Conclusions  Our study demonstrates that B cell-intrinsic IFN-γ receptor signals promote lupus pathogenesis via formation of spontaneous, autoimmune GCs. In addition, we have uncovered a novel cell-intrinsic program whereby IFN-γ, together with BCR-, TLR- and/or CD40 signals, orchestrates B cell expression of the GC master transcription regulator BCL-6. Our combined findings suggest that this IFN-γ signalling program may be a potential therapeutic target in SLE.

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Abstract AI19  METABOLIC INHIBITION BY 2-DEOXYGLUCOSE PREVENTS AND REVERSES LUPUS IN MICE

Background  Glucose is a primary substrate for cellular respiration. Glucose utilisation 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 that deviate from normal homeostasis by their uncontrolled proliferation and differentiation to effector cells. Therapeutic limitation of glycolysis is therefore an attractive approach for attenuating the highly energetic, pathogenic processes inherent to lupus. Here we investigate the potential of several metabolic inhibitors that target early and downstream aspects of cellular respiration to identify inhibitors that show potential in the prevention and treatment of lupus.

Materials and methods  Metabolic inhibitors included: 1) a classic glycolysis inhibitor, 2 deoxyglucose (2 DG); 2) a mitochondrial complex I inhibitor/AMPK activator metformin (MET); 3) an mTOR inhibitor, rapamycin (RAPA); and 3) a pyruvate dehydrogenase kinase inhibitor, dichloroacetate (DCA). The drugs were provided in drinking water or mouse chow for 4-8 wks. NZB X NZW F1 (BWF1) and BXSB.Yaa mouse models of lupus were evaluated in prevention studies and in treatment of mice documented to be undergoing autoimmune disease. Longitudinal and terminal immunophenotyping was performed using flow cytometric, serological, histopathological analyses.

Results  2 DG, MET, DCA and RAPA, and combinations thereof were applied prior to the onset of autoimmune disease to BWF1 and BXSB. Yaa mice. MET and DCA showed minimal effects and RAPA resulted in partial attenuation. In contrast, 2 DG acted potently to abrogate multiple disease biomarkers while not causing immunodeficiency. Given the strong immunologically normalising effects of 2 DG in disease prevention, we performed therapeutic interventions in which 2 DG was supplied for 8 weeks to already diseased BWF1 and BXSB. Yaa mice. Within 4 weeks of treatment, 2 DG normalised all cellular, serological and pathological features characteristic of the BWF1 and BXSB. Yaa lupus like syndromes. Furthermore, the lifespans of BXSB. Yaa mice were extended after withdrawal of treatment (Figure 1).

Conclusions  Overall, the results highlight the potent and remarkable normalising effect of 2 DG in the prevention and treatment lupus-like autoimmune disease in mouse models with differing genetic and mechanistic etiologies. Given findings, we propose that that therapeutic inhibition of early steps in glycolysis, as exemplified by 2 DG, has broad potential for the treatment of multiple autoimmune disorders. Our current efforts are focused on: 1) the potential of 2 DG in treatment of other autoimmune severe diseases; and 2) evaluation of potential downsides of metabolic inhibition by 2 DG and other inhibitors of glycolysis.

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