THE ROLE OF "NEW" CYTOKINES IN THE PATHOGENESIS RHEUMATOID ARTHRITIS

J. Polyakova1, O. Korolik2, Eugene Papichev1, L. Seewordova3, Akhverdyan Yury1, Tamara Kvilvidze2, B. Zavodovskij2,3.6.7Federal State Budgetary Institution «Research Institute of Clinical and Experimental Rheumatology named after A.B. Zborovsky», Treatment and Prevention of Joint Disease Laboratory, Volgograd Russian Federation; 2Volgograd State Medical University, Volgograd, Russian Federation

Background: Rheumatoid arthritis (RA) is an autoimmune rheumatic disease. Activated B- and T-lymphocytes, mast cells, macrophages, tissue fibroblasts play a leading role in its pathogenesis. The development of autoimmune inflammation is impossible without the influence of a large number of pro-inflammatory cytokines such as IL-1α and β, TNF α, IL-6, IL-17, IL-22. Currently, other classes of biologically active molecules, such as adiponectin, visfatin, nesfatin, fetuin A, are being actively studied in RA [1,2,4].

Pre-B-cell colony enhancing factor 1 (PBEF1) stimulates synthesis of matrix metalloproteinases and chemokines, supporting synovial inflammation caused by leukocyte infiltration. A positive correlation between visfatin and C-reactive protein confirms its role as a mediator of inflammation. It is believed that increased concentrations of PBEF1 can stimulate systemic inflammation.

Objectives: The study the relationship between serum PBEF1 level and disease activity in RA patients.

Methods: We observed 140 patients with a reliable diagnosis of RA, of whom 96 were women and 44 were men. The control group consisted of 20 women and 10 men aged from 22 to 55 years without complaints of pain in the joints during life. PBEF1 concentration in blood serum were determined by indirect enzyme-linked immunosorbent assay using commercial test systems (RaiBiotech, cat№ EIA- VIS-1) according to the manufacturer’s instructions.

Results: The level of normal values of PBEF1 in healthy individuals with a BMI of 18.5 to 24.9 kg/m2 was 0.14–3.9 ng/ml, with a BMI of 25 to 29.9 kg/m2–0.5–5.9 ng/ml. Elevated serum PBEF1 level was detected in 84.29% of RA patients. The ones with elevated PBEF1 levels of significantly more likely to have a higher degree of activity index DAS28 (χ²=48,293; p<0,001), high level of anti-cyclic citrullinated peptide (anti-CCP) (χ²=5,386; p=0,0203), higher levels of C-reactive protein (χ²=8,159; p=0,0043), erythrocyte sedimentation rate (p<0,001), extra-articular manifestations of the disease (χ²=7,354; p=0,0067).

Conclusion: PBEF1 can be regarded as an important link in the pathogenesis of rheumatoid arthritis and for the potential molecule for biological therapeutic agents.

REFERENCES
[3] Elevated Nesfatin-1 levels in patients with RA. The ones with elevated PBEF1 levels of significantly more likely to have a higher degree of activity index DAS28 (χ²=48,293; p<0,001), high level of anti-cyclic citrullinated peptide (anti-CCP) (χ²=5,386; p=0,0203), higher levels of C-reactive protein (χ²=8,159; p=0,0043), erythrocyte sedimentation rate (p<0,001), extra-articular manifestations of the disease (χ²=7,354; p=0,0067).

ASSOCIATION BETWEEN INTERLEUKIN-6–174 G/C POLYMORPHISMS AND VASCULITIS: A META-ANALYSIS

Jae Hyun Jung1,2, Gwan Gyu Song3,4, Jae-Hoon Kim2, Sung Jae Cho4,5.1Korea University College of Medicine, Internal Medicine, Seoul, Korea, Rep. of (South Korea); 2Korea University College of Medicine, Seoul, Korea, Rep. of (South Korea)

Background: Interleukin (IL)-6 is associated with the development and progression of vasculitis, and inhibitors of this cytokine are used to treat this disease. Polymorphisms of the promoter region of IL-6 are associated with the production and expression of IL-6.

Objectives: The aim of this study was to perform a meta-analysis of eligible studies to derive a precise estimate of the association between IL-6 polymorphisms and susceptibility to vasculitis.

Methods: A meta-analysis was conducted on the associations between IL-6-174 G/C polymorphisms and susceptibility to vasculitis. The literature was searched using the PubMed and Embase databases to identify available articles in which IL-6 polymorphisms were analyzed in vasculitis patients. The associations between the -174 G/C alleles and vasculitis were estimated by evaluating odds ratio (OR) and 95% confidence interval (CI). We performed meta-analyses using the 1 alleleic contrast (C vs. G), 2 recessive (CC vs. GC+GG), and 3 dominant (CC+GC vs. GG) models, and 4 heterozygote vs. dominant homozygote (GC vs. GG), 5 heterozygote vs. recessive homozygote (GC vs. CC), and 6 homozygote comparison (CC vs. GG).

Results: A total of 13 studies involving 1,294 vasculitis patients and 1,594 controls were considered in the meta-analysis. There were significant associations between IL-6-174 G/C polymorphisms and vasculitis in allele contrast, dominant genetic model, and heterozygote vs. dominant homozygote comparison (OR 1.80; CI 0.76–3.73, P=0.009 and OR 0.78; 95% CI 0.63–0.92, P=0.005, respectively). In subgroup analysis based on subtype, there were significant associations between IL-6 polymorphisms and susceptibility in large and medium vessel vasculitis, but not in small and variable vessel vasculitis.
Conclusion: The GC genotype of IL-6-174 G/C was suggested by the analyses to be related to low prevalence of vasculitis, especially for large and medium vessels.

Methods: RA-FLSs were stimulated by TNF-α with or without pre-treatment of tofacitinib. The expression levels of VEGF, TNC and GLS were determined using reverse transcription-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA).

Results: In cultured RA-FLSs, VEGF, TNC and GLS were significantly induced by stimulation with TNF-α alone and these inductions were significantly suppressed by treatment of tofacitinib in a dose-dependent manner.

Conclusion: These findings indicate tofacitinib inhibits the VEGF, TNC and GLS production through blockade of a JAK/STAT pathway. Tofacitinib may extinguish inflammatory synovitis through preventing excessive angiogenic factors in RA-FLSs.

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THE DOWNSTREAM EFFECT OF ADALUMAB INVOLVES INHIBITION OF SYNOVIAL CXCL SUBFAMILY CHEMOKINE EXPRESSION

Anne Faurschou Boisen1, Elisabeth Busk Rasmussen1, Tue Wenzel Kragstrup1, 2

1 Aarhus University, Department of Biomedicine, Aarhus C, Denmark; 2 Aarhus University Hospital, Department of Rheumatology, Aarhus C, Denmark

Background: The many different disease modifying anti-rheumatic drugs used for the treatment of immune mediated inflammatory arthritis have very distinctive modes of action. However, the downstream effects of the different drugs are not completely understood. As more treatment options become available detailed knowledge about the different drugs will be important in the future when planning treatment strategies. Adalimumab is a fully human monoclonal antibody against tumor necrosis factor-alpha (TNFα). Earlier studies have found that TNFα inhibitors can decrease the production of interleukin 1 (IL-1), IL-6, IL-8 (aka CXC motif chemokine 8 (CXCL8)) and tumor necrosis factor-like weak inducer of apoptosis (TWEAK). However, these studies have been limited to the measurement of a subset of predefined downstream signaling molecules.

Objectives: The aim of this study was to make an unbiased investigation of downstream effects of adalimumab on production of a wide range of cytokines, chemokines and growth factors by synovial fluid mononuclear cells (SFMCs).

Methods: SFMCs were obtained from a study population consisting of patients with active RA or peripheral SpA with at least one swollen joint (for obtaining synovial fluid) (n=14). SFMCs were cultured for 48 hours with and without addition of adalimumab 5 μg/ml measuring the secretion of 96 cytokines, chemokines and growth factors by an Olink proseek multiplex panel.

Results: In SFMCs cultured for 48 hours, adalimumab decreased the production of IL-8 (CXCL8) (P=0.0001), CXC motif chemokine 5 (CXCL5) (P=0.0003), CXCL9 (P=0.03) and CXCL10 (P=0.03), and monocyte chemotactic protein 2 (MCP-2) (P=0.04) and increased the production of hepatocyte growth factor (HGF) (P=0.008) and tumor necrosis factor-like weak inducer of apoptosis (TWEAK) (P=0.03) after Bonferroni correction (all corrected P values). In this unbiased analysis, adalimumab did not change the production of several other