.1%) in all groups (Figure 1A). Interestingly, expanded clones (>0.1% of total TCR analysed) tended to occur more frequently in later preclinical phases and established disease. A significant difference among groups was observed for highly expanded clones (HEC) (p=0.001). Specifically, the absolute number of HEC was significantly higher in RA patients (group 4; mean 4.65, p=0.003) and tended to be higher in symptomatic RA-FDR (group 3; mean 3.4, p=0.07) compared to "healthy" RA-FDR (group 1; mean 1.55) (Figure 1B). A trend towards a higher frequency of the top 50 expanded clones was also observed in symptomatic RA-FDR (group 3; mean 0.17%) compared to "healthy" RA-FDR (group 1; mean 0.11%). At risk individuals defined by the presence of high ACPA levels (group 2) did not differ from "healthy" RA-FDR in terms of absolute number and frequency of clones.

Conclusion: For the first time, highly expanded T cell clones were detected in the peripheral blood of at risk individuals before the clinical onset of RA, in particular in the later pre-clinical phases of RA development. Tracking these dominant T cell clones in longitudinal analyses and elucidating their role might help to better understand the earliest pathogenic events in RA.

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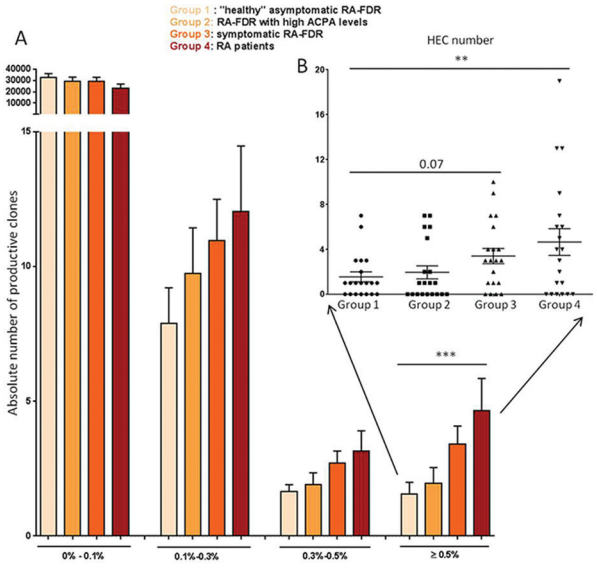

Figure 1. Absolute number of productive TCR clones by clonal size. (A) Bars show mean and standard error of the mean (mixed effect regression model). (B) Each dot represents the HEC number observed for 1 individual (mixed effect regression model).

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SAT0006 T-CELL IMMUNOGLOBULIN AND MUCIN DOMAIN 3 (TIM-3) IS INCREASED IN ACTIVE RHEUMATOID ARTHRITIS AND ASSOCIATED WITH CLINICAL DISEASE ACTIVITY AND RADIOGRAPHIC PROGRESSION

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Background: Co-inhibitory receptors are important for the regulation of inflammation in autoimmune diseases. Among these, T-cell Immunoglobulin and mucin domain-3 (Tim-3) has recently gained attention, as it is expressed on exhausted T cells co-expressing PD-1 (1).

Objectives: To investigate Tim-3's role in rheumatoid arthritis (RA).

Methods: Early RA (eRA) patients were randomized to conventional methotrexate (MTX) treatment + placebo or MTX + adalimumab (ADA) (2). Plasma were analysed by ELISA at baseline (n=98) and after 3 and 12 months of treatment. Clinical follow up including 28-joint Disease Activity Score with CRP (DAS28CRP) and Total Sharp Score (TSS) were available. Intrasubject differences in sTim-3 between baseline and 3 months were assessed by parametric paired t tests and compared with plasma from HV (n=44) by parametric unpaired t tests. Spearman correlation and Mann-Whitney test were used to investigate relations between sTim-3 and clinical follow up. From chronic RA (cRA) patients (n=17) plasma and synovial fluid were analysed by ELISA and peripheral blood mononuclear cells (PBMC) and synovial fluid mononuclear cells (SFMC)