PO.1.3 IL-18 DEFICIENCY DOES NOT AFFECT DEVELOPMENT OF RENAL TERTIARY LYMPHOID STRUCTURES IN IMIQUIMOD INDUCED SLE

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Purpose Tertiary lymphoid structures (TLS) are organized aggregation of immune cells at sites of inflammation. The development of TLS in autoimmune settings indicate that they may be sites for both activation and regulation of immune responses, and a local site for autoantibody production.

The aim of this study was to investigate if imiquimod, an TLR7 agonist, induce TLS in kidneys, of normal mice and if IL-18 expression plays a role in the induction of TLS.

Methods The ears of 5 to 10 weeks old (wo) C57BL/6J (C57BL) and B6.129P2-Il18tm1Aki/J (IL-18 KO) mice were topically treated with 1.25 mg of 5% IMQ three times a week. Blood samples were analyzed every week using IDEXX ProCyte Dx for hematological analyses and ELISA for anti-dsDNA and anti-RNA antibodies. Immune cells isolated from kidney, spleen and LN at 10 and 14 wo were analyzed by flow cytometry. Total mRNA were isolated from kidney, spleen and LN and gene expression of TNF, IL1β, INFα, IFNγ, IL-18, and CXCL13 were analyzed by qPCR. Kidney sections from 10 and 14 wo treated and control mice were analyzed by immunohistochemistry (IHC) and immunofluorescence (IF).

Results Both anti-dsRNA and anti-dsDNA antibody (ab) production increased in treated mice at week 7. The anti-dsRNA ab production was significantly higher than the anti-dsDNA ab production at weeks 8–14. IMQ treated IL18-KO mice produced more anti-DNA antibodies at 10 wo compared to C57Bl mice. The number of reticulocytes and mean platelets volume (MPV) increased while platelets were reduced in IMQ treated C57Bl mice. TLS were observed in both 10 and 14 wo C57Bl and IL-18 KO mice treated with IMQ. Flow cytometric analyses of kidney infiltrating immune cells showed an increase in both CD4+ and CD8+ T cells in 14 wo IMQ treated C57BL mice. This increase was not observed in IL-18 KO mice. Gene expression of TNF and CXCL13 increased in IMQ treated C57Bl mice, but there were little differences in the expression of IL1β, INFα, and IFNγ. Individual differences were observed in IL-18 KO mice

Conclusion IMQ induce anti-RNA and anti-dsDNA ab production in normal and IL-18 KO mice. IL-18 deficiency does not affect the development of renal TLS.

PO.1.4 THE EIF4 TRANSLATIONAL INHIBITOR PATEAMINE A IMPROVES IMMUNOLOGICAL AND NEUROLOGICAL FUNCTIONS IN BXSB.YAA LUPUS MICE

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Purpose In this work we analyzed the therapeutic potential of a natural compound, Patemine A (PatA) to treat SLE. Pat A is an inhibitor of the eIF4 complex, involved in the translation initiation process, with immunosuppressive properties that has been tested successfully in cancer mouse models.

Methods To evaluate Pat A efficiency in SLE we used the BXSB.Yaa lupus model. In this strain the presence of Yaa in males results in autoimmune disease manifestations, renal failure, and a mortality rate of 60% by 20 weeks of age. BXSB.Yaa males were treated with PatA administered intraperitoneally 3 times per week for 8 weeks starting at the initial stage of disease (12 weeks). Sera was collected every three weeks to follow disease progression and at final point (20 weeks) we performed serological analysis (cytokines and autoantibodies), flow cytometry on spleen, kidney histological and functional assays and behavioral tests to evaluate neurological signs of the disease.

Results Pat A treatment increased survival rates and reduced circulating levels of proinflammatory cytokines and autoantibodies in the BXSB.Yaa lupus model. Kidney function was also improved in the animal that received Pat A with no major changes at the histological level. Treated mice also showed an improvement on cognitive function (learning/memory, and depression) together with a reduction of proinflammatory cytokines locally in the hippocampus.

Conclusions These data suggest that translation inhibition improves disease signs at the immunological and neurological level opening a new line of research based on translation inhibition to treat lupus and other autoimmune diseases.

PO.1.5 SCORING PERSONALIZED MOLECULAR PORTRAITS IDENTIFY SYSTEMIC LUPUS ERYTHEMATOSUS SUBTYPESAND PREDICT TRANSCRIPTIONAL DRUG RESPONSES, SYMPTOMATOLOGY AND DISEASE PROGRESSION

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Purpose Systemic Lupus Erythematosus is a complex autoimmune disease that leads to important worsening of quality of life and mortality. Flares appear unpredictably during the disease course and therapies used are often only partially effective. These challenges are mainly due to the molecular heterogeneity of the disease, such that personalized medicine offers major promise. With this work we intended to advance in that direction by developing My PROSLE, an omics-based workflow for measuring the molecular portrait of individual patients to support clinicians in their therapeutic decisions.

Methods Immunological gene-modules were used to represent the transcriptome of the patients. A dysregulation score for each gene-module was calculated at the patient level based on averaged z-scores. Almost 4300 lupus and 750 healthy samples were used to analyze the association between dysregulation scores, clinical manifestations, prognosis, flare and remission events and transcriptional drug response to Tabalumab. Machine learning-based classification models were built to predict around 90 different clinical parameters based on personalized dysregulation scores.