Results: NZB/W mice at 3 months and 6 months of age exhibit depressive-like disorder as assessed by SPT and TST (P <0.05 and <0.0001, respectively). Anx-

iety-like phenotype was evident in lupus-prone mice at both time points based on EPM test (Graph 1). Open-field test revealed decreased locomotor activity and rotarod (Graph 2) showed impaired motor coordination in 3 month-old and 6 month-old NZB/W mice (P<0.001 and <0.01, respectively). NZB/W mice exhibit cognitive dysfunction at 3 and 6 months of age based on NOR test (P<0.05). No differences in cognitive function was observed between the two groups (P=0.11).

Prepulse inhibition test revealed decreased sensorimotor gating in 3 month-old NZB/W mice, a difference not reaching statistical significance (P=0.078). It was not possible to interpret correctly the PPI at second time point (6 months of age) due to age-related hearing loss in B6 at 6 month-old. NZB/W become more anxious over the course of the disease as assessed by EPM (3 mo. versus 6 mo. P<0.001, paired t-test, Graph 1).

Conclusion: The NZB/W lupus-prone strain exhibit depressive-like behavior, anxiety, cognitive impairment and motor disturbances both at early and late stages of the disease. This polygenic murine model may be more suitable for investigating the autoimmune-mediated neuroinflammation in human SLE.


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Background: Recently, immunometabolism has gathered attention of many immunologists. It has been widely recognized that metabolic reprogramming in each immune cell brings different effects on different cells and is important for regulating their functions. Along with the progress of statistical genetics, serum metabolites were shown to be under genetic regulations1. Metabolic changes are now considered not only to be mere phenotypes of cells but also to be key factors for controlling immune cell differentiation, proliferation and function through regulating gene expressions eventually. Although genome-wide association studies have brought deep insights into SLE pathogenesis, the precise pathway from genome to metabolome has been largely unknown, and vice versa.

Objectives: The aim of this study is to investigate metabolic regulation in SLE in relation to gene expressions by integrating plasma metabolome data and transcription data.

Methods: We collected plasma samples from patients with SLE (n=57) who met the 1997 American College of Rheumatology criteria for SLE. Gender- and age-matched healthy controls (HCs) (n=56) were recruited. Metabolic profiles focusing on 39 amino acids were analyzed with liquid chromatography (LC)-mass spectrometry. Transcriptome data of SLE patients were obtained from our RNA-sequencing data of each immune cell subset (total 19 subsets). Whole-genome sequencing was also performed.

Results: Our previous experiment showed that about 160 peaks were detected from HCs, whose plasma level was lower in SLE patients. In addition, inverse correlation between His level and titer of ds-DNA as well as damage index (SDI) was detected. His level was correlated neither with PSL dosage nor with type I interferon (IFN) signature. Receiver operating characteristic (ROC) analysis showed the best predictability for SLE with the combination of specific amino acids including His. Our transcriptional analysis revealed the significance of oxidative phosphorylation (OXPHOS) in B cells for SLE pathogenesis. Interestingly, OXPHOS signature was inversely correlated with His level in SLE B cells.

Conclusion: His may be an important factor for SLE pathogenesis especially in B cells independently from IFN signal. SLC15A4, a transporter of His on lysosome, is one of the SLE GWAS SNPs and has been reported to play an and highly abundant cytokine in the CLE lesions and confirmed this finding by IHC.

Conclusion: Conclusions Our data confirm evidence on IFN-regulated processes in CLE/SLE. Importantly, we identified IL-16 as a novel cytokine most strongly upregulated locally in the skin lesions. Moreover, we identified activation of MAC, complement regulating proteins as well as involvement of coagulation/fibrinolysis system. The study brings information on novel pathways involved in the inflammatory foci of the skin lesions in CLE patients. Our findings are of interest in further search of new therapeutic processes for SLE.

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important role in IFN production in B cells through regulation of TLR7/9 activation. 2) We also identified that SLE patients with risk allele of SLC15A4 had tendency to show higher plasma His level, indicating His homeostasis could become a novel treatment target for SLE. Moreover, the inverse correlation of His level to SDI as well as OXPHOS signature suggests that His might play a key role for promoting organ damages in SLE.

References:

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Figure 1. MSCs ameliorated SS symptoms and decreased MDSCs in NOD mice.

THU0226  
MESENCHYMAL STEM CELL TRANSPLANTATION AMELIORATES EXPERIMENTAL SJÖGREN’S SYNDROME BY DOWREGUALTING MDSCS VIA COX2/PGE2 PATHWAY

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Background: Although mesenchymal stem cells (MSCs) transplantation have been demonstrated to be an effective therapeutic approach to treat experimental Sjögren’s syndrome (ESS)1, the specific underlying mechanisms remain to be elucidated. Myeloid-derived suppressor cells (MDSCs) were significantly increased with decreased suppressive capacity during disease development in ESS2-3. However, the therapeutic effects and mechanisms by which MSCs regulate MDSCs in SS still remain unknown.

Objectives: Here we aim to explore whether regulation of MDSCs was responsible for the beneficial effects of MSC transplantation on SS.

Methods: The MSCs were infused into/nose diabetic (NOD) mice via the tail vein. The histological features of submandibular glands, lung, saliva flow rate were evaluated. The number and immune-suppressive activity of MDSCs, the subsets of MDSCs, polymorphonuclear MDSCs (PMN-MDSCs) and monocytic-MDSCs (M-MDSCs) in NOD mice were determined. The bone marrow cells under MDSCs differentiation conditions were co-cultured with or without MSCs. The COX2 inhibitor NS-398, anti-TGF-β1, or anti-IFN-γ antibodies were added to coculture medium of MSCs and MDSCs induced from bone marrow cells respectively.

Results: We found that MDSCs in bone marrow and peripheral blood increased in ESS mice. MSC transplantation ameliorated SS-like syndrome and down-regulated the percentages of MDSCs, PMN-MDSCs and M-MDSCs and promoted their suppressive ability in ESS mice significantly (Figure 2). In vitro, MSCs could down-regulate the differentiation and up-regulate the suppressive ability of MDSCs. Mechanistically, MSCs inhibited the differentiation of MDSCs and PMN-MDSCs via secreting prostaglandin E2, and inhibited the differentiation of M-MDSCs by secreting interferon-γ (Figure 2).

Figure 2. MSCs inhibited the differentiation of PMN-MDSCs and M-MDSCs by COX2/PGE2 and IFN-γ respectively.

Conclusion: Our findings suggested that MSCs alleviated SS-like symptoms by suppressing the aberrant accumulation and improving the suppressive function of MDSCs in ESS mice via COX2/PGE2 pathway.

References:

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THU0227  
CAFFEINE INTAKE MODULATES DISEASE ACTIVITY AND CYTOKINES LEVELS IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Background: Systemic lupus erythematosus (SLE) is an autoimmune disease mainly affecting women of childbearing age. The interplay between genetic and environmental factors may contribute to disease pathogenesis. At today, no robust data are available about the possible role of diet in SLE. Caffeine, one of the most widely consumed products in the world, seems to interact with multiple components of the immune system by acting as a non-specific phosphodiesterase inhibitor. In vitro dose-dependent treatment with caffeine seems to down-regulate mRNA levels of key inflammation-related genes and similarly reduce levels of different pro-inflammatory cytokines. Objectives: We evaluated the impact of caffeine consumption on SLE-related disease phenotype and activity, in terms of clinimetric assessment and cytokines levels.

Methods: We performed a cross-sectional study, enrolling consecutive patients and reporting their clinical and laboratory data. Disease activity was assessed by SLE Disease Activity Index 2000 (SLEDAI-2k). Caffeine intake was evaluated by a 7-day food frequency questionnaire, including all the main sources of caffeine. As previously reported, patients were divided in four groups according to the daily caffeine intake: <29.1 mg/day (group 1), 29.2-153.7 mg/day (group 2), 153.8-376.5 mg/day (group 3) and >376.6 mg/day (group 4). At the end of questionnaire filling, blood samples were collected from each patient to assess cytokines levels. These were assessed by using a panel by Bio-Plex assays to measure the levels of IL-6, IL-10, IL-17, IL-27, IFN-γ, IFN-α and Blys.

Results: We enrolled 89 SLE patients (F/M 87/2, median age 46 years, IQR 14; median disease duration 144 months, IQR 150). The median intake of caffeine was 195 mg/day (IQR 160.5). At the time of the enrollment, 8 patients (8.9%) referred a caffeine intake < 29.1 mg/day (group 1), 27 patients (30.3%) between 29.2 and 153.7 mg/day (group 2), 45 patients (51%) between 153.8 mg/day and 376.6 mg/day (group 3) and >376.6 mg/day (group 4). The cytokines levels were: IL-6: group 1, 2, 3, 4 = 15.8 pg/mL, 9.7 pg/mL, 9.2 pg/mL, 9.5 pg/mL; IL-10: group 1, 2, 3, 4 = 13.6 pg/mL, 7.8 pg/mL, 7.4 pg/mL, 7.2 pg/mL; IL-17: group 1, 2, 3, 4 = 1.2 pg/mL, 0.6 pg/mL, 0.6 pg/mL, 0.6 pg/mL; IL-27: group 1, 2, 3, 4 = 1.2 pg/mL, 0.6 pg/mL, 0.6 pg/mL, 0.6 pg/mL; IFN-γ: group 1, 2, 3, 4 = 1.2 pg/mL, 0.6 pg/mL, 0.6 pg/mL, 0.6 pg/mL; IFN-α: group 1, 2, 3, 4 = 1.2 pg/mL, 0.6 pg/mL, 0.6 pg/mL, 0.6 pg/mL; Blys: group 1, 2, 3, 4 = 1.2 pg/mL, 0.6 pg/mL, 0.6 pg/mL, 0.6 pg/mL.