Non-alcoholic fatty liver disease is rapidly becoming the leading cause of chronic liver disease, affecting 25% of the world's population. The development of non-alcoholic fatty liver disease ranges from simple steatosis to the advanced form, non-alcoholic steatohepatitis. Non-alcoholic steatohepatitis is characterized by hepatocyte injury and ballooning, inflammation, and hepatic fibrosis. The progression of nonalcoholic steatohepatitis can lead to subsequent cirrhotic liver disease and hepatocellular carcinoma. In this article, researchers from the United States and China investigated whether the Western-type diet contributes to the pathogenesis of nonalcoholic steatohepatitis in a clinically relevant mouse model.

The gut and liver have close anatomical and functional communication through their connection *via* the portal vein. This gut-liver axis enables the transport of dietary and microbial components from the gut into the liver. The liver secretes factors like primary bile acids that affect gut homeostasis. Gut microbiota plays an important role in non-alcoholic fatty liver disease. It affects hepatic carbohydrate and lipid metabolism, and the balance between pro-inflammatory and anti-inflammatory effectors. The interaction between diet and gut microbiota results in a wide range of bioactive metabolites that affect the pathogenesis of nonalcoholic steatohepatitis.

Increasing evidence suggests that the interaction between the Western-type diet, which is rich in fructose, sucrose, and saturated fats, and gut microbiota, results in the production of metabolites that contribute to the development and further progression of non-alcoholic fatty liver disease. However, the specific bacteria and metabolites that promote non-alcoholic fatty liver disease, as well as the underlying mechanisms, are not understood.

About the Study and Results

The authors successfully developed a clinically relevant mouse model of non-alcoholic steatohepatitis by feeding wild-type mice with a choline-low, high-fat, and high-sugar diet, representing a typical Western-type diet, named CL-HFS. CL-HFS more closely recapitulates the typical Western-type diet than a choline-deficient HFD diet (CD-HFD). Because the prevalence of non-alcoholic fatty liver disease is higher in males than in females of all ages, the authors selected male mice.

The CL-HFS diet successfully induced nonalcoholic steatohepatitis in male mice with features of human disease, such as hepatic inflammation, steatosis, and fibrosis. Staining revealed a significant increase in the infiltration of inflammatory cells, accumulation of lipid droplets, and hepatocyte ballooning. This increased the non-alcoholic fatty liver disease Activity Score. Sirius red staining detected a significant increase in collagen production, forming pericellular and bridging hepatic fibrosis. The polymerase chain reaction test detected increased mRNA expression of extracellular matrix genes and inflammatory cytokine genes. These changes were consistent with human non-alcoholic steatohepatitis.

Previous studies reported an increase of Blautia producta, a genus of the Lachnospiraceae family, in human patients with non-alcoholic fatty liver disease and its decrease in rodents after treatment of non-alcoholic fatty liver disease. *In vitro* and *in vivo* studies have shown that Blautia producta can produce and accumulate 2-oleoylglycerol in the liver, a microbial metabolite that activates hepatic stellate cells to produce extracellular matrix proteins in a macrophage-dependent manner.

In the present study, the authors identified Blautia producta and its metabolite, 2-oleoylglycerol, as clinically relevant bacterial and metabolic mediators that promote the onset and development of non-alcoholic fatty liver disease. The reduction of Blautia producta was associated with suppressed pathogenesis of nonalcoholic steatohepatitis. In contrast, repopulation with Blautia producta significantly promoted hepatic inflammation and fibrosis and further progression of nonalcoholic steatohepatitis in CL-HFS-fed mice.

Conclusion

This study showed that the Western-type diet contributes to the pathogenesis of nonalcoholic steatohepatitis in a clinically relevant mouse model. The authors stated that these cellular and molecular findings significantly advance understanding of the gut-liver-immune axis in the pathogenesis of nonalcoholic steatohepatitis. This study should also advance the development of therapeutic strategies based on dietary and microbiota.

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