Short Oral Presentation

Short oral presentation session 1: SLE etiology & pathogenesis 1

LSO-001 MODULATING T-BET-PROMOTED ENERGY METABOLISM IN PATHOGENIC AGE/AUTOIMMUNE-ASSOCIATED B CELLS AMELIORATES LUPUS AUTOIMMUNITY

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Background Emerging evidences indicate that a distinct CD11c +T-bet+ B cell subset termed age/autoimmune-associated B cells (ABCs) is the major pathogenic autoantibody producer in lupus. Human lupus is associated with significant metabolic alterations, but how ABCs orchestrate their typical transcription factors (TFs) and metabolic programs to meet specific functional requirements is unclear. Our goal is to characterize the metabolism of ABCs and identify the regulators of metabolic pathways for developing new therapies for ABC-mediated autoimmunity.

Methods We developed a T-bet-tdTomato reporter mouse strain to trace live T-bet+ B cells and adoptively transferred CD4+ T cells from Bm12 mice to induce lupus. Then CD11c +tdTomato+ B cells were sorted and conducted RNA sequencing and extracellular flux assay. Metabolic restriction to constrain ABC formation was tested on human and mouse B cells. The metabolic intervention was conducted in the Bm12-induced lupus model.

Results ABCs exhibited a hypermetabolic state with enhanced glycolytic capacity. The increased glycolytic rate in ABCs was promoted by IFN-Y signaling. T-bet, a downstream TF of IFN-Y, regulated the gene program of the glycolysis pathway in ABCs by repressing the expression of Bcl6. Functionally, glycolysis restriction could impair ABC formation. The engagement of glycolysis promoted survival and terminal differentiation of antibody-secreting cells. Administration of glycolysis inhibitor ameliorated ABCs accumulation and autoantibody production in Bm12-induced lupus model.

Conclusions T-bet can couple immune signals and metabolic programming to establish pathogenic ABC formation and functional capacities. Modulating ABC favored metabolic program could be a novel therapeutic approach for lupus.

LSO-002 THE TRANSCRIPTIONAL FACTOR PBX1 ADJUSTS PERIPHERAL B CELL HOMEOSTASIS TO CONSTRAIN LUPUS AUTOIMMUNITY

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Background Disruption of B-cell homeostasis and subsequent dominance of effector B-cell subsets are critical for the development of systemic lupus erythematosus (SLE). Revealing the key intrinsic regulators involved in the homeostatic control of B cells has important therapeutic value for SLE. This study aims to uncover the regulatory role of the transcription factor Pbx1 in B-cell homeostasis and to provide new targets for SLE treatment.

Methods We constructed mice with B-cell-specific deletion of Pbx1. T-cell-dependent and independent humoral responses were induced by intraperitoneal injection of NP-KLH or NP-Ficoll. The regulatory effects of Pbx1 on autoimmunity were observed in a Bm12-induced lupus model. Mechanisms were investigated by combined analysis of RNA-sequencing, Cut&-Tag, and Chip-qPCR assay. B-cells from SLE patients were transduced with Pbx1 overexpression plasmids to explore the in vitro therapeutic efficacy.

Results Pbx1 was specifically downregulated in autoimmune B-cells and negatively correlated with disease activity. The deficiency of Pbx1 in B-cells resulted in excessive humoral responses following immunization. In a Bm12-induced lupus model, mice with B-cell-specific Pbx1 deficiency displayed enhancements in germinal center responses, plasma cell differentiation, and autoantibody production. Pbx1-deficient B-cells gained a survival advantage upon activation. Pbx1 regulated genetic programs by directly targeting critical components of the proliferation and apoptosis pathways. In SLE patients, PBX1 expression was negatively correlated with effector B-cell expansion and enforced PBX1 expression attenuated the survival capacity of SLE B-cells.

Conclusions Our study reveals the regulatory function and mechanism of Pbx1 in adjusting B-cell homeostasis and highlights Pbx1 as a therapeutic target in SLE.

LSO-003 EFFECTS OF PROGESTERONE-INDUCED BLOCKING FACTOR 1 ON THE ALLEVIATION OF LUPUS NEPHRITIS IN MRL/LPR MICE

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Background Progesterone-induced blocking factor 1 (PIBF1), a protein produced by maternal lymphocytes upon exposure to progesterone during pregnancy, acts as an immunomodulator by suppressing several immune pathway cytokines including Th1-based cytokines. Considering the female susceptibility to systemic lupus erythematosus, we aimed to determine the role of recombinant PIBF1 in the alleviation of lupus nephritis (LN) in MRL/MpJ-Faslpr/J (MRL/lpr) mice.

Methods MRL/lpr mice were ovariectomized at 6 weeks of age, and recombinant PIBF1 was administered intraperitoneally from 8 to 26 weeks of age (twice a week). Serum anti-dsDNA level was examined every 2 weeks from 8 to 24 weeks of age. The levels of serum cytokines at 16 and 24 weeks of age and urine albumin/creatinine (uACR) at 26 weeks of age were measured. At 26 weeks, the mice were sacrificed, and kidney biopsy was performed. Pathologic grading of disease activity and chronicity was performed by an animal pathologist according to the criteria of the NIH activity and chronicity indices. Additionally, splenocytes were analyzed by flow cytometry.

Results Serum anti-dsDNA level was increased in MRL/lpr mice that underwent ovariectomy; however, recombinant