THU0033 ALTERATIONS IN THE PHENOTYPIC LANDSCAPE AND SPECIFICITY OF CD4+ T CELLS IN CCP+ AT-RISK SUBJECTS BEFORE THE ONSET OF RHEUMATOID ARTHRITIS


Background: The "Targeting Immune Responses for Prevention of RA" (TIP-RA) collaboration studies individuals at high risk for developing rheumatoid arthritis (RA) because of serum anti-citrullinated protein antibody (ACPA) positivity in absence of arthritis at baseline, and is focused on defining how they transition from at-risk to classifiable disease. One potential mechanism is the expansion of antigen specific T cells that recognize self-antigens and acquisition of disease associated T cell phenotypes. ACPA emerge years prior to clinically apparent disease and subsequently increase in their titer and breadth of specificity. However, few studies have characterized T cells during this transition.

Objectives: To identify features associated with progression to RA by examining the specificity and surface phenotype of CD4+ T cells in individuals from the TIP-RA cohort by HLA class II tetramer staining and multi-parameter flow cytometry.

Methods: Tetramer staining and flow cytometry were performed on peripheral blood samples from a baseline visit from CCP3- controls (n=34), CCP3+ at-risk (n=26), CCP3+ positive individuals who transitioned in the near-term to RA (called "RA converters", n=4), and seropositive early-RA (n=21). Our staining panel allowed us to measure the frequencies of T cells specific for citrullinated alpha-enolase, aggrecan, cartilage intermediate layer protein (CILP), fibrinogen alpha chain, and vimentin. We then applied both supervised phenotyping and a cluster-based computational approach to compare the phenotypic landscape and specificity of antigen specific and total CD4+ T cells in each cohort.

Results: We observed higher overall frequencies of T cells that recognize citrullinated epitopes in CCP3+ at-risk subjects than CCP- controls (p<0.05). Among the antigen specificities, elevated frequencies prior to disease onset were most prominent for CILP specific T cells. Suppressed phenotypic analysis revealed an increase in CCR4+ CD4+ T cells in CCP3+ at risk subjects (p<0.001) and a corresponding decrease in CXCR3+ CD4+ T cells that was most pronounced in RA converters and seropositive early-RA (p<0.05). Cluster-based phenotypic analysis defined ten distinct phenotypic states present within all subjects. Each of these ten immunotypes contained T cells that recognize citrullinated epitopes. However, the predominant immunotype varied for different antigens. During progression, the frequencies of Ag specific T cells diminished when onset was imminent, but rebounded shortly after diagnosis. Concomitantly, Ag specific T cells with memory phenotypes were diminished, but subsequently reverted to TSCM, Th1, and Th1-17 like phenotypes.

Conclusion: Our data show that disease associated changes in the antigen specificity of CD4+ T cells are present in CCP3+ at-risk subjects. Furthermore, the number of antigen specific T cells and their phenotype are perturbed before the onset of symptoms and development of classifiable RA. These findings support the hypothesis that disease specific T cells recognize self-antigens and acquisition of disease associated T cell phenotypes before the onset of symptoms and development of classified RA. These findings support the number of antigen specific T cells and their phenotype are perturbed before the onset of symptoms and development of classified RA. Furthermore, these findings support the hypothesis that disease specific T cells acquire phenotypic states present within all subjects. Each of these ten immunotypes contained T cells that recognize citrullinated epitopes. However, the predominant immunotype varied for different antigens. During progression, the frequencies of Ag specific T cells diminished when onset was imminent, but rebounded shortly after diagnosis. Concomitantly, Ag specific T cells with memory phenotypes were diminished, but subsequently reverted to TSCM, Th1, and Th1-17 like phenotypes.

Disclosure of Interests: Janssen and BMS and Microdrop, Sunil Nagpal Shareholder of: Janssen

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Disclosure of Interests: None declared.

References:

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THU0035 OX40L EXPRESSING NEUTROPHILS INDUCE CD4+ T FOLLICULAR AND PERIPHERAL HELPER CELLS DIFFERENTIATION IN SYSTEMIC LUPUS ERYTHEMATOSUS


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Background: Neutrophils have been described as potential antigen-presenting cells. We have previously shown that OX40L+ neutrophils can activate T cells by MHC/TCR interaction and costimulatory molecule engagement in the absence of dendritic cells in tumor immunity. However, little is known about the direct interaction between neutrophils and CD4 T cells with respect to systemic lupus erythematosus (SLE). We have previously shown that OX40L expression is induced by monocytes from SLE patients promote the differentiation of naive and memory cells into IL21 secreting T cells that are able to help B cells.

Objectives: In this study, we investigated OX40L expression on neutrophils from SLE patients and contribution of these OX40L+ neutrophils in SLE pathogenesis to modulation of the B cell helper role of CD4 T cells.

Methods: Surface expression of co-stimulatory molecules (OX40L, ICOSL, GITRL, 4-1BBL) on neutrophils from SLE patients and healthy donors (HD) was measured by flow cytometry (FC). Neutrophils from HD were stimulated with TLR7 or TLR8 agonists and IFNα/β after 5 hours of culture, OX40L expression was measured by FC and Western Blotting. CD4 T cells were cultured with the stimulated neutrophils for 3 days. At the end of the co-culture, percentages of