activation of B cells and induce autoantibody production. Natural infections with curli-expressing *S.* Typhimurium triggered autoantibodies production in NZBxW/F1 mice and control mice, suggesting curli/DNA complexes break tolerance in SLE. Finally, sera from lupus patients during flares showed elevated levels of anti-curli antibodies.

Conclusions Biofilm-derived curli/DNA complexes are potent activators of innate and adaptive immune cells and can mediate the acceleration of lupus by infections. These studies may provide a novel biomarker of flare and suggest targeting biofilms and bacterial infections as new therapeutic tools in lupus.

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AI-28 HLA-DR3RESTRICTED RESPONSES TO SMD, A LUPUS-RELATED ANTIGEN PROVIDE INSIGHTS TO THE ORIGIN OF LUPUS-RELATED AUTOANTIBODIES AND THE UNIQUE FEATURES OF THE TARGETED ANTIGENS

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Background The presence of complex autoantibodies (auto-Abs) is a hallmark of SLE. The most cited hypotheses for their origin are the "B cell epitope mimicry hypothesis between SmB and EBV" and the "particle hypothesis". Neither is adequate to explain the characteristics of SLE–related Abs. Our studies showed that HLA-DR3 and DR2 transgenic mice in contrast to DR4 respond well to SmD and Ro60 with DR3 mice being the best responders. In addition, certain bacterial mimics of SmD and Ro60 T cell epitopes were shown to induce auto-Abs to SnRNP and Ro60/La.

Materials and methods T cell epitope mapping was done by the generation and characterisation of T-T hybridomas to SmD and Ro60 and their 15 mers. Antibody specificities to SLE-related antigens (Ags) and their peptides were done by ELISA.

Results At least seven SmD core T cell epitopes were identified. They have no sequence homology. 18 of reactive T-T hybridomas used multiple TCRα and TCRβ. Bioinformatics analysis identified more than 10000 potential bacterial mimic peptides with many from commensal bacteria. The binding affinities of the SmD T epitopes were in the medium range among all the relevant mimics. Selected mimic peptides showed that only those with medium binding affinities stimulated related T-T hybridomas to the SmD peptides and only they were able to stimulate Ab responses in patterns similar to that induced by the related SmD peptide. A significant number of T-T hybridomas were reactive with multiple T cell epitopes within the SmD molecules. Some of these hybridomas also were reactive with SmD, SmB and/or A-protein within the snRNP particles and Ro60. In addition, the bacterial T cell mimic peptides often shared B cell epitopes with the related SmD peptide. Also healthy $DR3^+$ blood donors had significantly higher Ab titers against SmD. Similar results were obtained in the Ro60/La system.

Conclusions Autoreactive TCRs are part of the normal repertoire that are positively selected for host defense against microbial agents. The presence of multiple intra- and inter-molecular T and B cell epitopes are characteristic of SLE-related auto-Ags. These characteristics provide a scenario for the inevitability of the presence of auto-Ab and autoreactive-T cells in healthy individuals with susceptible HLA-D regions and provide a mechanism for B cell epitope spreading in SLE. SLE-related Abs are the results of our reaction to exposure to commensal and/or pathogenic microbes. Innate immunity plays an amplifying role. These observations provide the rationale to target microbiome and both adaptive and innate immunities in the treatment of SLE.

AI-29 METABOLOME CHECKPOINTS OF MTOR ACTIVATION AND CLINICAL RESPONSIVENESS IN SLE

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Background The mechanistic target of rapamycin (mTOR) serves as a metabolic sensor of genetic and environmental cues that effectively regulates physiological T-cell activation and lineage specification. mTOR complex 1 (mTORC1) promotes pro-inflammatory T-cell development, B-cell activation and production of antinuclear autoantibodies (ANA) both in patients and mice with systemic lupus erythematosus (SLE). Therefore, we initiated a prospective clinical trials with rapamycin and N-acetylcysteine (NAC), the latter of which blocks redox-dependent mTORC1 activation.

Materials and methods 36 SLE patients were enrolled in a 3-month placebo-controlled trial with NAC which involved 212 metabolic and immunological markers prior to enrollment, and follow-up at 1-month intervals. 42 healthy controls, matched at each visit for age, ethnicity, and gender, were studied in parallel. 258 metabolites were measured mass spectroscopy. 40 SLE patients were enrolled in a 12-month open-label intervention with rapamycin; patients and 88 matched controls were studied in parallel at 3-month intervals. Analysis of pathways, area under the curve (AUC) logistic regression, two-factor (NAC versus placebo) time series within individual subjects were performed with Metaboanalyst. SLEDAI, BILAG, and SRI disease activity indices were calculated.

Results Rapamycin reduced disease activity in 126 ± 18 days as evidenced by well-tolerated rapamycin plasma levels of 8.7 ± 1.2 ng/ml, which was within the targeted therapeutic range of 6–15 ng/ml. SLEDAI disease activity scores were reduced to 5.7 ± 1.0 from 11.8 ± 1.1 at baseline ($p = 0.0028$). Among the patients who completed the 1 year intervention, a SLE Responder Index of 64.3% was achieved. Rapamycin inhibited the pro-inflammatory T cell skewing (Figure 1), including the expansion and IL-4 production of $CD4^-CD8^-$ double-negative (DN) T cells and reversed the contraction of $CD4^+CD25^+FoxP3^+$ regulatory T cells (Tregs) and $CD4^+$ and $CD8^+$ central and effector memory T cells. Treatment with NAC exerted lesser but statistically significant reduction of SLEDAI and BILAG over 3-month. Metabolome changes involved 27 of 80 KEGG pathways at FDR $p < 0.05$ with most prominent impact on the pentose phosphate pathway (PPP). While cysteine was depleted, a PPP-regulated compound, kynurenine, was the most increased metabolite and the top predictor of SLE (AUC = 0.859). Kynurenine directly stimulated mTORC1 activity of DN T cells *in vitro*. Relative to placebo, NAC reversed these metabolite changes *in vivo*.

Conclusions The PPP-connected accumulation of kynurenine and its stimulation of mTORC1 are identified as metabolic