The study of mechanisms of immune-inflammation in RP patients may exacerbate the disease progression by not being inhibited Th cells.

**REFERENCES**


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SAT0020

BLOOD RNA SEQUENCING REVEALS IMMUNOLOGICAL PROCESSES ASSOCIATED WITH THE RESPONSE TO ABATACEPT IN RHEUMATOID ARTHRITIS

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Background: Abatacept (CTLA4-Ig) is an approved biological therapy for the treatment of rheumatoid arthritis (RA). Similar to other biological agents, most patients (60%) respond significantly to this therapy. To date, however, the biological mechanisms underlying the lack of efficacy for this drug are unknown.

Objectives: The objectives of the present study were to characterize the biological processes underlying the lack of efficacy of abatacept and to evaluate the blood transcriptome as a valid source for drug response prediction.

Methods: A total of n=57 patients diagnosed with RA were recruited for this study from 16 rheumatology departments in Spain. All patients were >18 years old and had >6 months of disease evolution. The primary clinical response to abatacept was defined at week 12 using the EULAR criteria. Good and moderate responders were aggregated into a single response group, and compared to the no response group of patients.

Blood RNA was collected from all patients at baseline. From a subgroup of patients (n=31), blood RNA was also obtained at weeks 12, 24 and 48 of treatment with abatacept. Gene expression levels were determined using paired-end RNA-seq (Illumina). Differential gene expression, association to biological processes, longitudinal association analysis and building of the multigenic predictor were performed using the R software and the specialized Bioconductor libraries. The prediction accuracy was evaluated using the ROC AUC.

Results: From the 57 patients treated with abatacept, n=10 (17.5%) were good EULAR responders, n=24 (42%) moderate EULAR responders and n=23 (40.5%) non-responders at week 12 of therapy. Biological process analysis identified two significantly distinct biological profiles between responders and non-responders. In responders, we found an association to pathways involved with the effector phase of T cells (e.g. interleukin-15 and 2 signaling, P < 0.05). Non-responder patients showed instead a strong association to biological processes associated with antigen presentation and activation of T cells (P < 0.005). Using the baseline gene expression profiles, we built a multigenic predictor of response to abatacept with an AUC = 75%. In the longitudinal cohort, patients were stratified based on reaching an inactive state (i.e. DAS28 < 3.2). Using this endpoint measure, the longitudinal analysis of the 4 time points corroborated the association of response with antigen presentation (P < 0.01).

Conclusion: The analysis of blood RNA profiles of RA patients has rated the association of response with antigen presentation (P < 0.01). Using the baseline gene expression profiles, we built a multigenic predictor of response to abatacept with an AUC = 75%. In the longitudinal cohort, patients were stratified based on reaching an inactive state (i.e. DAS28 < 3.2). Using this endpoint measure, the longitudinal analysis of the 4 time points corroborated the association of response with antigen presentation (P < 0.01).

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Background: Various alterations of the peripheral T-cell compartment have been reported in granulomatosis with polyangiitis (GPA) such as elevated populations of CD4+CD8+ double-positive and CD4+CD161+ and CD28- single-positive effector memory T-cells (TEM) within the total CD3+ T-cell population (1). Analysis of antigen-specific T-cell subpopulations shows that PR3-specific T-cells display a Th1 profile, whereas Th17 and Th22 cytokine profiles in GPA (2). Moreover, concomitant cellular CMV- and Epstein Barr virus (EBV)-infection has been found to be associated with the expansion of CD28- TEM in GPA (1, 2). Notably, C-type lectin CD161+ cells are involved in the pathogenesis of early stage autoimmune hepatitis (3). CD161 expression on proteinase 3 (PR3)-specific T-cells in comparison to other antigen-specific T-cells has not been described in GPA as yet.

Objectives: To determine the amount of C-type lectin CD161 on antigen-specific CD8+ single-positive and CD4+CD8+ double positive T-cells in patients with GPA.

Methods: In this study, we analyzed the expression of CD161 and CD28 on circulating antigen-specific CD8+ single-positive and CD4+CD8+ double positive T-cells in HLA-A2 positive patients with GPA (n=21) and healthy controls (n=21) using flow cytometry. Antigen-specific T cells were detected using peptide/MHC class 1 dextramers containing major peptide epitopes for PR3, Epstein Barr virus (EBV) BMLF1, and Cytomegalovirus (CMV) pp65 (aa 196-277, aa 280-288, and aa 495-504, respectively).

Results: Patients with GPA showed a higher frequency of circulating CD8+ single-positive and CD4+CD8+ double-positive PR3-specific T-cells with increased expressions of CD161 compared to HC. Compared to EBV- or CMV-specific T-cells, there was an increased expression of CD161 on PR3-specific T-cells in GPA. In contrast to HC and EBV- or CMV-specific T-cells, the percentage of CD28+ T-cells was expanded within the PR3-specific CD8+ T-cell subset in GPA.

Conclusion: These findings suggest a potential role of CD161 as an additional TCR-independent co-stimulatory receptor on PR3-specific T-cells in GPA. The role of these cells in the pathophysiology and as a potential therapeutic target remains to be further investigated.

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