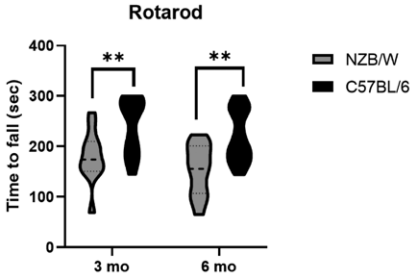
Results: NZB/W mice at 3 months and 6 months of age exhibit depressive-like disorder as assessed by SPT and TST (P <0.05 and <0.0001, respectively). Anxiety-like phenotype was evident in lupus-prone mice at both time points based on EPM test (Graph 1). Open-field test revealed decreased locomotor activity 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=.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 autoimmunity-mediated neuroinflammation in human SLE.



Graph 2. Rotarod performance demonstrates impaired motor coordination in NZB/W F1 strain both at 3 and 6 months of age (P < 0.01, unpaired t-test).

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THU0224 SKIN PROTEOME INVESTIGATION IN CUTANEOUS LUPUS ERYTHEMATOSUS (CLE) REVEALS NOVEL UNIQUE DISEASE PATHWAYS

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Background: Cutaneous lupus erythematosus (CLE) is an autoimmune disease. It can be limited to the skin or be one of manifestations of systemic LE (SLE). The typical histopathologic pattern in CLE/SLE is interface dermatitis, which can also be observed in dermatomyositis (DM). While LE may affect any organ system, DM most commonly affect muscles and skin.
Objectives: The aim of this study was to investigate the whole proteome of skin inflammatory foci in the cohort of CLE and DM patients in a comparatory, hypothesis-free manner and identify disease-unique molecular mechanisms.
Methods: CLE (n=6), DM (n=5) patients and controls (n=6) were recruited at diagnosis or disease exacerbation. Skin biopsies were acquired, examined by a pathologist and selected inflammatory foci were laser micro-dissected. The total protein content was analyzed by mass-spectrometry, further analysis was performed by string-db.org platform. Certain proteomic findings were confirmed by immunohistochemistry (IHC).
Results: CLE infiltrates were more protein rich in comparison to DM lesions. There ratio of 5x upregulated proteins in LE/DM was 60, while ratio for DM/LE was 13. Our results confirmed high abundance of (IFN)-regulated proteins both in CLE and DM, including: IFIT, MX and OAS families. Proteins expressed differentially in CLE covered complement proteins (C1b), including membrane attack complex (MAC) (C5, C6, C7, C8A and B) and complement regulators (CFHR1, CFHR2, CFHR5), as well as regulators of coagulation: thrombospondin 2 (THBS2), thrombin (F2), fibrinogen (F12) and annexin A3 (ANXA3). Importantly, we identified interleukin (IL) -16 as the only detectable 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 targets.
Disclosure of Interests: : Timothy Niewold: None declared, Karin Popovic-Silwerfeldt: None declared, Julia Lehman: None declared, Alexander Meves: None declared, Cristine Charlesworth: None declared, Benjamin Madden: None declared, Aliisa Hayry: None declared, Aleksandra Antovic: None declared, Ingrid E. Lundberg Grant/research support from: Bristol Meyer Squibb, Corbus Pharmaceuticals, Inc and Astra Zeneca, Marie Wahren-Herlenius: None declared, Elisabet Svenungsson: None declared, Vilija Oke: None declared
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THU0225 INTEGRATIVE PLASMA METABOLOME AND TRANSCRIPTOME ANALYSIS REVEALED THE IMPORTANCE OF HISTIDINE HOMEOSTASIS IN SLE PATHOGENESIS WITH POTENTIAL FOR IMPROVED SLE PATIENTS STRATIFICATION

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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 metabolomic regulation in SLE in relation to gene expressions by integrating plasma metabolome data and transcriptome 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 comprehensive LC-TOFMS and amino acids were useful for distinguishing SLE patients from HCs. Both partial least squares discriminant analysis (PLS-DA) and random forest, a machine learning algorithm, revealed the importance of histidine (His), one of the essential amino acids, to classify SLE patients 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 transcriptome analysis has 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

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.

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[1] *Nat Genet.* 2017;49:568. 2) *Immunity*. 2014;41:375. 3) *Semin Arthritis Rheum.* 2019;48:1142

Disclosure of Interests: : Yukiko Iwasaki: None declared, Yusuke Takeshima: None declared, Masahiro Nakano: None declared, Mineto Ota: None declared, Yasuo Nagafuchi: None declared, Akari Suzuki: None declared, Yuta Kochi: None declared, Tomohisa Okamura: None declared, Takaho Endo: None declared, Ichiro Miki: None declared, Kazuhiro Sakurada: None declared, Kazuhiko Yamamoto Grant/research support from: Astellas, BMS, MitsubishiTanabe, Pfizer, Ayumi, Takeda, Chugai, Eisai, Taisho Toyama, UCB, and ImmunoFuture, Keishi Fujio Grant/research support from: Astellas, BMS, MitsubishiTanabe, Pfizer, Ayumi, Takeda, Chugai, Eisai, Taisho Toyama, Eli Lilly, Sanofi, and UCB

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THU0226 MESENCHYMAL STEM CELL TRANSPLANTATION AMELIORATES EXPERIMENTAL SJÖGREN'S SYNDROME BY DOWNREGUALTING 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 ESS[2-3]. However, the therapeutic effects and mechanisms by which MSCs regulating 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 intonon-obese 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-β 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 1). 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-β (Figure 2).

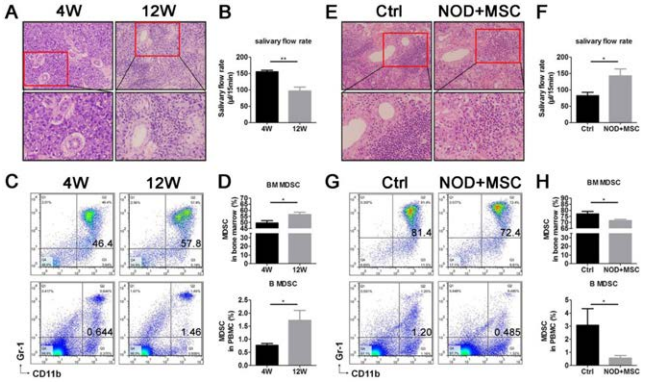

Figure 1. MSCs ameliorated SS symptoms and decreased MDSCs in NOD mice.

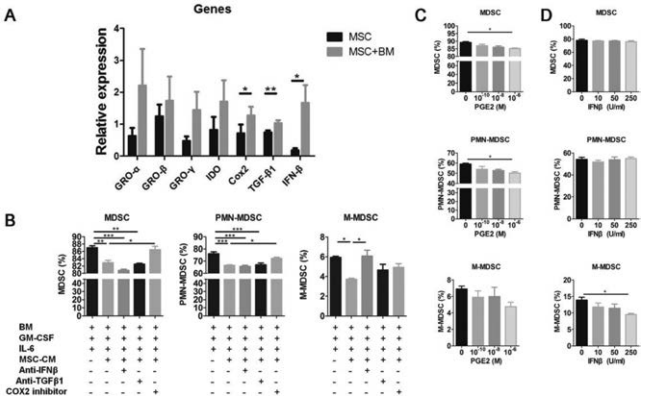

Figure 2. MSCs inhibited the differentiation of PMN-MDSCs and M-MDSCs by COX2/PGE2 and IFN-β respectively.

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.

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Disclosure of Interests: None declared

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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[1]. At today, no robust data are available about the possible contribute 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[2]. *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[3].

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)[4]. 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)[5]. 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