glucose cotransporter 2 inhibitors (SGLT2i) have proven efficacious in preventing adverse renal outcomes in patients with a variety of chronic diseases. The mechanisms of protection by SGLT2i include their capacity to modulate hypoxia and fibrosis. Other literature supports a role for local hypoxia in the lupus nephritis (LN) kidney in driving pathogenic immune cell function, including in CD8 T cells. Here, we hypothesized that by alleviating hypoxia, SGLT2i will modulate local inflammation and fibrosis in lupus nephritis.

Methods 10 weeks old MRL/lpr female mice were daily treated with dapagliflozin at 10 mg/kg or vehicle by gavage for 11 weeks. Sera was collected to measure autoantibodies and creatinine by ELISA. Immune cells and SGLT2 expression were quantitated in the spleen, renal lymph nodes (RLNs) and kidneys by flow cytometry and immunofluorescence. Inflammation, fibrosis, and infiltration by CD8 T cells or regulatory T cells were assessed in kidneys of MRL/lpr mice at baseline and 8 weeks after starting SGLT2i therapy.

Results Consistent with a slow induction of SGLT2i therapeutic effect in humans and despite the efficient targeting of SGLT2 in MRL/lpr mice, proteinuria was not affected after 11 weeks of daily SGLT2i administration. Unexpectedly SGLT2i therapy had a remarkable impact on the formation of germinal centers (GCs) and the production of autoreactive plasma cells in the spleen. In line with the induction of regulatory T cells by SGLT2i in diabetic kidney disease, T follicular helper cells with a regulatory phenotype significantly increased in the GCs. In addition, skin and lymph node inflammation were attenuated by SGLT2i. However, inflammatory cell infiltration in the kidney was not affected by SGLT2i (figure 1).

Conclusions Despite modest effects on kidney inflammation, SGLT2i surprisingly modulated splenic autoreactive GCs via significant accumulation of T follicular regulatory T cells, impairing the production of autoreactive plasma cells. One of the potential explanations for the modest kidney effects is the rapid disease progression in MRL/lpr mice and the slow therapeutic induction with SGLT2i. Thus, future studies are planned in NZB/NZW mice treated for longer periods of time and with combination immune suppressive therapy.

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1202 UNVEILING METABOLIC VULNERABILITIES IN LUPUS B CELLS: TARGETING BCMA AND GLUCOSE DEPENDENCY FOR THERAPEUTIC STRATEGIES

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Background Lupus is a complex autoimmune disease characterized by loss of self-tolerance, leading to dysregulated functions of T and B cells. Broadly increased glucose metabolism has been reported in many immune/inflammatory disorders, but little is known of its role in specific cell types during lupus pathogenesis. B-cell maturation antigen (BCMA) has been shown to be greatly upregulated in B cells in human SLE patients but has been primarily regarded in the context of a biomarker, with no therapeutic consideration. Current lupus treatments utilize broad-spectrum immunosuppressive agents, and targeted therapies are needed to effectively counteract this systemic autoimmune disorder. Investigating the metabolic profiles of lupus B cell subsets can offer insights into disease mechanisms and potential treatments.

Objective We aimed to investigate the metabolic characteristics of germinal center B (GCB) cells in murine models of lupus, with a primary focus on elucidating their reliance on specific metabolic pathways. Moreover, we aimed to compare the metabolic differences between lupus $BCMA^+$ and $BCMA^-$ GCB cells and those generated in response to foreign antigen immunization. Additionally, we sought to assess the therapeutic efficacy of chimeric antigen receptor (CAR)-T cells, which specifically target $BCMA^+$ B cells, in improving disease outcomes in lupus-prone mice.

Methods The metabolic profiles of GCB cells were investigated in spontaneous murine models of lupus using Seahorse extracellular flux analysis, focusing on glycolysis and oxidative phosphorylation rates and mitochondrial fuel dependency. We also analyzed the glycolytic reliance in lupus $BCMA^+$ and $BCMA^-$ GCB cells and those generated in response to foreign antigen immunization. To assess the efficacy of 2DG treatment in targeting GCB cells in vivo, flow cytometric analyses of cell viability and apoptosis were conducted in BXSB.Yaa lupus-prone mice. Furthermore, chimeric antigen receptor (CAR)-T cells expressing a proliferation inducing ligand (APRIL), a powerful ligand to BCMA, were designed to test the potential improvement of disease outcomes through the targeted removal of BCMA-expressing GCB cells.

Results We found that GCB cells obtained from lupus-prone mice exhibited elevated levels of BCMA compared to those from immunized mice. Additionally, BCMA-expressing GCB cells also showed greater glucose uptake and glycolysis rate over $BCMA^-$ GCB cells. Notably, a differential dependency on glucose oxidation for survival between $BCMA^+$ and $BCMA^-$ GCB cells was determined, rendering $BCMA^+$ GCB cells highly susceptible to oxidative stress-induced apoptosis triggered by glycolysis inhibition via 2DG. Importantly, GCB cells from immunized mice showed no significant reliance on glycolysis, regardless of BCMA expression. Finally, the mortality of mice to lupus disease was significantly decreased upon the depletion of $BCMA^+$ GCB cells through APRIL-based CAR-T therapy.

Conclusions This study unveils differential metabolic requirements and vulnerabilities in GCB cells compared to immunization-induced GCB cells, with $BCMA^+$ GCB cells from lupus mice showing heightened glucose oxidation dependency and susceptibility to glycolysis inhibition-induced apoptosis. Immunized GCB cells exhibit distinct metabolic characteristics and limited reliance on glycolysis, independent of BCMA expression. These findings shed light on the complex B cell metabolism in lupus, offering new insights for understanding lupus pathogenesis and developing innovative and targeted treatments, including transient 2DG exposure or APRIL-based CAR-T cell-based immunotherapy that effectively reduce lupus severity and prolong lifespan.

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Lay summary We conducted a study to understand how the metabolism of certain immune cells, called B cells, is related to lupus. We focused on a protein called BCMA, which is found in higher levels on B cells from lupus patients. We discovered that $BCMA^+$ B cells in lupus-prone mice have a higher dependence on glucose for survival, compared to

BCMA$^-$ B cells. Interestingly, we found that B cells generated through immunization showed different metabolic characteristics and did not heavily rely on glucose metabolism, regardless of BCMA expression. Furthermore, targeting BCMA$^+$ B cells using a specialized immune therapy reduced the risk of death in mice with lupus. These findings provide new insights into lupus disease and suggest potential avenues for developing treatments.

Clinical – Pediatric rheumatology

1301 FACTORS DRIVING DISPARITIES IN GLUCOCORTICOID EXPOSURE AMONG CHILDREN WITH SLE IN THE CARRA REGISTRY

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Background Differential glucocorticoid exposure and related toxicity may exacerbate racial and ethnic disparities in lupus-related organ damage and mortality. Pediatric-onset systemic lupus erythematosus (pSLE) confers an even greater lifelong burden of cumulative medication exposure than adult-onset disease. Access to care and other social determinants of health may drive differential medication use. Therefore, we sought to determine how race and social determinants of health associate with cumulative glucocorticoid exposure over time in children with SLE. We hypothesized that minoritized race and living in more disadvantaged neighborhoods would be associated with greater average oral glucocorticoid exposure among children with pSLE in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry.

Methods This was a retrospective cohort study of children with pSLE enrolled in the CARRA Registry between March 2017-December 2021 with a baseline enrollment visit and $\geq$1 follow up Registry visits as well as a valid U.S. zip code. The primary exposures were self-identified race and/or ethnicity and national area deprivation index (ADI) linked to census tract. Time-averaged mean prednisone dose (mg/day) was used as the primary measure of cumulative glucocorticoid exposure, calculated using oral prednisone- equivalent milligram doses at each Registry visit. As secondary outcomes, we also evaluated occurrence of any prednisone restarts or dose increases between Registry visits during the study period and disease

Abstract 1301 Table 1 Demographic and clinical characteristics of children with pSLE in the CARRA Registry (March 2017 – December 2021)

	Total N=540	Asian N=58	Black N=146	Latino/a N=124	Other N=30	White N=135	More than one race N=47
Age at enrollment (years), median (IQR)	15 (12, 16)	15 (12,16)	15 (13, 17)	15 (13,16)	15 (12, 16)	15 (13, 16)	14 (11,16)
Female sex, N (%)	467 (87)	41 (81)	127 (87)	107 (86)	25(83)	119 (88)	42(89)
Insurance, N (%)							
Private	257 (48)	40 (69)	50 (35)	32 (26)	18 (60)	90 (67)	27 (58)
Public	248 (46)	16 (27)	92 (63)	77 (62)	12(40)	35 (26)	16 (34)
Other/Non-U.S.	19 (3)	1 (2)	2 (1)	6 (5)	0 (0)	8 (6)	2 (4)
None	16 (3)	1 (2)	2 (1)	9 (7)	0 (0)	2 (1)	2 (4)
Area Deprivation Index† (ADI), N (%)							
0–25%ile	169 (31)	37 (64)	18 (12)	38 (31)	14 (47)	45 (33)	17 (36)
26–50%ile	144 (27)	17 (29)	29 (20)	38 (30)	6 (20)	39 (29)	15 (32)
51–75%ile	114 (21)	3 (5)	39 (27)	28 (23)	7 (23)	30 (22)	7 (15)
76–100%ile	113 (21)	1 (2)	60 (41)	20 (16)	3 (10)	21 (16)	8 (17)
Major Organ Involvement, N (%)							
CNS	78 (14)	6 (10)	26 (18)	13 (11)	9 (30)	11 (8)	13 (28)
Renal	277 (51)	24 (41)	83 (57)	61 (49)	16 (53)	68 (50)	25 (53)
CV/Pulm	152 (28)	12 (21)	56 (38)	35 (28)	5 (17)	32 (24)	12 (27)
Baseline Medication, N (%)							
Belimumab	43 (8)	3 (5)	20 (14)	5 (4)	2 (7)	9 (7)	4 (9)
Conventional DMARD*	462 (86)	53 (91)	125 (86)	102 (82)	28 (93)	115 (85)	39 (83)
Rituximab or Cyclophosphamide	163 (30)	13 (22)	59 (40)	34 (27)	10 (33)	27 (20)	20 (43)
Anti-malarial	523 (97)	54 (93)	144 (99)	120 (97)	30 (100)	129 (96)	46 (98)
Any secondary rheumatologic disease, N (%)	63 (12)	6 (10)	22 (15)	9 (7)	4 (13)	16 (12)	6 (13)
Time from diagnosis to enrollment (years), median (IQR)	0.4 (0.1, 1.2)	0.8 (0.1, 2.0)	0.4 (0.1, 1.4)	0.3 (0.1, 0.8)	0.3 (0.1, 1.0)	0.4 (0.1, 1.2)	0.3 (0.1, 1.2)
Duration of Registry follow-up time (years), median (IQR)	2.1 (1.3, 2.8)	2.4 (1.8, 2.9)	1.9 (1.0, 2.7)	2.1 (1.3, 2.7)	2.1 (1.5, 2.7)	2.2 (1.3, 2.9)	2.0 (1.1, 3.0)
Time adjusted mean prednisone dose (mg), median (IQR)	6.6 (1.7, 12.6)	4.1 (0, 7.4)	8.3 (3.5, 19.0)	6.5 (1.9, 12.5)	5.9 (2.6, 9.9)	6.4 (0.2, 11.4)	6.5 (1.4, 13.5)
Any prednisone restart or dose increase during study period, N (%)	199 (37)	19 (33)	66 (45)	42 (34)	13 (43)	43 (32)	16 (34)

†Area Deprivation Index (ADI) is a national measure of neighborhood social disadvantage at the level of census block group incorporating U.S. Census data (including American Community Survey results) that incorporates multiple social domains. Higher scores suggest more disadvantaged areas.
*Conventional DMARDs include azathioprine, leflunomide, methotrexate, mycophenolate mofetil, mycophenolic acid, sirolimus, sulfasalazine, and tacrolimus.