LSO-039 PROTEOMIC ANALYSIS OF CUTANEOUS LUPUS ERYTHEMATOSUS AND DERMATOMYOSITIS DERMAL INFILTRATE REVEALS DIFFERENTIALLY EXPRESSED CANONICAL PATHWAYS

[1]Aliisa Häyry*, [2]Timothy B Niewold, [3]Alexander Meves, [3,4]Julia S Lehman, [5]Karin Popovic-Silwerfeldt, [6]Cristine M Charlesworth, [6]Benjamin Madden, [1,7]Elisabet Svenungsson, [1,8]Vilija Oke. *[1]Division of Rheumatology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [2]Rheumatology, Hospital for Special Surgery, New York, NY, USA; [3]Department of Dermatology, Mayo Clinic, Rochester, MN, USA; [4]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA; [5]Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; [6]Mayo Clinic Medical Genome Facility – Proteomics Core, Mayo Clinic, Rochester, MN, USA; [7]Rheumatology, Karolinska University Hospital, Stockholm, Sweden; [8]Center for Rheumatology, Academic Specialist Center, Stockholm, Sweden*

10.1136/lupus-2023-KCR.80

Background Cutaneous lupus erythematosus (CLE) and dermatomyositis (DM) are autoimmune diseases with characteristic cutaneous rashes. Both are histopathologically characterized by interface dermatitis and they are difficult and sometimes impossible to differentiate based on skin biopsies. The specific pathogenesis of both conditions remains enigmatic.
Methods Punch biopsies were obtained from lesional skin from patients with CLE (n=6) or DM (n=5), and control skin (n=6). Equal volumes of tissue were microdissected within the CLE and DM dermal inflammatory infiltrates and control dermis. Proteomic database was constructed using nano-LC tandem mass spectrometry. Qiagen Ingenuity pathway analysis was performed, and identified canonical pathways were compared between CLE, DM, and controls.
Results Comparing CLE vs controls we identified 246 pathways, while 51 of them were enriched (threshold $p<0.05$). Comparing DM vs controls 200 pathways were identified, 72 enriched. Canonical pathways enriched in both CLE and DM were those involved in antigen presentation, protein ubiquitination, acute phase response, interferon signaling, GP6 signaling, tRNA charging, and B cell development. Analysis of CLE vs DM showed 237 pathways, 70 of them enriched ($p<0.05$). The top differentially enriched canonical pathways in CLE compared to DM included EIF2 signaling, complement system, LXR/RXR and FXR/RXR activation, acute phase response signaling, mTOR and granzyme A signaling, clathrin mediated endocytosis signaling, and coagulation system.
Conclusions Canonical pathways enriched in both CLE and DM skin are associated with activation of innate and adaptive immune systems, including the interferon system. A major difference between CLE and DM was that the EIF2 pathway, involved in cellular stress and induction of cell death, was enriched in CLE. Enhanced granzyme A signaling in CLE coincides with the top upregulated cytokine in the CLE proteomics being IL-16,[1] majorly expressed by CD8 T lymphocytes. Further, results indicate differentially activated metabolic pathways and deposition of complement and coagulation components in CLE dermal infiltrate.

REFERENCES

1. Niewold TB, Meves A, Lehman JS, *et al.* Proteome study of cutaneous lupus erythematosus (CLE) and dermatomyositis skin lesions reveals IL-16 is differentially upregulated in CLE. *Arthritis Res Ther* 2021;**23**:132. doi:10.1186/s13075-021-02511-0

LSO-040 MITOCHONDRIA PROMOTES AUTOIMMUNE PLASMABLASTS GENERATION IN LUPUS

[1]Sung Hoon Jang*, [1]Joo Sung Shim, [1]Jieun Kim, [2]Ho-Keun Kwon, [1]Jason Jungsik Song. *[1]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Republic of Korea; [2]Department of Microbiology, Yonsei University College of Medicine, Republic of Korea*

10.1136/lupus-2023-KCR.81

Background Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the overproduction of autoantibodies. Recent studies showed that CD11c+ extrafollicular (EF) B-cells plays a central role for the development of lupus. We investigated the role of mitochondria in CD11c+ EF B cells and autoimmune plasmablasts in lupus.
Methods We investigated EF B cells, CD11c+ plasmablasts in B6 mice stimulated with CpG-Oligodeoxyribonucleotides (ODN) every other day for 10 days. Immune cell subtypes were analyzed by flow cytometry. Mitochondria membrane potential and mass were measured by JC-1, MTDR, and MTG. Generation of autoimmune plasmablasts were evaluated by measuring serum anti-dsDNA antibody by ELISA and anti-dsDNA antibody secreting cells by ELISPOT. Furthermore, mouse spleen B cells and human peripheral blood B cells from lupus patients were stimulated with CpG-ODN for 3 days and generation of EF B cells and mitochondria were evaluated by FACS. Mitochondria were inhibited by IM156 (complex I inhibitor), and CB-839 (GLS1 inhibitor) with in vivo or in vitro CpG-ODN stimulation.
Results In vivo injection of CpG-ODN induced anti-DNA antibody in mice. Mitochondria membrane potential and mass of EF B cells and plasmablasts were increased by CpG-ODN. Autoimmune plasmablasts measured by anti-dsDNA antibody ELISPOT were increased in bone marrow from CpG-ODN injected mice. CpG-ODN induced EF B cells and plasmablasts in in vitro culture condition with mouse splenic B cells and lupus B cells. Furthermore, CpG-ODN also increased mitochondria membrane potential and mass in in vitro culture condition. IM156 or CB-839 inhibited EF B cells and autoimmune plasmablasts in vivo and in vitro.
Conclusions This study demonstrated that the central role of mitochondria in generation of autoimmune plasmablasts in lupus. CpG-ODN induced autoimmune plasmablasts while IM156, or CB-839 inhibited autoimmune plasmablasts by suppression of mitochondria.

LSO-041 LOSS-OF-FUNCTION NADPH OXIDASE VARIANTS PROMOTE LUPUS PATHOGENESIS BY MODULATING B CELL-INTRINSIC TLR SIGNALS

[1]Aaron Liu, [1,2]Mridu Acharya, [1,2]Shaun Jackson*. *[1]Center for Immunity and Immunotherapies, Seattle Children's Research Institute, USA; [2]Pediatrics, University of Washington, USA*

10.1136/lupus-2023-KCR.82

Background GWAS have linked loss-of-function mutations in phagocytic NADPH oxidase complex (NOX2) genes, including NCF1 and NCF2, to lupus pathogenesis. The prevailing model holds that reduced NOX2 promotes SLE via defective

Lupus Sci Med: first published as 10.1136/lupus-2023-KCR.81 on 6 August 2023. Downloaded from http://lupus.bmj.com/ on October 10, 2024 by guest. Protected by copyright.