Gut microbiota dysbiosis and nonalcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is an emerging public health problem with an increasing incidence and prevalence globally, which is characterized histopathologically by predominantly macrovesicular steatosis with varying amounts of inflammation, cytological ballooning and liver fibrosis, and it is associated with significant morbidity and mortality. However, few diagnostic and therapeutic strategies for NAFLD are established well. Cumulative data demonstrates that gut microbiota dysbiosis is closely associated with NAFLD, although the underlying mechanisms remain largely uninvestigated. Structural disruption of gut microbiota and associated inflammation are considered important etiological factors, that can result in immunologic dissonance and disturbance of metabolites produced by gut microbiota, both of which appear to play critical roles in the onset and development of

NAFLD via the gut-liver axis.

Recently, increasing evidences suggest that ‘gut microbiota-targeted’ intervention strategies may be effective for the treatment of NAFLD. Hence we investigated that whether total fecal microbiota transplantation (FMT), single butyrate producing probiotic *Clostridium butyricum* B1 (CB) and gut metabolite sodium butyrate (NaB, one kind of short chain fatty acids, SCFAs) would be effective to attenuate high-fat diet (HFD) induced steatohepatitis in mice, and further explored the associated mechanisms. Finally, we found that no matter directly gut microbiota intervention (FMT or CB) or indirectly gut metabolites treatment, steatohepatitis induced by 16-week HFD in mice were significantly alleviated. Furthermore, the unbalanced gut microbiota induced by HFD was significantly improved after the three interventions of 8 weeks. The concentrations of butyrate in the gut were significantly increased after either FMT or CB intervention. And the unbalanced immunity caused by HFD was reversed after either FMT or CB intervention, which exhibited that the ratios of Th1/Th2, Th17/Th22, Th1/Treg were significantly decreased, and the liver microenvironment was also significantly improved compared with the model group. To further study the mechanisms, we observed that *in vitro* NaB could regulate T cells differentiation which attributed to its HDAC inhibition. And compared with the model group, gut GLP-1 secretion was significantly increased and serum GLP-1 was also obviously elevated in the three intervention groups, the most noteworthy was that NaB could increase the expression of GLP-1 receptor in the liver which seem to increase the GLP-1 sensibility of liver and further attenuate fat accumulation and liver inflammation.

Over all, our study confirmed the close association between NAFLD and gut microbiota in mice. We found that not only gut microbiota itself but also gut metabolites are also very pivotal to the genesis and development of NAFLD. Further work is urgently needed.