00388 Alterations in Gut Microbiome and Liver DNA Methylation in Mice Despite Reversal of Fatty Liver Disease

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Aims: Non - alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease and is associated with the incidence of metabolic disease. To understand the long - term effect of epigenetic modification and gut microbiome function on NAFLD treatment, we used a mouse model of high fat diet (HFD).

Methodology: 8 weeks of C57BL/6 male mice were fed with normal chow diet (NC) or HFD for 9 weeks, and followed by NC diet feeding for another 9 weeks. Glucose tolerance test, insulin tolerance test and MRI quantification performed at 9 weeks and 18 weeks of feeding. Liver tissue was used for genome-wide DNA methylation sequencing, and the gut microbiome composition changes were interrogated using metagenomics shotgun sequencing.

Result: We found that HFD induced lipid droplet accumulation in the liver with glucose intolerance, indicating the development of NAFLD. Surprisingly, a return to the normal diet for 9 weeks only partially rescued the fatty liver phenotype, with persistently increased triglyceride (TG) levels in serum of HFD. Altered microbiome composition by HFD was reversed by reversal diet, however, increased Odoribacter in HFD was persistently remained even after reversal diet. Genome-wide DNA methylation analysis further revealed an analogous fatty liver priming effect of DNA methylation in key liver genes, including persistent hypomethylation of Apoa4—a gene intimately linked to lipid metabolism.

Conclusion: We showed that there are persistent changes in microbiome composition and DNA methylation despite reversal of NAFLD by dietary intervention. These results strongly suggest a novel perspective on a clinical level, that previous dietary habits leave molecular imprints that may predispose patients to NAFLD upon subsequent exposure to HFD diet.