A MOLECULAR NETWORK FOR FATIGUE IN PRIMARY SJÖGREN'S SYNDROME

K. Bårdsen1, C. Brede2, I. Kvikvik1, J.T. Kvaløy1, K. Jonsdottir1, A.B. Tjensvoll1, P. Ruoff5, R. Omdal6,7.

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 (IVAS), 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 (R²=0.23, p<0.01), and the biochemical variable IL-1Ra (R²=0.37; p<0.001). In multiple regression with fatigue as a dependent variable a model was obtained with depression, pain and IL-1Ra as significant contributors (R²=0.37; p<0.001). In multiple regression with fVAS as dependent variable a model was obtained with depression, pain and IL-1Ra as significant contributors (R²=0.37; p<0.001). In simple univariate regression analysis with fatigue as a dependent variable

Conclusions:

The main findings in this study indicate a molecular network in which several IL-1-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.

Disclosure of Interest:

None declared

DOI:


FR0281

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

M.R. Hillen1,2, A. Pandi2,3, S.L.M. Blokland2, S.A.Y. Hartging3,4, K.M.G. Van der Wurff-Jacobs5, A.A. Kruize6, M. Rossato2,3, J.A.G. van Rooij1, R.T. D. J. Radstake1,2,3, Laboratory of Translational Immunology, Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

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 Sjögren’s pathogenesis and plasmacytoid dendritic cell interferon-alpha autoamplification.

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.

Disclosure of Interest:

None declared

DOI:


FR0282

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

M. Ushiku1,2, S. Sato2, J. Kikuchi2, M. Takeshita2, K. Yoshimoto2, H. Yasukawa3, K. Yamaoka1, N. Seki4, K. Suzuki4, H. Oshima1, T. Takeuchi2,1 Department of Connective tissue disease, National Hospital Organization Tokyo Medical Center, Division of Rheumatology, Keio University School of Medicine, Division of Rheumatology, School of Medicine Keio University, Tokyo; Research Units/ Immunology and Inflammation, Mitsubishi Tanabe Pharma Corporation, Yokohama, Japan

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, 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, it may possibly provide the
classification of the disease by pathological conditions. 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 > 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±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 concurrently 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 FRIO282 – Table 1. Correlation with SLEDAI and serological markers (Spearman’s rho)

<table>
<thead>
<tr>
<th>Variable</th>
<th>MFG-E8 positive monocyte</th>
<th>Serum MFG-E8</th>
</tr>
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<tbody>
<tr>
<td>SLEDAI-2K</td>
<td>0.570**</td>
<td>-0.110</td>
</tr>
<tr>
<td>CH50</td>
<td>-0.303**</td>
<td>0.049</td>
</tr>
<tr>
<td>Anti-dsDNA antibody</td>
<td>0.425**</td>
<td>0.449</td>
</tr>
<tr>
<td>C1q</td>
<td>0.529**</td>
<td>0.548**</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01 by Spearman’s correlation coefficient

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.

REFERENCES:

Disclosure of Interest: None declared


FRIO283 DYNAMIC CONTRAST ENHANCED MRI (DCE-MRI) DEMONSTRATES HIPPOCAMPU PERMEABILITY IN SLE

M. Mackay, B. Diamond, D. Eidelberg, A. Hoang, P.C. Sanelli. The Feinstein Institute for Medical Research, Manhasset, USA

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 DNRAbs on hippocampal neurons following blood brain barrier (BBB) breach. We previously identified abnormal hippocampal glucose hypermetabolism in SLE patients that correlated with serum DNRAb titers and poor performance on neuropsychological (NP) testing. However, little is known about how antibodies access brain in humans.

Objectives: BBB permeability (BBBP) in SLE and healthy control (HC) patients was evaluated with DCE-MRI. We hypothesised that brain areas with abnormal hypermetabolism 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 128×256. Magnesivist 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 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 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.

Abstract FRIO283 – Table 1. Subject characteristics and neuropsychological testing scores

<table>
<thead>
<tr>
<th></th>
<th>Healthy Control (n=6)</th>
<th>SLE (n=6)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35.04±9.6</td>
<td>38.0</td>
<td>.669</td>
</tr>
<tr>
<td>NP Testing*</td>
<td>40.9±9.7</td>
<td>25.8±9.2</td>
<td>.023</td>
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<tr>
<td>Match to Sample</td>
<td>35.4±13.5</td>
<td>16.4±5.9</td>
<td>.01</td>
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<tr>
<td>Continuous</td>
<td>66.3±13.9</td>
<td>65.6±5.2</td>
<td>.013</td>
</tr>
</tbody>
</table>

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