$p < 0.001$) and this was independent of disease activity. Recombinant IFN- α decreased EPC differentiation in healthy control cells (32.44 ± 0.09 vs $79.69 \pm 0.27\%$, $p = 0.001$), and this was attenuated in the presence of CYM-5442 and exacerbated in the presence of W-146. Moreover, type I IFN regulated genes were modulated by these compounds.

Conclusions: The S1P1 pathway is involved in the regulation of EPC differentiation by type I IFNs. Defects in S1P1 signalling pathway in lupus EPCs may contribute to the development of endothelial dysfunction in SLE.

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FRI0280

A MOLECULAR NETWORK FOR FATIGUE IN PRIMARY SJÖGREN'S SYNDROME

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Background: Fatigue is a common phenomenon in primary Sjögren's syndrome (pSS) and other chronic inflammatory diseases, cancer, and neurodegeneration. The underlying mechanisms for fatigue are not completely understood, but increasing evidence point to a biological basis for the phenomenon.

Objectives: Following the sickness behaviour hypothesis for fatigue, where pro-inflammatory cytokines and particularly interleukin 1 β (IL-1 β) related signalling are essential, we wished to investigate how molecules that influence IL-1 β activity may influence fatigue through complex networks (IL-1 β , IL-1Ra, IL-1RII, IL-6 and S100B). We also hypothesised that the neuropeptide hypocretin-1 (Hcrt1), a regulator of sleep and wakefulness, could be an element in a network for fatigue.

Methods: In cerebrospinal fluid (CSF) from 49 patients with pSS, Hcrt1 was measured by RIA and the other proteins by ELISA. Fatigue was rated using the fatigue visual analogue scale (fVAS), and results analysed by univariate-, multiple regression, and principal component analysis (PCA).

Results: It was not possible to measure IL-1b due to very low concentrations in CSF. In simple univariate regression analysis with fatigue as a dependent variable a significant association was observed for depression ($R^2 = 0.20$, $p < 0.01$), and pain ($R^2 = 0.23$, $p < 0.01$) and the biochemical variable IL-1Ra ($R^2 = 0.09$, $p = 0.04$). In multiple regression with fVAS as dependent variable a model was obtained with depression, pain, and IL-1Ra as significant contributors ($R^2 = 0.37$; $p < 0.001$). In PCA two significant components were revealed (figure 1a). The first component (PC1) was dominated by variables related to IL-1 β activity. The second component (PC2) showed a negative correlation between IL-6 and Hcrt1. fVAS was then introduced as an additional variable. In this new model fVAS correlated with the IL-1 β related variables on PC1 and to a lesser degree with Hcrt1 on PC2 (figure 1b).

Abstract FRI0280 – Figure 1. a) PCA of biochemical variables only. b) PCA of biochemical variables including fatigue. Biplot illustrates scores of individuals and variables for PC1 and

PC2. Individual's scores are illustrated by dots. Arrows illustrate correlations of the variables to the components. Longer arrows mean higher correlation and arrows close to a component has higher contribution in generation of the component.

Conclusions: The main findings in this study indicate a functional network in which several IL-1 β related molecules in CSF influence fatigue in addition to the clinical factors depression and pain. The neuropeptide Hcrt1 seem to participate in fatigue signalling, but probably not through the IL-1 pathway.

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FRI0281

TRANSCRIPTOMIC PROFILING OF PDCs FROM PATIENTS WITH PSS IDENTIFIES CONSISTENTLY ALTERED GENE NETWORKS THAT INDICATE AN ACTIVATED PHENOTYPE AND ENHANCED ANTI-VIRAL STATE

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Background: Primary Sjögren's syndrome is an autoimmune disease characterised by lymphocytic infiltration of the exocrine glands and dryness of mouth and eyes. Type-I interferons (IFN) are thought to play an important role in pSS pathogenesis and plasmacytoid dendritic cells (pDCs) are capable of producing high levels of IFN. These cells infiltrate the salivary glands of pSS patients and their numbers correlate with local IFN-production.

Objectives: To understand the molecular mechanisms behind systemic dysregulation of pDCs, we performed RNA sequencing on pDCs isolated from peripheral blood of patients with pSS, non-Sjögren's sicca (nSS) and healthy controls.

Methods: We established two independent cohorts (each $n = 31$), of patients and controls. pSS patients ($n = 25$) were classified according to the 2002 AECG criteria. nSS patients ($n = 20$) presented with dryness complaints without a known cause, did not have any generalised autoimmune disease, and did not fulfil the classification criteria for pSS. Healthy donors ($n = 17$) were included as control group. Peripheral blood pDCs were isolated using MACS and RNA sequencing was performed for both cohorts. ± 20 million paired-end sequencing reads per sample were obtained using Illumina HiSeq 2500 platform.

Results: 8556 genes were differentially expressed (p -value < 0.05) between all three groups in the discovery cohort. Of these, 3144 genes were also differential in the replication cohort. We generated gene modules from both cohorts and found 5 gene clusters comprising 1259 genes that were consistently dysregulated in both analyses. Pathway analysis showed that the 5 modules contain genes associated with cellular activation, including a group of genes involved in IFN-signalling and viral sensing, as well as regulation of intracellular transport. Generally, pDCs from patients with nSS displayed an intermediate phenotype.

Conclusions: We mapped transcriptomic differences in circulating pDCs from patients with nSS and pSS and identified gene clusters that are robustly replicated in two independent cohorts. We found 5 gene clusters that are dysregulated in patients with pSS and indicate enhanced cellular activation, including IFN-signalling and viral sensing which are key pathways in pSS pathogenesis. nSS patients showed similar transcriptomic dysregulation at an intermediate level. These data can help us better understand the role of pDCs in pSS.

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FRI0282

MILK FAT GLOBULE EPIDERMAL GROWTH FACTOR 8 ON MONOCYTES IS A NOVEL BIOMARKER OF DISEASE ACTIVITY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Milk fat globule epidermal growth factor 8 (MFG-E8) is an apoptosis-related secreted protein. It has been reported that MFG-E8 deficient or excess mice developed a systemic lupus erythematosus (SLE)-like autoimmune disease due to impaired clearance of apoptotic cells,¹ suggesting that abnormal expression of MFG-E8 is involved in the pathogenesis of SLE. Since elevated serum MFG-E8 level has been found in SLE patients,² it may possibly provide the