Adaptive Immunity

AI-01 KV1.3 EXPRESSION ON SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) URINARY LEUKOCYTES

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Background Effector memory T lymphocytes (T_{EM}) implicated in the immunopathogenesis of SLE have been detected in the urine of patients with lupus nephritis. As T_{EM} depend on the voltage-gated potassium channel Kv1.3 for activation-induced calcium signalling, activated T_{EM} represents a potential target for the novel Kv1.3 blockade therapy dalazatide. In active SLE nephritis, Kv1.3 is upregulated on peripheral blood CD8 + T_{EM} and cytokine production was inhibited in SLE T lymphocytes. We therefore hypothesized that Kv1.3 is expressed on urinary leukocytes from patients with lupus nephritis.

Methods Urinary cells were isolated in 33 samples from patients with SLE ages 15–41 years, (mean 19, IQR 16.2–19.3). Immunofluorescence was performed to quantify and characterize cells expressing Kv1.3. Urinary leukocytes were defined as non-epithelioid cells by morphology. Leukocyte subsets were defined as CD3+ T lymphocytes, CD20+ B lymphocytes, or CD14+ macrophage.

Results In the urine, leukocytes expressing Kv1.3 were found in samples from every subject studied. Overall, Kv1.3 expression was detected on a mean of 3.5% of leukocytes (range 0.1%–13.4%; IQR 0.8%–5.1%) with higher levels in patients with active disease (4.8%, IQR 1%–6.7%) compared to patients with inactive disease (2.1%, IQR 0.8%–2.7%, *p*=0.04). CD3+ lymphocytes expressing Kv1.3 were found in all subjects (mean 52% of CD3+ cells, IQR 33%–100%). In 90% of subjects, Kv1.3 was detected on CD20+ B lymphocytes (mean 68%, IQR 46%–100%), and in 90% of subjects CD14+ macrophages (mean 69%, IQR 46%–100%). Patients with class III or IV nephritis had increased frequencies of leukocytes expressing Kv1.3 (6%) compared to patients with Class V nephritis (2%, *p*=0.01) or no nephritis (1.8%, *p*=0.01).

Conclusions Kv1.3 is detectable on SLE urinary B lymphocytes, T lymphocytes, and macrophage, implying that inflammatory cells in the kidney may be targeted by this channel. Peripheral blood cell expression and functional data suggest that SLE activated T_{EM} lymphocytes may be susceptible to inhibition by dalazatide.

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AI-02 DISSECTING IMMUNE PHENOTYPES IN SLE

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Background There are many possible explanations for the high percentage of failed clinical trials in systemic lupus erythematosus (SLE). Our preferred explanation relates to the heterogeneity of immune phenotypes in SLE patients. We have, therefore, put

considerable effort into dissecting immune phenotypes among patients.

Methods First, we hypothesize that in each SLE patient, either myeloid cells or B cells drive the disease. This hypothesis is supported by the transcriptional profiles of SLE patients and both serologic analyses and transcriptional profiles of unaffected sisters of SLE patients. This paradigm, if confirmed, will influence the appropriate therapy for maintenance of remission. Second, we believe we can identify patients in whom IgG autoantibodies are made by plasma cells maturing through an extrafollicular pathway and patients in whom IgG autoantibodies are made by germinal center derived plasma cells.

Results Patients might be stratified by plasma cell differentiation pathway so that therapies could be designed to target only one subset of plasma cells and therefore might be less immunosuppressive.

Conclusions These approaches to patient stratification need further exploration in clinical trials for distinct therapeutic interventions.

AI-03 EFFICACY AND SAFETY OF INTERMITTENT 2-DEOXYGLUCOSE THERAPY IN MOUSE MODELS OF LUPUS

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Background Glucose is a primary substrate for cellular respiration. Glucose utilization increases in highly metabolic cells including activated, proliferating T cells and B cells as well as cancers. Lupus is a disorder in which autoreactive CD4 +T cell and B cells deviate from normal homeostasis by their uncontrolled proliferation and differentiation. Therapeutic limitation of glycolysis is therefore an attractive approach for attenuating such highly energetic, pathogenic processes inherent to lupus. Here we investigate the potential of the classic glycolysis inhibitor, 2-deoxyglucose (2DG), to prevent and reverse severe forms of autoimmune lupus-like disease in mice. As untoward side effects of 2DG therapy have also been reported, we further evaluate potential complications and biomarkers of 2DG therapy.

Methods For autoimmune disease studies, the following mouse models for spontaneous lupus-like autoimmune disease were utilized: NZB × NZW F1 (BWF1) females (adult onset) and BXSB.Yaa Cd8^{-/-} Il15^{-/-} males (acute adolescent onset). 2DG was provided *ad libitum* in acidified drinking water (2DG 2–6 g/L) for intervals of 8 wks. Mice were monitored longitudinally for weight loss, proteinuria, and survival. To assess potential effects of 2DG in non-diseased mice, C57BL6/J mice treated with 2DG and controls were analyzed for a series of metabolic, serum chemistry, cardiac, behavioral, immunological and histopathological phenotypes after short and long term exposure.

Results An 8 wk 2DG treatment of young BXSB.Yaa Cd8^{-/-} Il15^{-/-} mice prevented their development of prototypic cellular abnormalities and greatly extended lifespans. Given the strong normalizing effects of 2DG in disease prevention, we performed therapeutic interventions in which 2DG was intermittently supplied to 37 wk old BWF1 mice (figure 1A). This treatment abrogated proteinuria even in heavily diseased mice