

Abstracts

via flow cytometry to identify immune cell subsets. Spleen cells were treated with vehicle or TLR7/8 agonist overnight prior to supernatant analysis. In a parallel experiment, mice were treated for two weeks with a topical TLR7 agonist (R848) to assess effects on immune cell populations.

Results Immune cell subsets in spleen were similar in all mice. Cell counts of *ex vivo* and Flt3L- cultured BM-DCs were reduced in NOER mice. Conventional DCs (cDCs) were increased in MOER mice, and NOER mice trended higher in CD19+ cells. Other immune populations remained similar. NOER mice trended lower in IL-6 response after overnight R848 stimulation.

Conclusion Preliminary results suggest membrane ER α -initiated events are required to develop certain innate immune cell subsets and for robust expansion of DCs. Membrane and nuclear functions of ER α may compensate for each other in some cases. More studies are needed to clarify the role of ER α localization in modulating immune cell development and function.

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1005 CHARACTERIZATION OF REGULATORY RECEPTORS ON PLASMACYTOID DENDRITIC CELLS IN LUPUS

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Regulatory or suppressive receptors on plasmacytoid dendritic cells (PDCs) are an attractive therapeutic target in systemic lupus erythematosus (SLE), given the role type I interferon (IFN) plays in this disease. In this study, we determine

whether SLE patient PDC regulatory receptor expression and function associates with disease features in SLE. We used quantitative multicolor flow cytometry to measure regulatory receptors on PDCs from SLE patients and control subjects, including immunoglobulin like transcript 7 (ILT7), bone marrow derived antigen 2 (BDCA2), ILT3, leukocyte-associated immunoglobulin-receptor 1 (LAIR1), natural killer cell P44-related protein (NKP44), bone marrow stromal cell antigen 2 (BST2), and dendritic cell (DC) immunoreceptor (DCIR). For functional studies, cells from 9 SLE patients and 9 controls were treated with ILT7 and BDCA2 crosslinking antibodies followed by TLR9 agonists. ILT7 and BDCA2 expression on SLE patient PDCs were inversely correlated with disease activity by SLEDAI score. High IFN SLE patients had increased levels of the ILT7 ligand BST2, and at the same time reduced ILT7 expression. BDCA2 levels were 5-fold higher than ILT7 levels, and crosslinking ILT7 only weakly inhibited IFN secretion. Crosslinking BDCA2 significantly reduced IFN production in SLE patient cells, but this effect on IFN was much greater in patients with low SLEDAI scores than those with high SLEDAI scores. In conclusion, we identify associations between PDC regulatory receptor expression and clinical disease in SLE, and dominant inhibitory function of BDCA2 over ILT7 in PDC type I IFN secretion with dependency upon disease activity.

1101 URINE COMPLEMENT ACTIVATION PRODUCTS IN LUPUS NEPHRITIS

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Background Complement activation plays a critical role in the development of kidney injury during lupus nephritis (LN). Clinical trials targeting the complement pathway are now underway in LN. It is therefore important to understand the

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Parameter	Spearman r			P Value			95% Confidence Interval		
	Ba	C5a	C5b-9	Ba	C5a	C5b-9	Ba	C5a	C5b-9
Activity Index	0.31	0.25	0.37	0.0004	0.005	<0.0001	0.14,0.47	0.07,0.41	0.20,0.52
●Endocapillary Hypercell	0.25	0.23	0.36	0.005	<0.01	<0.0001	0.07,0.41	0.05,0.39	0.19,0.51
●Hyaline Deposits	0.19	0.23	0.23	0.036	0.018	0.0094	0.008,0.36	0.031,0.38	0.05,0.39
●PMN/Karyorrhexis	0.18	0.18	0.32	0.044	0.044	0.0003	0.0005,0.35	0.0004,0.35	0.15,0.47
●Necrosis	0.19		0.21	0.027	0.42	0.017	0.018,0.37		0.034,0.38
●Crescents	0.21		0.21	0.019	0.06	0.004	0.03,0.38		0.08,0.42
●Interstitial Inflammation	0.35	0.26	0.27	<0.0001	0.003	0.002	0.18,0.50	0.08,0.42	0.097,0.43
Chronicity Index	0.29	0.19		0.0005	0.022	0.22	0.13,0.44	0.02,0.35	
●Glomerulosclerosis				0.23	0.36	0.73			
●Fibrous Crescents				0.94	0.37	0.83			
●Tubular Atrophy	0.31	0.24		0.0002	0.031	0.17	0.15,0.45	0.079,0.39	
●Interstitial Fibrosis	0.31	0.24		0.0002	0.031	0.16	0.15,0.45	0.079,0.39	
Proteinuria	0.41	0.54	0.42	<0.0001	<0.0001	<0.0001	0.25,0.54	0.42,0.66	0.27,0.55
Serum Creatinine	0.51	0.31		<0.0001	0.0001	0.61	0.38,0.63	0.15,0.46	
Complement C3	-0.31			0.0002	0.06	0.16	-0.46,-0.15		
Complement C4				0.09	0.18	0.25			
Urine Ba		0.71	0.46		<0.0001	<0.0001		0.62,0.78	0.31,0.58
Urine C5a			0.68			<0.0001			0.59,0.76

relationship between intra-renal complement activation and kidney histology in LN, and whether complement activation products (CAPs) can serve as biomarkers to guide complement-directed therapies. In this investigation, urine CAPs levels were measured, and associations with kidney injury were determined.

Methods A cohort of 149 patients had urine and blood collected at the time of kidney biopsy for suspected LN. The CAPs C5a, C5b-9, and factor Ba were measured in the urine by ELISA. Biopsies were examined by routine histology, and the NIH activity and chronicity indexes (AI, CI) were calculated by two nephropathologists. CAPs levels were correlated with clinical and histologic data using the spearman correlation r .

Results The results are summarized in the table 1. The highest levels of CAPs were found in patients with proliferative or proliferative plus membranous LN, with lower levels in pure class II and V. All three urine CAPs correlated with AI, but the strongest correlation was between C5b-9 and AI. Only Ba and C5a correlated with CI, but this correlation was, at best, modest. All CAPs correlated with proteinuria, while only Ba and C5a correlated with serum creatinine.

Conclusion Urine C5b-9 was the best measure of histologic activity in LN. Given the size of the C5b-9 complex, it is unlikely to be filtered, even by glomeruli with a damaged glomerular permeability barrier. Urine C5b-9 therefore only reflects intra-renal complement activity. C5a and Ba associated modestly with active lesions, as well as kidney damage, likely accounting for their association with serum creatinine. We suggest levels of urine C5b-9 could be used to follow the success of anti-complement therapies in mitigating intra-renal complement activation in LN.

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THE TRAJECTORY OF GLOMERULAR AND TUBULOINTERSTITIAL LESIONS AFTER TREATMENT OF LUPUS NEPHRITIS

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Background Proliferative lupus nephritis (LN) is characterized histologically by glomerular and tubulointerstitial (TI) inflammation that presumably must resolve with treatment to achieve remission. Here we sought to document the trajectory of lesion resolution using serial kidney biopsies during LN treatment.

Methods A cohort of proliferative LN patients was prospectively followed during treatment with standard LN therapy. Patients had a diagnostic kidney biopsy (Bx1), a biopsy generally within the first year of treatment (Bx2), and a biopsy after at least 3 years of total immunosuppression (Bx3). The NIH activity and chronicity indices (AI, CI) were calculated at each biopsy.

Results The cohort (n=110) was followed for a median (range) of 109 (34, 202) months. Patients were treated with either MMF or cyclophosphamide initially. Overall, the patients did very well. Only 2 patients developed ESKD by last follow-up and only 9 patients had CKD (eGFR <60 ml/min/1.73m²), but this was pre-existing in 4 patients. AI followed an exponential decline after starting treatment. At the time of Bx2 (an average 9.7 months after Bx1), the percent

of biopsies positive for cellular crescents (CC), fibrinoid necrosis (FN), and neutrophil infiltration (NEU) fell precipitously, while the decline of endocapillary hypercellularity (EH) and hyaline deposits (HD) was more gradual. At Bx3 (an average of 42.6 months after Bx1) fewer than 5% of biopsies had residual CC, FN, NEU, or interstitial inflammation, but 25% still had EH and HD. By immunofluorescence microscopy over 90% of Bx1 biopsies had IgG and complement components C3 and C1q. At Bx3 only 30-40% of biopsies continued to show IF for complement, but IgG was still present in 66% of biopsies. The CI increased after Bx1. The rate of increase of all CI components was greatest from Bx1 to Bx2, slowed between Bx2 and Bx3, and actually declined for fibrous crescents.

Conclusion These data show that the most inflammatory lesions found in proliferative LN are rapidly responsive to immunosuppression, but EH and HD are more resistant. Complement deposition resolves quickly, but IgG is present in glomeruli for a long time. Despite rapid improvement in active inflammation, kidneys sustain chronic damage early in the disease course.

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LUPUS CLINICAL FLARES IN PATIENTS WITH GUT PATHOBIONT BLOOMS SHARE A NOVEL PERIPHERAL BLOOD TRANSCRIPTOMIC IMMUNE ACTIVATION PROFILE

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Background SLE is an inflammatory condition associated with hyperactivation of the immune system, with mounting evidence that imbalances in the gut microbiota communities are common. These imbalances can range from subtle patterns of dysbiosis to blooms in abundance of individual species that are concordant with clinical disease flares. Based on preliminary longitudinal surveys, almost half of Lupus nephritis (LN) flares were concurrent with transient expansions of a pathobiont, *Ruminococcus (blautia) gnavus*. As the transcriptomic patterns in the cells in our bloodstream can reflect disease activity, we sought to investigate gene expression patterns in groups of lupus patients, with comparisons to healthy controls (HC).

Methods From a well-characterized cohort, exploratory studies were performed on a selected group of 15 active female SLE patients, based in part on SLEDAI scores ≥ 4 . Patients were grouped as without a history of renal involvement (i.e., non-renal) (N=7) or with LN in flare with Urine Protein creatinine ratio >0.5. Based on 16S rRNA fecal microbiota analyses, LN were subsetted as without bloom of individual species (N=4), or with a bloom (> 20-fold increased from HC, 3-9% abundance) of *R. gnavus* (N=4). In comparisons with 8 female HC, bulk RNA-seq was completed and after standard QC and filtering, 24,319 genes passed a minimum threshold of 4 reads in >50% samples and were used in downstream analysis.

Results Unsupervised clustering based on gene expression demonstrated significant separation between SLE samples and HC (figure 1). While there was no clear distinction between non-renal and renal (i.e., LN) groups, there were striking differences in the group of active LN without detectable gut