members of the Fcγ receptor (FcγR) family. FcγRIIA is the most abundantly expressed FcγR in human blood circulation. However, mice do not express FcγRIIA, and murine platelets are completely devoid of FcγRs.

Methods To model IC-mediated response more accurately, as they occur in humans, transgenic FcγRIIA (FcγRIIA^{TGN}) mice expressing FcγRIIA on platelets and certain leukocytes, were used in this study. As acute model, we intravenously injected ICs in FcγRIIA^{null} and FcγRIIA^{TGN} mice and monitored mouse reaction and platelet activation. To model platelet response to chronic exposure to ICs, we backcrossed NZB mice with FcγRIIA^{TGN} mice, generating NZB::FcγRIIA^{TGN} mice and crossed the mice with NZW mice, thus generating NZB::NZW::FcγRIIA^{TGN} and NZB::NZW::FcγRIIA^{null} mice. Platelet activation was monitored through time in these mice.

Results Platelet activation by acute exposure to ICs through a mechanism requiring expression of platelet FcγRIIA resulted in the induction of systemic shock. IC-driven shock was dependent on release of serotonin from platelet dense granules secondary to platelet outside-in signaling by αIIbβ3 and its ligand fibrinogen. On FcγRIIA activation, platelets underwent sequestration, but surprisingly they returned in the blood circulation with emptied granules after activation. Strikingly, reminiscent observations were made in lupus NZB::NZW::FcγRIIA^{TGN} mice. We found significant platelet activation and circulating degranulated platelets, uniquely in mice expressing FcγRIIA.

Conclusions Platelet activation in IC-mediated pathogenesis is well recognized. In lupus patients, platelets are found activated in blood circulation, however, to what extend ICs and FcγRIIA contribute to platelet activation was unknown. Here, we showed that the expression of FcγRIIA is critical to adequately examine platelet role in lupus.

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AI-06 LUPUS NEPHRITIS IS LINKED TO DYSBIOSIS, INCREASED GUT LEAKINESS AND IMMUNITY TO AN INTESTINAL COMMENSAL LACHNOSPIRACAEA SPECIES

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Background A transmissible agent has long been suspected in the pathogenesis of SLE, yet the potential contribution of the human intestinal microbiome has been little examined. We therefore characterized the gut microbiota of patients with SLE, with special interest in those with lupus nephritis (LN).

Methods Blood and fecal samples from SLE patients were obtained, with strict inclusion/exclusion of criteria. Fecal 16S rDNA sequencing, as well as cytokine and autoantibody assays were performed. In addition, sera from two independent lupus cohorts were studied for validation. Biomarkers of gut leakiness were assessed.

Results Compared to controls, the intestinal microbiome from SLE patients (n=61) showed decreased species richness diversity with reductions in taxonomic complexity most

pronounced in those with high disease activity. Notably, SLE patients had an overall 5-fold greater representation of a species in the Lachnospiraceae family of obligate anaerobic Gram-positive cocci, with reciprocal contractions of two other commensal species with putative protective properties. Abundance of the Lachnospiraceae species correlated with serum IgG to a cell wall component, postulated to represent a lipoglycan, from a strain of this same species (p=0.002, n=61, Spearman) but not with 7 other strains. There was also a significant direct correlation between SLEDAI scores and levels of these circulating anti-strain IgG antibodies (p=0.02, n=48). Levels of antibodies to strain-specific bacterial antigen, treated with RNase/DNase/proteinase K, were significantly higher in those with active nephritis at time of sampling compared to SLE without renal activity (Cohort 1 p=0.01 n=48; Cohort 2 p=0.006, n=28, Mann-Whitney). Levels of serum IgG anti-strain antibodies also significantly correlated with high-titer serum IgG to native DNA (p<0.0001, n=27), and inversely correlated with C3 and C4 levels. High titers of these anti-bacterial antibodies were associated with active Class III, IV and V (overlap) LN (Cohort 3).

Conclusions These findings suggest a novel paradigm for the pathogenesis of LN in which a common intestinal commensal bacteria may contribute to the immune-complex mediated disease process, with features akin to poststreptococcal GN but without outward signs and symptoms of clinical infection.

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AI-07 A NEW B CELL EFFECTOR PATHWAY WITH DEFECTIVE NEGATIVE REGULATION OF TLR7 SIGNALING IN HUMAN SLE

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Background B cell homeostasis is perturbed in SLE patients. In particular, many patients have a large expansion of IgD-CD27- B cells (DN). The DN population is heterogeneous for CXCR5 expression, and CXCR5- DN2 are the majority population in SLE patients but not in HCD (figure 1A). To further understand how these expanded cells differ from other B cell subsets and how they may be dysregulated in SLE, we phenotypically and functionally characterized DN2 in SLE patients and healthy control donors (HCD).

Methods B cells subsets were quantified by flow cytometry in HCD and two separate cohorts of lupus patients. Purified DN2 and other B cell subsets were flow sorted and transcriptionally analyzed using RNA sequencing. Toll-like-receptor 7 (TLR7) signaling after stimulation with R848 was measured by staining with anti-phospho-tyrosine specific anti-ERK. Antibody secreting cell differentiation was induced using *in vitro* stimulation of sorted B cell subsets with a combination of TLR7 and cytokines.

Results DN2 were only a minor B cell subset in HCD (less than 5%) but were elevated in 20% of cohort 1 patients and 60% of cohort 2 (figure 1B). In the patients with the largest