

attributed to the investigational product. Given the blind of the study, we cannot report on efficacy, though there are a number of participants who met the primary outcome of an SRI of 4 at 24 weeks. COVID had a profound impact on the study due to halting of enrollment for 5 months and a need for video visits due to institutional policies. A significant issue was protocol changes regarding disease activity measures in video visits. Other delays included a designed 12-week safety assessment upon completion of Cohort 1 prior to enrollment in Cohort 2 as well as a staggered start for the first six patients in Cohort 2 requiring a safety assessment by the DSMB chair at week 1 post infusion prior to the screening of the next patient.

Conclusions There is no safety signal between the active treatment and placebo group in either Cohort to this date. Efficacy assessments await completion of the study as the two cohorts are combined for determination of efficacy. COVID has a profound impact on enrollment and management of the study. Results of the validity of assessment of different disease measures via video appointments is being assessed to inform future trials. We believe we will reach our enrollment goal and the study will answer the primary aim of whether MSCs are a potential therapeutic for patients with refractory lupus.

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DIFFERENTIAL RELIANCE ON GLUCOSE OXIDATION BY ACTIVATED AUTOREACTIVE B CELLS PROVIDES A NOVEL TARGET OF THERAPEUTIC INTERVENTION

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Background Lupus is an autoimmune disease characterized by antibodies directed against nuclear components that induce immune complex-mediated injury to multiple organs. Underlying lupus is the induction of T-cell-dependent activation and clonal expansion of autoreactive B cells in germinal centers resulting in their differentiation into plasma cells that secrete pathogenic autoantibodies. Heightened glucose metabolism is inherent to immune/inflammatory disorders, but little is known of its role in lupus pathogenesis. Present treatments for lupus rely heavily on broad-spectrum immunosuppressive agents, and there is a need for targeted therapies that effectively counteract this systemic autoimmune disorder.

Methods Here we examined the metabolic and gene expression profiles of key autoimmune populations in spontaneous murine models of lupus and their responses to treatment with the glycolysis inhibitor 2-deoxyglucose (2DG) in drinking water. Therapeutic efficacy in terms of primary autoimmune-cell population sensitivity and survival after 2DG administration was assessed on BXS.B.Yaa and NZBWF1 lupus-prone mice. Furthermore, a chimeric antigen receptor (CAR)-T cell approach was used to determine whether a targeted removal of an identified B cell subset can improve disease outcomes.

Results We found greater glucose uptake and glycolysis rates in spontaneous activated autoreactive B cells (AABC) closely resembling germinal center B (GCB) cells compared to those in follicular helper T (Tfh) cells. The differential dependency

on glucose oxidation between GCB and Tfh cells was determined, rendering GCB cells highly susceptible to oxidative stress-induced apoptosis triggered by short-term glycolysis inhibition via 2DG. The treatment selectively targeted AABC/GCB cells with high glycolytic dependence, sparing other autoreactive populations, including Tfh cells with greater metabolic flexibility. This reduction of AABC/GCB cells is, in turn, linked with significantly reducing proteinuria and improving lifespan of treated mice. Moreover, we identified a subset of AABC/GCB cells, which express TNFSF17 and exhibit a higher reliance on glucose metabolism than TNFSF17⁻ B cells. Their depletion through its ligand TNFSF13-based CAR-T treatment significantly decreased mortality in lupus-prone mice.

Conclusions Differential metabolic requirement for glucose between autoreactive AABC/GCB cells and Tfh cells dictates different sensitivity to apoptosis via glycolytic inhibition, and our data provide a metabolic niche for novel targeted lupus treatment. Combining therapies that selectively dampen AABC/GCB-cell metabolism with T cell-based immunotherapy could provide new effective treatments for lupus.

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Lay summary The primary metabolic adaptation of activating T and B cells is an increase in glucose metabolism. We found that autoreactive B cells have elevated consumption of glucose over other T or B cell types. Using murine models of lupus, we uncovered that treatment of lupus-prone mice with 2-deoxy-glucose, an inhibitor of glucose utilization, resulted in the preferential reduction of these pathogenic B cells. This reduction resulted in improving kidney function, and extending lifespan. We also used a T cell-based immunotherapy approach targeting a subset of these B cells and successfully reduce the mortality of lupus-prone mice. Overall, these results indicate the promise of two new and highly effective treatments for lupus via targeted removal of autoreactive B cells.

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LACTOBACILLUS SPP. ACT IN SYNERGY TO ATTENUATE SPLENOMEGALY AND LYMPHADENOPATHY IN LUPUS-PRONE MRL/LPR MICE

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Commensal bacteria and the immune system have a close and strong relationship that maintains a balance to control inflammation. Alterations of the microbiota, known as dysbiosis, can direct reactivity to self-antigens not only in the intestinal mucosa but also at the systemic level. Our laboratory previously reported gut dysbiosis, particularly lower abundance of bacteria in the family *Lactobacillaceae*, in lupus-prone MRL/lpr mice, a model of systemic autoimmunity. Restoring the microbiota with a mix of 5 different *Lactobacillus* species

(spp.), *L. reuteri*, *L. oris*, *L. johnsonii*, *L. gasseri* and *L. rhamnosus*, attenuated lupus-like clinical signs, including splenomegaly and lymphadenopathy. However, our understanding of the mechanism was limited. In this study, we used the lupus-prone MRL/lpr mouse model to delineate the mechanisms through which *Lactobacillus* spp. modulate lupus pathogenesis. We first investigated the effects of individual species. Surprisingly, none of the species individually recapitulated the benefits of the mix. Instead, *Lactobacillus* spp. acted synergistically to attenuate splenomegaly and renal lymphadenopathy through secreted factors and a CX₃CR1-dependent mechanism. Interestingly, oral administration of MRS broth exerted the same benefits likely through increasing the relative abundance of endogenous *Lactobacillus* spp. Mechanistically, we found increased percentages of FOXP3-negative type 1 regulatory T cells with administration of the mix in both spleen and mesenteric lymph nodes. In addition, oral gavage of *Lactobacillus* spp. decreased the percentage of central memory T cells while increasing that of effector memory T cells in the lymphoid organs. Furthermore, a decreased percentage of double negative T cells was observed in the spleen with the mix. These results suggest that *Lactobacillus* spp. might act on T cells to attenuate splenomegaly and lymphadenopathy. Together, this study advances our understanding of how *Lactobacillus* spp. attenuate lupus in MRL/lpr mice. The synergistic action of these bacteria suggests that multiple probiotic bacteria in combination may dampen systemic autoimmunity and benefit lupus patients.

Microbiome

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THE THERAPEUTIC EFFECT OF GLYCOLYSIS INHIBITION IN LUPUS-PRONE MICE IS TRANSFERABLE THROUGH THE FECAL MICROBIOME

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Gut microbial dysbiosis has been reported in patients with lupus. Results obtained with mouse models suggest that dysbiosis contributes to lupus pathogenesis through the pathogens that induce inflammation by translocating out of the gut and/or producing proinflammatory metabolites. We and others have shown that fecal microbiota transfers (FMT) from lupus-prone mice induced autoantibodies and immune activation in non-autoimmune mice. On the other hand, we have shown that the production of autoantibodies and associated expansion of follicular T (T_{fh}) cells and germinal center (GC) B cells can be eliminated by treating lupus-prone mice with 2-deoxy-D-glucose (2DG), a glycolysis inhibitor. Here, we investigated the effect of 2DG on the fecal microbiome in two models of lupus with different etiologies, the (NZB × NZW) F1 and (NZW × BXSB)F1 mice.

Anti-dsDNA IgG-positive (NZB × NZW)F1 and (NZW × BXSB)F1 mice were treated with 2DG. The composition of their fecal microbiome was determined by 16S rDNA sequencing and their metabolome by LC-MS analysis, and compared to age-matched controls. Fecal samples from these mice were used for FMT 3 times per week in pre-autoimmune lupus-prone mice of the same strain that were pre-treated with antibiotics for 2 weeks. FMT lasted for 26 weeks in (NZB × NZW)F1 mice and 9 weeks in (NZW × BXSB)F1 mice. Age-matched controls were gavaged with PBS. Autoantibodies were measured by ELISA and indirect immunofluorescence. Immunophenotypes were assessed by flow cytometry in the spleen and mesenteric lymph nodes. Renal pathology was evaluated by light microscopy on PAS-stained sections and immunofluorescence on frozen sections with antibodies to complement C3, IgG2a, F4/80 and CD3.

We showed that a 2DG treatment started in reduced the changes in bacterial populations that occurred as disease developed in control mice in both models. 2DG also altered the distribution of fecal metabolites in these treated mice. Next, we investigated the effect of serial FMT from 2DG-treated or control mice into pre-autoimmune lupus-prone mice of the same strain that were pre-treated with antibiotics. In both models, FMT from 2DG-treated mice was protective, with a reduction of anti-dsDNA IgG production, immune cell activation, and renal pathology as compared to FMT from control mice.

Overall, our results demonstrated for the first time that the therapeutic effect of glucose inhibition in lupus is transferable through the gut microbiota. These results suggest that the enhanced glucose metabolism in lupus-prone mice promotes the expansion of pathogenic gut bacteria either directly or indirectly through the immune system that normalized by glucose inhibition.

Lay summary High glucose metabolism sustains the activation of the immune system in lupus. Inhibition of glucose metabolism with a drug called 2DG reverses the production of pathogenic autoantibodies in mice. Here we showed that 2DG also changes the gut microbiome in lupus-prone mice. Further, transfers of fecal bacteria from 2DG-treated lupus mice protected younger mice to develop lupus. The results showed that the gut microbiome contributes significantly to the pathogenic effects of glucose metabolism in lupus, and suggest that the beneficial effect of reducing glucose metabolism includes the restoration of a healthy gut microbiome.

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BACTERIAL DNA INDUCES REGULATORY B CELLS AND ATTENUATES LUPUS THROUGH A B CELL-EXTRINSIC, TLR9-DEPENDENT MECHANISM

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