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 ($P = 0.078$). 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 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 comparative, 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: 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.

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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