$p < 0.001$) 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

classification of the disease by pathological conditions.³ However, the association with MFG-E8 expression and clinical features of SLE patients is not fully understood.

Objectives: To clarify the clinical significance of MFG-E8 in SLE, we analysed the correlation between the expression level of MFG-E8 in circulating phagocytic leukocytes and clinical parameters of the patients.

Methods: A multi-centre, exploratory and prospective SLE cohort was established. Among SLE patients who visited our division from May 2015 to March 2017 and satisfied the 1997 revised criteria, patients with one or both of BILAG A or B, or with SLEDAI-2K $\geq$ 4 and clinical symptoms were defined as active SLE. These patients were then matched with randomly selected patients by age, gender, history of nephritis, and daily glucocorticoid dose as an inactive SLE group. Age and sex matched healthy controls (HC) were also recruited. The expression level of MFG-E8 in monocytes and its concentration in serum of the patients were measured by FACS and ELISA, respectively. The clinical parameters of the patients were collected from their clinical records.

Results: A total of 108 cases were enrolled, consisting of 36 active (mean age: 44.2 $\pm$ 18.6, female: 80.6%, nephritis: 69.7%), 38 inactive SLE and 24 HC cases. The absolute number and the proportion of MFG-E8 positive-monocytes to total monocytes were significantly higher in the active SLE group ($p<0.01$), whereas serum MFG-E8 level showed no significant difference among the group. Importantly, the proportion was also significantly correlated with SLEDAI-2K, serum levels of anti-ds-DNA antibody and complement and C1q (table 1). Notably, elevated proportion of MFG-E8-positive monocytes to total monocytes was observed in the patients with cutaneous or musculoskeletal involvement or leukocytopenia. In addition, the proportion of MFG-E8-positive monocytes to total monocytes significantly decreased from the baseline in active SLE patients after 6 months treatment and increased concordantly with disease activity in 6 refractory cases. Then we further analysed the accuracy to discriminate between active and inactive SLE patients and found that the proportion of MFG-E8 monocytes showed significant accuracy of disease activity, which is equivalent to serum levels of anti-ds-DNA antibody, complement and C1q, by receiver operating characteristic curve analysis (figure 1).

Abstract FRI0282 – Table 1. Correlation with SLEDAI and serological markers (Spearman's rho)

		n	Number of MFG-E8 positive monocyte	Proportion of MFG-E8 positive monocyte	Serum MFG-E8
a) Activity	SLEDAI-2K	74	0.570**	0.634**	-0.110
b) Serological markers	CH50	51	-0.503**	-0.591**	0.049
	Anti-ds-DNA antibody	74	0.425**	0.449**	-0.027
	C1q	69	0.526**	0.568**	0.001

* $p<0.05$, ** $p<0.01$ by Spearman's correlation coefficient

Abstract FRI0282 – Figure 1. Receiver operating characteristic curve analysis for discriminating active from inactive SLE

Conclusions: Our study indicate that the proportion of MFG-E8-positive monocytes to total monocyte in peripheral blood was positively associated with disease activity of SLE and may be a novel mechanistic biomarker to determine the disease activity.

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FRI0283

DYNAMIC CONTRAST ENHANCED MRI (DCE-MRI) DEMONSTRATES HIPPOCAMPUS PERMEABILITY IN SLE

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Background: Cross-reactive, anti-dsDNA/N-methyl d-aspartate receptor antibodies (DNRAb) have been implicated in the pathogenesis of cognitive impairment in SLE. The mouse model demonstrates selective effects of DNRAb on hippocampal neurons following blood brain barrier (BBB) breach. ¹ We previously identified abnormal hippocampal glucose hypermetabolism in SLE patients that correlated with serum DNRAb titers and poor performance on neuropsychological (NP) testing.² However, little is known about how antibodies access brain in humans.

Objectives: BBB permeability (BBBP) in SLE and healthy control (HC) subjects was evaluated with DCE-MRI. We hypothesised that brain areas with abnormal hypermetabolism² in SLE subjects would also demonstrate altered BBBP.

Methods: 6 SLE subjects with no history of NP symptoms and 6 HCs were recruited (all female). All subjects underwent NP testing and DCE-MRI on a 3.0 tesla magnet (Siemens Healthineers, GERMANY). MRI sequences were acquired according to standard protocols; permeability imaging used DCE technique with axial 3D-SPGR T1-WI sequences and 80 cine phases using TR=25 ms, TE=3.8 ms, FOV=24 mm, and matrix size of 128 $\times$ 256. Magnevist Gadolinium contrast (Bayer Healthcare, GERMANY) was dosed IV at 0.1 mmol/kg, at 5cc/sec following a 5 s delay. Post-processing of images into BBBP parameters of K-trans (mL/100 gm/min) and VE (mL/100 gm) was performed using Olea Sphere 2.2, 2.3 (Olea Medical, France) with the Tofts extended permeability model. This technique was standardised with the arterial input function centred in the cavernous ICA segment for all subjects.

Analyses: Regions-of-interest (ROI) from previously identified hypermetabolic regions (hippocampus, orbitofrontal cortex, posterior putamen/globus pallidus/thalamus) were selected. Mirror ROIs were placed in bilateral MRI cerebral hemispheres for sampling at same brain levels. Regional DCE curves were generated to compare permeability phases. T-tests were used to evaluate demographic and NP testing differences.

Results: SLE subjects performed significantly worse than HCs on cognitive testing (table 1). Mean DCE curves (figure 1) show perfusion (initial spike) and permeability phases of contrast in the sampled tissues. Compared to HCs, SLE subjects demonstrate significantly increased signal in the permeability phase in the hippocampus, indicating leakage of contrast into the extravascular space.

Abstract FRI0283 – Table 1. Subject characteristics and neuropsychological testing scores

	Healthy Control (n=6)	SLE (n=6)	p
Age	35.04 $\pm$ 9.6	38.0 $\pm$ 13.2	.669
NP Testing*			
Matching Grids	40.9 $\pm$ 9.7	25.8 $\pm$ 9.2	.023
Match to Sample	35.4 $\pm$ 13.5	16.4 $\pm$ 5.9	.01
Continuous Processing	86.3 $\pm$ 13.9	65.6 $\pm$ 5.5	.013

*Automated Neuropsychological Testing Metric: resulted as throughput scores that represent efficiency as a function of accuracy and time

Abstract FRI0283 – Figure 1. Dynamic Contrast Enhanced MRI Curves show increased hippocampus permeability in SLE