

MYLUPUSGUIDE, A LUPUS-SPECIFIC WEB INTERACTIVE NAVIGATOR, IMPROVES SELF-EFFICACY AND ACTIVATION IN PATIENTS WITH LOW ACTIVATION AND IN MEN

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Background Systemic Lupus Erythematosus (SLE) is an unpredictable multisystem chronic disease that leads to insecurity, requires life-style adaptations, work accommodations and long-term medication use. We previously reported that a web-based interactive navigator named MyLupusGuide (MLG) was well accepted by lupus patients and met with their informational needs. When used without reinforcement however MLG did not change patient activation towards self-management. We performed additional analyses to test if subgroups of patients were more likely to become activated than others in a large lupus population.

Methods Population and recruitment strategy: Patients from ten lupus centers were randomized to either immediate access to MLG (NOW) or usual care (LATER). Partial cross-over occurred at three months and there was a final assessment at six months. Data collected: Demographic and socioeconomic data were collected at baseline. The 13-item Patient Activation Measure (PAM) was used to assess patient's healthcare engagement. Higher PAM score relates to greater engagement. Additional self-reported measures for self-efficacy (Lupus Self-Efficacy Scale - LSES) and coping strategies (Coping with Health Injuries and Problems - CHIP) were obtained at baseline, 3 and 6 months. Statistical analyses: Linear mixed models

were used to test the evolution of PAM over time between groups. This abstract reports on the following subanalyses: analyses of the subgroup with low PAM score at baseline and of being male or female, and analyses of other outcomes such as LSES and CHIP.

Results A total of 541 of 1920 (28%) lupus patients responded at baseline, 399 at 3 months and 355 at 6 months. At baseline, mean (sd) age=50.1 (14.2) years, female=93%, Caucasian=74%, disease duration=16.9 (11.9) years and PAM score=61.1 (13.5). The following subanalyses (table 1) showed a beneficial effect of MLG on activation after three months in the subgroup of patients with low PAM at baseline, as well as for men. A significant improvement in LSES was also observed after 3 months of exposure to MLG but there was no change in CHIP.

Conclusions At 3 months, access to MLG improved activation in patients with a low activation at baseline and in men. Self-efficacy also improved significantly without changes in coping strategies. The MLG is a unique web-based resource that provides reliable information for patients with lupus to assist them with disease management and lifestyle adaptations.

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DISPARITIES OF B-CELL TYPE I INTERFERON PRODUCTION AND RESPONSES IN SLE

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Background Dysregulated responses to type I interferons (IFNs) is a hallmark of autoreactive B-cell development in SLE. This study investigated the source of IFN, the major type I IFN responsive B cells, and the disparities associated with B-cell IFN production and type I IFN responses.

Methods IFN expression in B, CD4 T and plasmacytoid dendritic cells (pDCs) in PBMCs were analyzed by flow cytometry. Single cell gene expression analysis was carried out using the Fluidigm/BioMark system for targeted expression of low abundance genes, and the 10x Chromium platform for unbiased transcriptome and BCR V(D)J analysis of approximately 2,000 B cells per subject. Autoantigen epitope targets were analyzed using a 4287 high-throughput PEPPER Autoimmune Epitope Microarray and a conventional ELISA analysis.

Results IFN was analyzed in B cells, CD4 T cells and pDCs in PBMCs of SLE patients and healthy controls (HCs). Endogenous IFN was significantly increased in transitional (Tr), mature naïve, and memory B cells of SLE patients compared to HCs. Endogenous IFN in B cells was equivalent to that in pDCs. B-cell endogenous IFN was highly correlated with renal disease, anti-dsDNA, anti-Sm and anti-SSA. Strikingly, the highest correlation of IFN with clinical manifestations was observed in African-American (AA) patients with IgG autoAbs against snRNP323-339, U1snRNP-C97-113. At the single cell transcriptome levels, Tr B cells could be divided into type I IFN expressing (IFN+) or type I IFN stimulated gene (ISG+) subpopulations. TLR7 and TLR3 were mainly expressed by IFN +cells whereas TLR9 was mainly expressed by ISG +B cells. Unbiased single cells analysis of B cells indicated highly

Abstract 191 Table 1 Improvement after three months in patient activation and self-efficacy in subgroup analyses of 541 patients given access to MyLupusGuide (analyses done on pooled groups after a 3 months exposure* to MLG)

Outcome	Subgroup	Mean±Standard Error	p value
PAM	Intention to treat	0.81±0.58	0.16
PAM	Per Protocol (complete visits+access to MLG)	0.57±0.74	0.45
PAM	Low PAM at baseline	2.24±0.80	0.01
PAM	Women	0.51±0.61	0.40
PAM	Men	6.46±2.42	0.01
Self-Efficacy	Intention to Treat	1.72±0.77	0.03
Palliative Coping	Intention to Treat	0.12±0.21	0.57
Distractive Coping	Intention to Treat	0.34±0.25	0.17
Instrumental coping	Intention to Treat	-0.14±0.23	0.54
Emotional coping	Intention to Treat	-0.46±0.25	0.06

* Pooled Difference Post vs Pre MLG access for time 0 to 3 months in the NOW group and time 3 to 6 months in the LATER group.

expressed ISG gene set in IGHM+, IGHD+, and IGHG +B cells in AA patients with autoantibodies and renal disease. Further, ISG highly expressing SLE B cells exhibited unique heavy- and light-chain repertoires including expression of the autoreactive IGHV4-34 gene, targeted with the 9 G4 anti-idiotypic antibody that recognizes DNA- and RBP-autoreactive B cells.

Conclusions (i) B cells are an important source of type I IFNs in modulating TLR and BCR responses in SLE; (ii) there are well-orchestrated distinct programs in type I IFN expression and response genes in subsets of B cells, (iii) distinct pathways of autoreactive B cell survival and activation are effected by combined signaling through BCR, TLR, and IFNAR with resultant distinct BCR heavy- and light-chain repertoire.

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193 THE ENVIRONMENT AND LUPUS: IMPACT OF INFLAMMATION AND DIET ON T CELL EPIGENETICS

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Background Lupus flares when genetically predisposed people encounter environmental agents that trigger the flares such as UV light and infections which cause oxidative stress, but the mechanisms by which environmental agents induce flares are unclear. Our group has shown that lupus-inducing drugs such as procainamide and hydralazine inhibit DNA methylation in dividing CD4 +T cells, converting normal antigen specific T cells into autoreactive, cytotoxic pro-inflammatory cells that are sufficient to cause lupus in mice, and that similar epigenetically altered T cells are found in patients with active lupus. The mechanism(s) by which environmental agents alter the T cell epigenome to create the pathogenic cells was unclear. The enzyme DNA methyltransferase 1 (Dnmt1) is upregulated as T cells enter mitosis by signals transmitted through the ERK pathway, then binds the replication fork where it copies methylation patterns from the parent strand to the daughter strand by transferring the methyl group from S-adenosylmethionine (SAM) to dC bases in the daughter strand. This suggests that environmental agents which inhibit Dnmt1 upregulation or decrease SAM levels may inhibit T cell DNA methylation to trigger lupus flares.

Methods CD4 +T cells from lupus patients and controls were stimulated with PHA then cultured in custom media with normal or low transmethylation micronutrient levels. Oxidative stress was induced by treating the normal CD4 +T cells with peroxyxynitrite (ONOO-) prior to culture or injection into SJL mice. Methylation sensitive gene expression (CD70, KIR, and perforin) was measured by RT-PCR and flow cytometry

Results PHA stimulated CD4 +T cells from healthy controls expressed higher levels of CD70, KIR, and perforin mRNA and protein when cultured in media with low transmethylation micronutrient levels relative to cells cultured in complete media. Similar increases were seen in cells cultured in media with low or normal media methionine levels. PHA stimulated CD4 +T cells from lupus patients also overexpressed KIR, CD70 and perforin relative to PHA stimulated T cells from

controls when similarly cultured. Treating PHA stimulated normal CD4 +T cells with ONOO- also increased methylation sensitive gene expression in normal CD4 +T cells, and low methionine or folate levels further increased gene expression relative to untreated T cells and T cells cultured in complete tissue culture media.

Conclusions Inflammation and transmethylation micronutrient deficiencies synergize to inhibit T cell DNA methylation, contributing to the onset of lupus flares.

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194 TRANSCRIPTOME ANALYSIS OF SKIN FIBROBLASTS DERIVED FROM LUPUS NEPHRITIS PATIENTS DEMONSTRATES FIBROTIC AND INTERFERON-RELATED CELLULAR BIOMARKERS

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Background The impact of renal injury in lupus nephritis is widespread with consequences to resident cells in other tissue beds, even non-lesional non-sun exposed skin. Faithful reflection of a relevant renal tissue pathway in a more readily accessible compartment would allow for less invasive diagnostic alternatives. Single-cell transcriptional states as performed in this study may provide a framework for understanding how *in vivo* biological function emerges from complex cell ensembles, thus allowing for a clearer understanding of potential mutual pathways.

Methods Patients with proteinuria and known ISN/RPS Class and controls were recruited to discovery 1 and 2 cohorts. Single cell RNAseq was performed on cell suspensions prepared from ~2 mm punch biopsies of non-lesional non sun-exposed skin from the buttocks. The libraries were prepared on the Fluidigm C1 platform (discovery 1) and 10X Genomics platform (discovery 2) along with Illumina HiSeq 2500 sequencing.

Results Sorting based on COL1A1, COL1A2, COL3A1, MFAP5 and MFAP4 expression yielded 12 fibroblasts from 3 patients. The 1 Class II subject yielded 5 single-cell transcriptomes. The other 2 subjects (1 Class IV,V; 1 Class III,V) yielded 7 single-cell transcriptomes. 22 transcriptomes were derived from 3 controls. The aggregate data were used to determine the top upregulated genes in cases versus controls, most of which belonged to the interferon-stimulated gene category and the extracellular matrix category (DAVID databases). Fewer cells were obtained using Fluidigm C1 (36 single-cell) than 10X Genomics (7280 single-cell). For the latter, the major biopsy classes were represented (Class III, III/IV, III/V, V and no LN). We applied graph-based clustering and identified 12 major clusters of cells from the patient skin as visualized by t-distributed stochastic neighbor embedding (t-SNE; figure 1). Differential gene expression analysis guided by established lineage markers revealed three keratinocyte clusters (KC1-KC3), two fibroblast clusters (FB1, FB2), smooth muscle cells (SMC), two endothelial cell clusters (VEC, LEC), melanocytes (MEL), sweat gland cells (SG), macrophages/dendritic cells (MAC-DC) and T cells (TC). Ranked by abundance, patient skin exhibited KC>FB>EC>MAC-DC>SMC>TC>SG> MEL.