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AB0020 COMPARATIVE DESCRIPTION OF CYTOKINES AND MATRIX METALLOPROTEINASES IN A GROUP OF PATIENTS WITH RHEUMATOID ARTHRITIS AND OSTEOARTHROSIS UNDER A STRICT FOLLOW-UP COMPARED WITH COVID-19 PATIENTS

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Background: COVID-19, rheumatoid arthritis (RA) and osteoarthrosis (OA) are diseases characterized by the secretion of cytokines related to the stimulation of the inflammatory response.
Objectives: To identify the differences in the cytokine and matrix metalloproteinases (MMP) profile within one acute infectious disease and two chronic inflammatory rheumatic diseases.
Methods: Analytical cross-sectional study. RA patients under a strict follow-up program (T2T evaluated every two months), OA patients without strict clinical follow-up, evaluated once or twice a year, and Severe (mortality) COVID-19 patients were included. Eleven proteins (cytokines, MMPs and its tissue inhibitors) were quantified through Luminex multiplex assay in serum samples. Univariate and bivariate analyzes were performed. Approval of Ethics Committee and informed consent were obtained.
Results: A total of 108 patients with RA and OA were compared with 20 severe COVID-19 patients. There were no significant differences through the method of Kruskall–Wallis, between RA and OA patients. IL1-B and MMP-2 were significantly lower in COVID-19 patients. Levels of IL-10, IL-1RA, IL-6, MMP-1, MMP-9, and TIMP-1 were significantly higher in COVID-19 patients. There were no differences in TNF-A, TIMP-2 and INF-G. (Table 1)

Table 1. Significant correlations between cytokines related to Covid-19, RA and OR.

Cytokine (pg/ml) Median values	RA (%)	OA	COVID-19	P-value
IL-10	54.92	54.49	116.38	<0.0001[a]
Il1-RA	62.19	51.82	110.08	<0.0001[a]
IL1-B	67.09	55.30	46.17	0.045
IL-6	56.09	51.34	84.98	<0.0001[b] 0.003[c]
TNF-A	17.5	14.6	16.3	NS
MMP-1[d]	57.84	54.84	90.81	<0.0001[b] 0.045[c]
MMP-2 [d]	70.38	70.59	48.56	0.040
MMP-9 [d]	66.25	58.16	86.4	0.007 [b]
TIMP-1 [d]	51.59	60.99	111.67	<0.0001[a]
TIMP-2 [d]	45.2	47.7	49.6	NS
INF-G	5.75	5.32	3.07	NS

[a] Between RA and Covid-19 and OA and Covid-19, without differences between RA and OA. [b] Between OA and Covid-19.[C] Between RA and Covid-19. [d] ng/ml.

Conclusion: Compared with RA and OA patients, severe COVID-19 patients have a great impact on the cytokines and MMPs addressed in this study, proving that COVID-19 patients suffer from a cytokine storm [1] when severely infected.

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AB0021 FEATURES OF IMMUNOLOGICAL MANIFESTATIONS OF COMMON VARIABLE IMMUNODEFICIENCY COMBINED WITH RHEUMATOID ARTHRITIS

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Background: The prevalence rate of common variable immunodeficiency (CVID), the most common symptomatic form of primary immunodeficiency disease (PID), is growing every year. In the Republican Register of PID in the Chuvash Republic (Russia) there are 32 patients with CVID, 5 (15.6%) of whom have CVID combined with an autoimmune disease - rheumatoid arthritis (RA). The immunological studies occupy a large place in the diagnosis of PID and autoimmune diseases.
Objectives: The aim of the study was to search for immunological criteria for the differentiation of RA from CVID combined with RA.
Methods: The object of the study were 2 groups of patients. Group 1 consisted of 20 RA patients; group 2 consisted of 5 patients with CVID in combination with RA. Patients with CVID, who had the results of an immunological study conducted before the appointment of immunoglobulin replacement therapy, were selected for this study. The control group consisted of 20 practically healthy people.
Results: The significant changes were revealed in the concentration of serum immunoglobulins in the studied groups of patients, in particular, a sharp decrease in IgG levels in group 2 (1.9±0.3 g/l vs. 15.2±2.3 in group 1, p<0.001), IgA (0.1±0.02 g/l vs. 3.1±0.7 g/l in group 1, p<0.001), IgM (0.2±0.03 g/l vs. 1.7±0.2 g/l in group 1, p<0.001). Immunoglobulin levels in both groups of patients were lower (p<0.001) compared to the control group. In both groups, the number of regulatory cells – Treg (CD4+CD25+FoxP3) was reduced: in group 1 - to 2.5±0.03%; in group 2 - to 2.3± 0.02%, while in the control group it was 4.2± 0.5%, p<0.001. The result of our study confirms that the development of RA and CVID is associated with the decrease in the number of Treg cells responsible for ensuring peripheral tolerance and preventing the development of autoimmune diseases.
Conclusion: CVID and RA have a common immunopathological sign - a decrease in the content of Treg cells in the blood. In the differential diagnosis between RA and CVID, combined with RA, it is necessary to rely on the results of the determination of immunoglobulins in the blood serum.
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AB0022 SELECTIVE ESTROGEN RECEPTOR MODULATORS AND TISSUE-SELECTIVE ESTROGEN COMPLEX DO NOT SHARE ESTROGENIC EFFECTS ON IGG SIALYLATION IN AUTOIMMUNE CONDITIONS

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Background: Women entering menopause, with a decrease in estrogen levels, display an increased incidence of rheumatoid arthritis (RA). Estrogen (E2) treatment has beneficial effects on IgG pathogenicity by altering the sialylation grade which affect the binding ability to FcR[1]. E2 replacement may therefore be beneficial in pre-RA patients having autoantibodies. Exposure to estrogen is associated with negative side effects, therefore selective estrogen receptor modulators (SERMs) have been developed with estrogenic protective effect on bone but minimal impact on the reproductive system[2]. The SERM, Bazeodoxifene (BZA), as well as tissue-selective estrogen complex (TSEC), a combination of conjugated estrogen and BZA, have been approved for treatment of postmenopausal bone loss[3-5]

Objectives: The purpose of this study was to investigate the impact of BZA and TSEC on IgG sialylation grade which affects the pathogenicity as well as to determine the effects on total serum protein sialylation.
Methods: C57Bl6 mice were subjected to ovariectomy to stop the endogenous E2 production and mimicked the postmenopausal status. Mice were then treated with E2, BZA, TSEC, or vehicle, followed by ovalbumin (OVA) immunization to induce the IgG levels. Blood was collected before treatment started and at termination. In serum total IgG, OVA specific IgG and the degree of IgG-sialylation were quantified with ELISA. Sialyation of total serum proteins was determined with sialic acid assay quantification kit. Expression of sialyltransferase protein was analyzed in the bone marrow (BM) and spleen cell compartment using flow cytometry. The mRNA expression of glycosyltransferase was analyzed by qPCR analysis.
Results: Neither BZA nor TSEC significantly altered the total IgG levels or sialylation grade of IgG. Indeed, E2 significantly altered IgG sialylation. We showed that BZA increased sialyltransferase protein in plasma cells in a similar manner as E2. Further, neither E2, BZA or TSEC had any significant impact on sialic acids in whole serum protein and not in the mRNA expression of glycosyltransferase in the liver, BM, or gonadal fat.
Conclusion: In this study, we were not able to detect any alteration by TSEC or BZA treatment on IgG-sialylation grade and thereby pathogenicity of the IgG. Neither E2 nor BAZ or TSEC show any significant alteration on general sialylation, but our results suggest that further studies are required to understand E2, SERM, and TSEC full effect on protein sialylation in autoimmune conditions.
Keywords: IgG sialylation, protein glycosylation, SERMs
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AB0023 JAK-INHIBITORS DISRUPT CD14+/CD4+ CELL INTERACTION SUPPRESSING RHO-GTPASE DEPENDENT LEUKOCYTE RECRUITMENT TO JOINTS OF RA PATIENTS

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Background: While examining arthritis development due hyperactivated Rho-GTPases in a mouse model, we found that macrophages with hyperactive Rho-GTPases regulate the migration of thymic T regulatory cells to peripheral lymphoid organs, which contributed to arthritis development Interestingly, T cells reciprocally upregulate Rho-GTPases leading to suppression of homing and formation of a mechanosensory complex of centered around β_1-intergrin facilitating migration.
Objectives: In response to the finding in mice we sought to explore this relationship in patients diagnosed with RA, aiming to expand understanding how different treatments affect the molecular mechanisms we observed in mice.
Methods: To confirm if similar interaction mechanisms between macrophages and T cells are present in RA patients, we used paired transcriptome (RNAseq) of $CD14^+$ and $CD4^+$ cells from 80 RA patients active on conventional DMARDs prior to treatment with TNF-inhibitors (exploratory cohort) and from 56 RA patients with inactive disease on various DMARD treatment (confirmatory cohort). In both cohorts, patients were stratified by mean expression of *CDC42* in $CD14^+$ cells to mimic hyper activation of Rho-GTPases. Transcriptomics of $CD14^+$ and $CD4^+$ cells were analyzed and translated into clinical correlates.
Results: Examining the exploratory cohort, we found a reciprocal upregulation of Rho-GTPases across the cell types. The $CDC42^{hi}$ group had upregulation of *RHOA* and *RAC1* in $CD14^+$ cells and *CDC42, RAC1* and *RHOA* in $CD4^+$ cells. Upregulation of *IL6*, *TLR4* and inflammasome units *IL18R1* and *IL1R2*, *NLRP3* signified pro-inflammatory phenotype of those cells. Furthermore, $CDC42^{hi}CD14^+$ and $CD4^+$ cells shared the upregulation of AP-1 TFs, and the circadian rhythm controlling molecules *PER1*, *AHR* and *KLF6* assisting cell migration. Next, $CDC42^{hi}$ cells were enriched with a synovial macrophage marker CD163, and *ITGB1* to facilitate focal adhesion and migration into joints. Moreover, high expression of CXCL-chemokines and *CCL5* on $CDC42^{hi}CD14^+$ cells indicated the ability to recruit T cells, and high *CXCR4* on $CDC42^{hi}CD4^+$ cells suggested their synovial destination. Unexpectedly, $CDC42^{hi}CD14^+$ and $CD4^+$ cells were not recognized by strong production of the key pro-arthritis cytokines TNF-α and IFN-γ. Consequently, the $CDC42^{hi}$ profile of $CD14^+$ and $CD4^+$ cells was not predictive for clinical response to TNF-inhibition in the exploratory cohort.
Examination of the confirmatory cohort revealed the majority of $CDC42^{hi}CD14^+$ cells belong to the patients treated with conventional DMARDS, while $CDC42^{lo}$ group were treated with JAK-inhibitors (20 vs 4, *OR*= 11.87, 95 % CI [3.387, 49.72], $p<0.0001$). We also found a correlation between *CDC42* expression in $CD14^+$ cells and DAS28 in patients treated with JAK-inhibitors ($r=0.5$, $p=0.0072$) pointing at tight relation between the treatment effect and Rho-GTPase dependent processes. This significantly affected the Rho-GTPase dependent interaction between $CD14^+$ and $CD4^+$ cells.
Transcriptional profile of $CDC42^{hi}CD14^+$ cells of the confirmatory cohort showed many similarities with the exploratory cohort including upregulation of the canonical Rho-GTPases, *ITGB1* and the inflammasome activation that were enhanced by upregulation *of* the vast number of ITGA and chemokines. Transcriptional regulation through *AHR* and *KLF6* persisted, while AP-1 and *PER1* was downregulated. In contrast to CD4+ cells of the exploratory cohort, $CD4^+$ cells of the patients with $CDC42^{hi}CD14^+$ cells were low in *CDC42*, *RAC1* and *RHOA* expression. Also, $CD4^+$ cells were deficient in AP-1, *AHR*/*KLF6* and *PER1*.
Conclusion: Taken together, these data show that Rho-GTPases regulate interaction between $CD14^+$ and $CD4^+$ cells and their migration to RA joints. Treatment with JAK-inhibitors suppress the Rho-GTPase dependent recruitment to joints by changing communication between $CD14^+$ and $CD4^+$ cells. This finding opens new perspective to use Rho-GTPase signature to identify patients suitable for treatment with JAK-inhibitors and in predicting the treatment response.
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AB0024 PLURIPOTENCY MARKER PBX1 PREDICTS TREATMENT EFFECT IN RHEUMATOID ARTHRITIS

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Background: Accelerated immunosenescence with contraction of T cell repertoire, demise of thymic function and expansion of $CD28^{null}$ T cells with poor T cell reconstitution is the hallmark of rheumatoid arthritis (RA)[1].
Objectives: In this study we assessed if PBX1 transcription factor that maintains the pluripotency of hematopoietic stem cells could be used to predict treatment response in RA patients.
Methods: $CD4^+$ T cells of 87 RA female patients (age, median 61y (23-76); disease duration, median 9y (0-45)) were isolated from the perpheral blood, activated with aCD3 and subjected to transcriptional analysis by RNAseq (Illumina). External RNAseq of $CD4^+$ T cells of 80 RA patients (f 56, m 24) was used for validation. The genes differentially expressed (DEG, nominal $p<0.05$) between $PBX1^{hi}$ and $PBX1^{lo}$ groups were identified by R-studio using Benjamini-Hochberg correction (Bioconductor, DESeq2 package). DEGs were clustered by covariance to identify PBX1 associated genes and biological processes. Clinical variates and treatment regimens in $PBX1^{hi}$ and $PBX1^{lo}$ groups were compared.
Results: The patients of $PBX1^{hi}$ and $PBX1^{lo}$ groups were of similar age and disease duration but differed in anti-rheumatic treatment. $PBX1^{hi}$ group was often treated with conventional DMARDs and monotherapy, while $PBX1^{lo}$ group was mostly treated with biologics and/or JAK-inhibitors in combination with cDMARDs (χ^2, p=0.0099). This treatment led to sufficient disease control in both PBX1 groups (median DAS28; 2.6 and 2.7, respectively). In the external RA cohort of the patients resistant to conventional DMARDs, $PBX1^{hi}$ patients had significantly fewer frequency of non-responders to anti-TNF treatment compared to $PBX1^{lo}$ (χ^2, p=0.026).
Pathway analysis of the DEGs identified strong enrichment for regulation of transcription ($cor.p=10^{-23}$), RNA metabolic processes ($cor.p=10^{-18}$) and differentiation ($cor.p=10^{-7}$) in $PBX1^{hi}$ $CD4^+$ cells, which corresponds to the known biological properties of $PBX1^2$. $PBX1^{hi}CD4^+$ cells in both datasets had imprinted features of pluripotency[3] and expressed higher levels of KIT and CAT, low proliferation