A DIET HIGH IN FIBRE DIET CAN MODERATE INFLAMMATION AND KIDNEY PATHOLOGY IN A MODEL OF SYSTEMIC LUPUS ERYTHEMATOSUS

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Background and Aims Systemic Lupus Erythematosus (SLE) is a complex, multifactorial autoimmune disease mediated by the deposition of immune complexes in tissues such as the kidney, skin, and brain, with the ensuing inflammatory cascade driving progressive tissue damage and dysfunction. Mice lacking Lyn tyrosine kinase (Lyn−/− mice) develop an autoimmune disease similar to SLE, driven by dysregulation of the immune system, immune complex deposition in tissue and systemic inflammation culminating in progressive glomerulonephritis. The gut microbiome has been shown to have an immunoregulatory effect on the development of autoimmune and inflammatory diseases, in large part due to the production of short chain fatty acids from the fermentation of dietary fibre.

Methods To determine whether dietary fibre could moderate systemic autoimmune and inflammatory pathology, Lyn−/− mice and control C57BL/6J mice were fed a high fibre diet (HFD) or a standard control diet from weaning until 42 weeks old.

Results On the control diet, Lyn−/− mice developed dysbiosis, lymphopenia, splenomegaly from enhanced splenic myelopoiesis, hyperactivation of immune cells, and pathogenic IgG anti-dsDNA autoantibodies that deposited in the kidney glomeruli leading to glomerulonephritis. These hallmarks of inflammation and autoimmune disease were significantly reduced in Lyn−/− mice fed a HFD, indicating that dietary intervention is effective at dampening chronic systemic inflammation and glomerular pathology.

Conclusions These findings highlight the contribution of diet and the gut microbiome in regulating systemic immune responses and controlling autoimmunity, inflammation, and preventing the progression of immunopathology and suggests that fibre supplementation may improve outcomes for those living with SLE or other chronic systemic inflammatory diseases.

IDENTIFICATION OF DISEASE-ASSOCIATED GUT MICROBIOTA IN LUPUS-PRONE BAFF-TG MICE

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Background and Aims Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease with environmental and genetic contributing factors. The gut microbiota (GM) interacts with the immune system to maintain homeostasis. However, microbiome dysbiosis has been shown to lead to the development of autoimmune diseases. We aimed to investigate the role of GM in SLE-prone BAFF-Tg mice and study the possible benefit of GM-targeted treatments.

Methods We used 16S metagenomics to compare the GM composition, before or after disease onset, and before or after treatment of established disease with several different fibre-enriched diets or antibiotics. Gut bacteria composition was identified by sequencing V3-V4 regions on an Illumina MiSeq platform in a 96-plex library configuration, and bioinformatics analysis was performed using QIME software. Matching data on mouse disease levels was obtained by flow cytometry, autoantibody ELISA, and kidney histology.

Results BAFF-Tg mice exhibited distinct GM compositions compared to WT, both before and after disease onset, with certain families of bacteria expanded or replaced prior to disease progression. GM-targeted therapy by high-fibre dietary modulation or antibiotics reduced anti-dsDNA autoantibodies to undetectable levels.

Conclusions GM dysbiosis, of some particular bacterial species we identified, can be linked to the level of disease development in this lupus-prone mouse model. Therapeutic strategies targeting GM, including easily implementable dietary modulations and antibiotics, could be investigated further as novel avenues for treating and managing SLE.