SAT0014

DECREASED CIRCULATING CD19⁺CD24^{hi}CD38^{hi} REGULATORY B CELLS IN ACPA POSITIVE RHEUMATOID ARTHRITIS: EFFECT OF IL-6 RECEPTOR BLOCKADE

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Background: CD19⁺CD24^{hi}CD38^{hi} B cells have a regulatory capacity and their frequency is altered in the peripheral blood of patients with various autoimmune conditions, including RA.

Objectives: To determine the frequency of circulating CD19⁺CD24^{hi}CD38^{hi} regulatory B cells (cBreg) in ACPA+ vs ACPA- patients with RA, and its possible modification by IL-6R blockade.

Methods: Peripheral blood was drawn from ACPA+ (n= 37) or ACPA- (n=19) RA patients treated with conventional synthetic DMARDs (csDMARDs), and from ACPA+ (n=31) or ACPA- (n=12) RA patients treated with tocilizumab; in addition one age and gender-matched healthy control was studied alongside with each patient (n= 99). After isolation by Ficoll-Hypaque gradient, PBMCs were stained with antibodies to CD3, CD4, CD19, CD24, and CD38, and examined by flow cytometry.

Results: A decreased frequency of cBreg cells was observed in ACPA+ but not ACPA- RA patients treated with csDMARDs. Interestingly, the frequency of cBreg cells showed a significant negative correlation with ACPA titers (r = -0.44, p = 0.021). In contrast, no correlation was found between the frequency of cBreg cells and either RF titres or disease activity as determined by the DAS28 score. However, not only in ACPA- but also in ACPA+ patients receiving tocilizumab, the percentage of cBreg cells was not different from that observed in HC. Four ACPA+ patients treated with csDMARDs who initiated tocilizumab, demonstrated a significant elevation of their cBreg frequency at 12 months.

Conclusion: A decreased frequency of cBreg cells is apparent in ACPA+ but not ACPA- RA patients receiving csDMARDs, that is related with ACPA titres but not with RF titres or disease activity. In contrast, in ACPA+ patients treated with tocilizumab, the frequency of CD19⁺CD24^{hi}CD38^{hi} B cells is comparable to that observed in HC, suggesting that IL-6R blockade is able to modify the altered Breg cell balance.

REFERENCE

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SAT0015

TREATMENT WITH ABATACEPT BUT NOT WITH TNF BLOCKERS, IS ASSOCIATED WITH A REDUCTION OF CONSTITUTIVELY ELEVATED CIRCULATING FOLLICULAR HELPER T CELLS IN RHEUMATOID ARTHRITIS

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Background: Circulating CD4⁺ T cells that express CXCR5 together with PD-1 and/or ICOS are considered as counterparts of bona fide Tfh cells and function as B cell helpers. In addition, circulating CD4⁺CXCR5⁺ T cells can be subdivided into three subpopulations: CXCR5⁺CXCR3⁺CCR6⁺ (Tfh-Th1), CXCR5⁺CXCR3⁺CCR6⁺ (Tfh-Th17) and CXCR5⁺CXCR3⁺CCR6⁺ (Tfh-Th2). Only Tfh-Th17 and Tfh-Th2 but not Tfh-Th1 cells seem to provide B cell help. Altered frequencies of circulating Tfh cells (cTfh) and of cTfh cell subpopulations have been associated with autoimmune conditions. We previously described that patients with RA treated with conventional synthetic DMARDs (csDMARDs), demonstrate constitutively altered frequencies of cTfh and cTfh cell subpopulations that are observed not

only in patients with an active disease but also in patients who are in remission.

Objectives: To determine if treatment with biological agents (TNF blockers or abatacept) is able to modify the constitutively altered cTfh and cTfh subpopulation numbers, observed in RA patients receiving csDMARDs

Methods: Peripheral blood was drawn from RA patients receiving csDMARDs (n=22), TNF blockers (n=21: 10 infliximab, 6 etanercept, 3 certolizumab, 2 adalimumab), or abatacept (n=17). For each patient, an age and gender-matched healthy control was also studied (n=60). cTfh and plasmablast frequencies were determined by flow cytometry of freshly isolated PBMCs.

Results: As described, RA patients receiving csDMARDs demonstrated, whether they had an active or inactive disease, an increased frequency of CD4⁺CXCR5⁺PD-1^{hi} and CD4⁺CXCR5⁺PD-1^{hi}ICOS⁺ T cells, together with an increased frequency of circulating plasmablasts. In addition, the frequency of Tfh-Th1 cells was significantly decreased and the frequency of Tfh-Th17 and Tfh-Th2 cells were significantly increased as compared with HC; subsequently, the ratio (Tfh-Th17+Tfh-Th2)/Tfh-Th1 was increased in RA: that is, RA patients demonstrated a higher proportion of Tfh cell subsets bearing a phenotype associated with B cell helping capacity. Interestingly, these alterations were also observed in RA patients treated with TNF blockers, whether they had an active or inactive disease. In contrast, in patients receiving abatacept, the frequencies of cTfh, cTfh cell subpopulations and plasmablasts, were not different from those observed in HC.

Conclusion: Patients with RA receiving csDMARDs or TNF blockers demonstrated a constitutively increased frequency of cTfh cells and an overrepresentation of cTfh subsets bearing a B cell helper phenotype, suggesting that altered germinal center dynamics play a role in RA pathogenesis. Remarkably, in RA patients treated with abatacept these frequencies and ratio were not altered, indicating that costimulation blockade is able to revert the increased generation of Tfh cells in RA; conversely, TNF neutralization does not seem to affect the generation or recirculation of cTfh.

REFERENCE

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SAT0016

RHEUMATOID ARTHRITIS PATIENTS DISPLAY B-CELL DYSREGULATION ALREADY IN THE NAÏVE REPERTOIRE

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Background: Seropositive rheumatoid arthritis (RA) is associated with autoreactivity to citrullinated proteins and rheumatoid factor activity. The adaptive immune system and B cells are postulated to be central in RA pathogenesis, yet possible B-cell dysregulations have not been extensively studied. Here, we use exploratory mass cytometry and next generation sequencing to study overall B cell repertoire shifts in RA patients compared to healthy individuals.

Objectives: We hypothesized that there are an underlying B cells repertoire distortion in RA that may be an important key to understanding the autoimmune pathogenesis.

Methods: B cells enriched from PBMCs from nine ACPA pos., seven ACPA neg. RA patients, and six matched healthy controls were phenotyped with mass cytometry (CyTOF) using a 35-marker panel. Single cell data from all samples were pooled clustered via flowSOM in R to identify distinct cell populations, and visualized with tSNE. Cell numbers in each cluster/population were calculated to identify over-representation in patient groups or controls. ANOVA was performed to account for confounding