P053

SERUM AMYLOID A CAN MODULATE NEUTROPHIL SURFACE EXPRESSION OF L-SELECTIN AND INTEGRIN ALPHA M

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Introduction Serum amyloid A (SAA) is one of the major acute phase proteins, elevated in the sera of newly diagnosed patients with giant cell arteritis (GCA).¹ SAA was previously shown to activate neutrophils and recently, neutrophils have been recognised as active players in GCA pathogenesis, exhibiting changes in surface protein expression of l-selectin (CD62L) and integrin α M (CD11b) during therapy tapering.² **Objectives** To determine the expression of CD62L and CD11b on neutrophils in peripheral blood of newly diagnosed, steroid naïve GCA patients (day 0) vs. healthy blood donors (HBDs). We also aimed to examine the ability of SAA and SAA1 α to activate neutrophils in whole blood of HBDs and GCA patients prior to receiving glucocorticoid therapy and 7 and 30 days after therapy.

Methods Whole blood of 37 GCA patients and 17 HBDs was stained with anti-CD62L and anti-CD11b (eBioscience), lysed and analysed by flow cytometer (Miltenyi). Whole blood of 5 GCA and 6 HBDs was stimulated with 10 μ M hrSAA and hrSAA1 α for 20 min at 37°C, lysed and incubated on melting ice for 15 min. Samples were then stained with anti-CD62L and anti-CD11b. SAA in sera of GCA patients was measured by nephelometry.

Results We observed higher neutrophil counts and surface expression of CD62L in peripheral blood of naïve GCA patients compared to HBDs ($p=0.006$). Stimulation of whole blood with hrSAA or hrSAA1 α significantly decreased CD62L and increased CD11b expression on neutrophils of HBDs and naïve GCA patients. Whole blood stimulation with hrSAA/SAA1 α caused significant attenuation of CD62L, while increasing CD11b expression on neutrophils of naïve GCA patients (day 0) as compared to 7 and 30 days after therapy. Levels of SAA in GCA patients decreased after receiving therapy.

Conclusions We show that hrSAA and hrSAA1 α activate neutrophils implying tight adhesion and transendothelial migration. Interestingly however, in patients with GCA, increased SAA did not shed CD62L, as we observed elevation of both. The latter indicates potential initial attachment of neutrophils to activated endothelium, as a possible mechanism in GCA pathogenesis.

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P054

MONOCYTE-RELATED BIOMARKERS OF RHEUMATOID ARTHRITIS DEVELOPMENT IN UNDIFFERENTIATED ARTHRITIS PATIENTS – A PILOT STUDY

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Introduction The enhanced/disturbed activities of monocytes are important for perpetuation and for development of rheumatoid arthritis (RA). Therefore, consistent analysis of monocytes activities and regulation of molecular pathways operating within monocytes, especially at early stages of RA development, may help to predict the progression to the full-blown disease.

Objectives In this study we aimed to investigate the profile of miRNAs expression in circulating monocytes and monocyte-related cytokines in peripheral blood of individuals at undifferentiated arthritis (UA) stage as potential new biomarkers for RA development.

Methods Magnetically sorted monocytes from peripheral blood (PB) of 20 individuals with UA served for total RNA isolation. RNA samples were used for microRNA profiling performed on the miRCURY LNA array. Concentrations of CCL3/MIP-1a, M-CSF, CCL2/MCP-1, IL-6, TNF α , IL-15 and eotaxin in sera of UA patients were measured using commercial ELISA assays. Verification of diagnosis after 4 years of follow-up led to the identification of patients who developed full-blown RA (UA→RA patients) and patients who remained in UA phase (UA→UA patients). Comparisons between patients groups were performed using two tailed Mann Whitney U test.

Results Following computational unsupervised analysis we identified 50 miRNAs in PB monocytes that have the largest variation of expression across all patients samples. From these 50 miRNAs, expression of three miRNAs: miR-642b-5p ($p=0.0380$), miR-483-3 p ($p=0.009$), miR-371b-5p ($p=0.0381$) were up-regulated, and two miRNAs: miR-25-3 p ($p=0.0317$) and miR-378d ($p=0.0059$) were down-regulated in monocytes from UA→RA vs UA→UA patients. This specific pattern of miRNAs expression in circulating monocytes paralleled elevated IL-15 ($p=0.003$) and M-CSF ($p=0.03$) concentrations in sera of UA patients who progressed to RA.

Conclusions Our results indicate that altered activity of monocytes can be detected at early stages of RA development. We found new miRNA candidates (miR-642b-5p, miR-483-3 p, miR-371b-5p, miR-25-3 p and miR-378d) differentially expressed in PB monocytes, and elevated concentrations of circulating IL-15 and M-CSF involved in monocyte activity and differentiation, as potential biomarkers identifying UA patients who subsequently developed RA.

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P055 INTERLEUKIN-7 IN AORTIC ADVENTITIA OF PATIENTS WITH RHEUMATOID ARTHRITIS AND CORONARY ARTERY DISEASE

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Introduction Rheumatoid Arthritis (RA) patients have increased cardiovascular risk (CV) due to accelerated atherosclerosis (ATS), which significantly contributes to excess mortality in RA.¹ The increased CV risk cannot be fully explained by traditional risk factors and systemic chronic inflammation appears to play a crucial role. Interestingly, IL-7, a proinflammatory cytokine involved in RA pathogenesis, appears to play a role also in ATS² but its effect on cardiovascular disease (CVD) in RA has not been studied yet.

Objectives To examine serum IL-7 levels and expression of IL-7, IL-7R, CD3 and CD20 in aortic adventitia of RA and non-RA patients with coronary artery disease (CAD) and to search for relationships between systemic IL-7 levels and expression of vascular markers, cardiovascular risk factors including metabolic and inflammatory parameters.

Methods We examined 19 RA and 20 non-RA patients undergoing coronary artery bypass graft surgery included in the Feiring Heart Biopsy Study. Serum IL-7 levels were measured by chemiluminescence (MSD). Biopsies from the adventitia of thoracic aorta from a subset of patients (12 RA and 14 non-RA) were stained for IL-7, IL-7R, CD3 and CD20 by immunohistochemistry and scored per mm² of tissue.

Results Non-RA patients had lower IL-7 serum levels than RA (3.4±3.3 vs. 6.7±3.5, p<0.05). Independently of RA diagnosis, IL-7 significantly correlated with CRP (rho=0.450, p=0.008), triglycerides (TG, rho=0.566, p=0.005), glucose (rho=0.642, p=0.001) and hypertension (p=0.036). Levels of IL-7 were associated with New York Heart Association class (rho=0.429, p=0.014) and this was stronger in non-RA patients (rho=0.577, p=0.010). No associations were found with smoking or markers of CVD severity (i.e., numbers of arteries with stenosis or previous myocardial infarcts (MI)). The number of IL-7 + and IL-7R+cells/mm² in adventitia were significantly higher in RA (134.2±45.5 and 144±49.9 respectively) than non-RA patients (46.9±22.8 and 54.4±20.2, p<0.005) and were associated with serum IL-7 levels (rho=0.551 and rho=0.588, p<0.01). Both IL-7 + and IL-7R+cells were associated with a positive history of MI (p=0.047 and p=0.005) and IL-7R+cells with the number of previous MIs (rho=0.408, p=0.038). Only in RA patients, IL-7R+cells showed a trend for correlation with TG (rho=0.771, p=0.072). IL-7 + and IL-7R+cells correlated with CD3 (rho=0.688, p=0.013 and rho=0.630, p=0.028), but no

correlation was found with CD20. Cholesterol and HDL levels were associated with IL-7 +cells only in non-RA patients (rho=0.729, p=0.04 and rho=0.733, p=0.038).

Conclusions Among patients with CAD, those with RA had higher serum IL-7 and a greater expression of both IL-7 and IL-7R in aortic adventitia. Systemic levels of IL-7 were related to its vascular expression. Thus, the IL-7/IL-7R axis may play a role in the accelerated ATS observed in RA; further studies are needed to elucidate the precise role of IL-7 in CV risk in RA.

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P056 IMPORTANT ROLE OF CD11C+ DENDRITIC CELLS IN INFLAMMATORY ARTHRITIS

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Introduction The main function of dendritic cells (DCs) is to present antigen to T-cells and therefore they play an important role in bridging the innate and the adaptive immune response. However, DCs can be divided in different subsets, which have intrinsic differences that lead to functional specialisation in the generation and maintenance of autoimmunity. Therefore the aim of our study was to investigate the role of CD11c⁺ conventional DCs and monocytes derived DCs in inflammatory arthritis.

Methods We analysed histological sections of K/BxN serum transfer arthritis as well as hTNFtg arthritis for the presence of CD11c⁺ cells by immunohistochemistry. We also performed synovial biopsies and analysed the cellular composition of the inflammatory infiltrate with respect to DCs. We used CD11c-diphtheria toxin receptor (DTR) transgenic mice, which express the human diphtheria-toxin receptor under the CD11c promoter, allowing for specific depletion of CD11c⁺ cells by administration of diphtheria toxin (DT). K/BxN serum transfer arthritis was induced, and mice were given either DT or PBS or in wt and BARF3 deficient mice. In addition CD11c DTR mice were crossed into hTNFtg animals and also received either DT or PBS. The severity of arthritis was determined clinically and histologically.

Results We show that Cd11c⁺ cells are present in significant numbers in the synovia of K/BxN and TNF driven arthritis. Both CD8⁺CD11c⁺ and CD11b⁺CD11c⁺, can be found in synovial tissue. In K/BxN serum transfer arthritis, clinical scores showed that CD11c-DTR transgenic mice that received DT had significantly reduced paw swelling and loss of grip strength compared to PBS treated animals. Histological analysis found reduced inflammation after the depletion of CD11c⁺ cells in K/BxN arthritis. In addition local bone destruction and the number of osteoclasts was significantly reduced. Analysis of K/BxN arthritis in wt mice and BATF3^{-/-} mice, which lack CD8⁺CD11⁺ DCs revealed no difference in arthritis severity between the two groups. In addition to K/BxN arthritis, we found that also in TNF-driven arthritis