NEUROPSYCHIATRIC LUPUS IS DEPENDENT ON LIPOCALIN-2

1Elie Mike, 2Carla Cuda, 3Hadjat Makinde, 2Harris Perlman, 1,3Chaim Putterman.
1Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY, USA; 2Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; 3Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY, USA

10.1136/lupus-2018-lsm.101

Background
Neuropsychiatric manifestations of systemic lupus erythematous (NPSLE) affect approximately 40% of patients. Lipocalin-2 (LCN2), an acute-phase reactant protein, is an established urinary biomarker in lupus patients. Previous studies using LCN2-deficient mice have demonstrated its role in glial migration and chemokine regulation in the brain. We therefore hypothesized that LCN2 is involved in NPSLE pathogenesis.

Methods
We investigated the lupus prone B6.Sle1.Sle3 (Sle1,3) mouse and the effects of LCN2 deficiency on the development of the neuropsychiatric phenotype exhibited by this strain. Sle1,3, B6.LCN2KO, B6, and Sle1,3-LCN2KO mice (6–10 month old; n=5–10/group) underwent comprehensive neurobehavioral assessment, and brains were evaluated by flow cytometry and RNA sequencing.

Results
Sle1,3 mice exhibited significant impairment in spatial (p<0.04, figure 1A) and recognition (p<0.02, figure 1B) memory when compared with B6 mice, and these deficits were attenuated in Sle1,3-LCN2KO mice (p<0.001, p<0.02, figure 1A-B). Furthermore, Sle1,3 mice demonstrated anhedonia, and this depression-like behavior was significantly reduced with LCN2 deficiency (p=0.01, figure 1C). Flow cytometry showed a significant increase in brain infiltrating CD8+ T cells in Sle1,3 mice, with a reduction in infiltration in the Sle1,3-LCN2KO strain (p=0.06). Preliminary analysis of RNA sequencing from sorted microglia revealed differential expression of genes between B6 and Sle1,3 mice (figure 1D) and between Sle1,3 and Sle1,3-LCN2KO mice (figure 1E). Moreover, genes involved in cognition and memory that were differentially expressed in Sle1,3 mice were restored to background B6 expression levels in Sle1,3-LCN2KO mice.

Conclusions
Our findings establish the Sle1,3 mouse as an NPSLE model and demonstrate that LCN2 deficiency attenuates neurobehavioral deficits and regulates microglial expression of genes essential to NPSLE development.
BONE MARROW MESENCHYMAL STEM CELLS FROM PATIENTS WITH SLE MAINTAIN AN INTERFERON SIGNATURE DURING IN VITRO CULTURE

Lin Gao, 1Mary O’Connell, 1Maria Allen, 2Andrew McDavid, 1Jennifer H Anolik, 1Richard J Looney*. 1Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester New York, USA; 2Department of Biostatistics and Computational Biology, University of Rochester School of Medicine and Dentistry, Rochester New York, USA

Abstract

Background We have previously shown that SLE BMSCs have a pro-inflammatory mediated by a MAVS and IFNβ feedback loop. Compared to healthy controls, SLE BMSCs produced increased amounts of IFNβ and had increased mRNA for several genes induced relatively specifically by IFNβ. They also had decreased proliferation, increased ROS, increased DNA damage and repair (DDR), a senescence associated secretory phenotype, and increased senescence-associated β-galactosidase. To better understand the phenotype of SLE BMSCs we conducted RNA sequencing.

Methods Patients fulfilling SLE classification criteria and age and sex matched healthy controls were recruited under an Institutional Review Board approved protocol (6 pairs). Bone marrow aspirates and peripheral blood samples were obtained. BMSCs were isolated with low density Ficoll/Hypaque and grown in tissue culture. Purity of BMSC cultures were verified by flow cytometry. Early passage BMSC were harvested and mRNA samples were sent for RNAseq through the University of Rochester Genomics Core. Serum samples with assayed for IFNβ using an ELISA from PBL.

Results Hierarchical clustering of normalized RNAseq profiles found SLE patients with high levels of serum IFNβ (>13 units per XXX) grouped together while SLE patients with low levels of IFNβ grouped together with healthy controls. Principal component analysis found the majority of the variance could be explained by PC1 (32.3%) and PC2 (25.5%). While PC1 did not separate SLE or SLE IFNβ high from the other samples, PC2 clearly differentiated SLE IFNβ low samples from SLE IFNβlow and control samples. SLE IFNβ low and control sample overlapped in both PC1 and PC2. The top upregulated genes in PC2 were RSAD2, MX1, IFIT1, IFIT2, OAS1, CMPK2, OASL, IFIT3, ISG15, IDO1, IFI6, MX2, HERC5, and IFIH1 … all type I interferon-induced genes.

Conclusions BMSCs from SLE patients are heterogeneous. A subgroup of SLE BMSC are distinguished from other SLE BMSC and from controls by increased levels of mRNAs induced by type I interferons. Moreover, SLE BMSC with increased levels of mRNA for type I interferon-induced genes when grown in vitro are derived from patients with increased levels of IFNβ in vivo.

Acknowledgements This work was supported in part by a grant from the Lupus Research Alliance.