Thursday 06 October 2022 from 08:00 to 10:00

S01 disease mechanisms

S01.1 EXTRAMEDULLARY HEMATOPOIESIS AND IMMUNE TRAINING CONTRIBUTE TO TISSUE INFLAMMATION IN SLE BY PROVIDING INFLAMMATORY LICENSE TO BONE MARROW-DERIVED HEMATOPOIETIC STEM AND PROGENITOR CELLS (HSPCS)

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Purpose We have previously shown dysregulation of hematopoiesis in the bone marrow (BM) in SLE, with skewing towards the myeloid lineage and evidence for extramedullary hematopoiesis (EMH). EMH results in the generation of effector cells in the periphery to meet the increased demands and has been linked to peripheral tissue injury by proving an inflammatory license to BM-derived cells. We sought to further explore their contribution to disease pathology.

Materials and Methods Meta-analysis of peripheral blood (PB-) and BM-derived CD34+ cells transcriptomic data and of BM-derived HSPCs from pre-diseased (F1-P) and lupus (F1-L) NZBW/F1 mice was conducted.[1,2] Immune profiling performed in BM, spleen and kidneys of NZBW/F1 mice and their age-matched controls (B6-Y and B6-O respectively). BM- and spleen-derived HSPCs were seeded for CFU-assay. For the trained immunity experiments, F1-P mice were injected ip with β-glucan/PBS every 15 days, until the emergence of nephritis.

Results In SLE patients, BM- and PB CD34+ transcriptome exhibited signature profiles consistent with activation and migration, with PB CD34+ appearing positively enriched in 'Migration'' and 'BM exit' pathways. Human results were mirrored in the murine transcriptomic data. CXCR4, a key factor for HSPC retention to the BM, was decreased in HSPCs and myeloid progenitors (MPs) from lupus mice. In the spleen of F1-L mice both HSPCs and GMPs (granulocyte-monocyte progenitors) were expanded and the latter was confirmed by CFU assay. HSPC and MP frequencies presented increase in the kidneys of F1-P. Administration of the innate immunity primer β-glucan exaggerated the histology of glomerulonephritis with increased activity indices of LN. GMP frequency increased in the BM with concomitant increase of LT-HSC frequency and splenic EMH.

Conclusions In SLE, HSPCs activation and exit from the BM is orchestrated by CXCR4 leading to engraftment and formation of differentiation clusters into the spleen and the kidneys. Consistent with the granulopoiesis profile observed in the BM, peripheral HSPC sustain their myeloid skewing. Reprogramming of innate effector cells exaggerate LN and augment EMH providing 'trained' immune cells that sustain and amplify the inflammatory response.

REFERENCES

1. Grigoriou M, Banos A, Filia A, *et al*. Transcriptome reprogramming and myeloid skewing in haematopoietic stem and progenitor cells in systemic lupus erythematosus. *Ann Rheum Dis* 2020;**79**:242–253.
2. Kokkinopoulos I, Banos A, Grigoriou M, *et al*. Patrolling human SLE haematopoietic progenitors demonstrate enhanced extramedullary colonisation; implications for peripheral tissue injury. *Sci Rep* 2021;**11**:15759.

S01.2 BANK1 SIGNALING SHAPES THE GUT MICROBIOTA COMPOSITION BY CONTROLLING THE GUT MUCOSAL B CELL RESPONSE IN LUPUS

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Purpose The purpose of this work was to determine the role of the Bank1 gene in the gut B cell response and its influence in gut microbiota composition during lupus inflammation. The BANK1 gene is a susceptibility gene for SLE and in lupus-prone B6.Sle1.yaa mice the absence of Bank1 resulted in diminished disease severity concomitant with reduced total IgG, anti-dsDNA IgG antibody production and type I interferon signaling. Furthermore, BANK1 was demonstrated to be implicated in the TLR signaling in B cells as BANK1 binds MyD88 and TRAF6 through its TIR domain and TRAF6-binding motifs, respectively. We thus hypothesized that the gut B cell response in steady state and in lupus inflammation may be altered in Bank1 deficient mice. Consequently, the altered microbiome composition may impact lupus pathogenesis.

Methods In this work we used two TLR7-mediated models of lupus: the spontaneous TLR7Tg lupus prone-mice and the induced-model with TLR7 agonist (imiquimod), both in C57Bl/6 Bank1-sufficient and Bank1-deficient mice. Mice were either raised in separate cages by genotype (single cage) or both genotypes together in the same cage (littermates). The B cell populations in the gut were characterized by flow cytometry, and immunoglobulin determination in serum and fecal matter were quantified by ELISA. Microbiome composition was determined by sequencing the V4 region of 16sRNA. Gut permeability was measured with FITC-Dextran.

Results In the TLR7tg lupus-prone mice, the absence of Bank1 diminishes disease severity with a concomitant reduction in serum pathogenic IgG antibodies. Bank1 KO mice have reduced frequency of CD19+B220+ and IgA+B220- B cell populations in the gut. Fecal free IgA was also reduced, and these differences in B cell populations were not observed after the development of lupus, however lupus inflammation increased gut permeability in the TLR7.Tg mice, but reduced in TLR7Tg.Bank1 KO mice. Additionally, single cage Bank1 KO mice had altered the baseline composition of their gut microbiome compared with control mice. These changes were more pronounced after lupus development. Particularly, we found significantly increased abundance of Parabacteroides distasonis in the fecal microbiome of Bank1 KO mice. Moreover, in littermate animals, which had homogeneous microbiome composition, the disease severity was equal in both, Bank1 KO and WT mice and was lower compared to WT single cage animals. Also, the abundance of Parabacteroides distasonis was similar in both Bank1 KO and WT mice.

Conclusions Our results link a susceptibility gene for lupus with the abnormalities in the microbiome composition of the gut and the production of IgA. Interestingly, we identified Parabacteroides distasonis as a prevalent species associated with