The Human Gut Microbiota and Liver Disease

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Abstract

The human gut microbiome is thought to have a major role in contributing to health and disease. In particular, evidence has arisen regarding the pathophysiology of certain liver diseases and the microbial flora of the intestines. Chronic alcohol ingestion may perturb the gut flora and cause increased gut permeability leading to the translocation of inflammatory bacterial components to the liver through the portal system. This inflammatory effect is in addition to the direct effects of ethanol on the liver. Additionally, altered gut flora are known to be associated with obesity, which is the major risk factor for non-alcoholic fatty liver disease (NAFLD). These changes are thought to increase the amount of energy extracted from the diet, contributing to obesity. The altered microbiota is also thought to produce alcohol endogenously and induce liver damage in NAFLD as well. There are specific changes in the gut flora associated with cirrhosis including the upregulation of bacterial enzymatic pathways for the metabolism of ammonia and GABA. In a 2014 study published in *Nature*, Qin et al. were able to distinguish cirrhotic patients from controls using a set of only 15 bacterial genes as a biomarker. Further research into the connection between the gut microbiota and liver disease may lead to new diagnostic and targeted therapeutics means.

Introduction

Our understanding of the human microbiota – the collection of microorganisms in and on the human body – is evolving at a rapid pace.[1] There is particular interest in the gut flora, a complex mixture of microbes residing in the GI tract that are predominantly obligate anaerobes concentrated in the colon.[2] Recently, evidence has emerged concerning the link between the gut flora and liver disease. There is a close, bi-directional connection between the liver and the intestines. The portal vein carries the absorbed contents of the small and large intestines to the liver, which includes the products of digestion, bacterial by-products, as well as immunological and inflammatory mediators. The liver produces bile which is released into the duodenum and can affect the metabolism, abundance and distribution of the gut microbiota.[3] The close relationship between the liver and gut suggests that intestinal microbes may play a role in liver disease and there is growing indication that the gut microbiota contributes to the pathogenesis of alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD) and cirrhosis.

Gut Microbiota and Alcoholic Liver Disease

It has been shown that the gut-liver axis is an important factor in the development of alcoholic liver disease. Chronic alcohol ingestion disturbs the normal gut flora causing bacterial overgrowth and dysbiosis (loss of symbiosis) which together increase the intestinal concentration of inflammatory microbial products such as lipopolysaccharides (LPS, endotoxin) and other pathogen-associated molecular patterns (PAMPs).[4] These products can contribute to tight junction dysfunction by inducing inflammation in addition the direct effect of ethanol on tight junctions.[5] Together, this causes a leaky membrane scenario whereby bacteria and inflammatory molecules can translocate from the intestine to the liver through the portal circulation. In the liver, bacteria and associated PAMPs are recognized by toll-like receptors (TLRs), stimulating hepatic inflammation that contributes to alcoholic hepatitis and cirrhosis.[6] Additionally, chronic alcohol increases the bacterial synthesis of acetaldehyde that can further weaken the mucosal barrier and alcohol may diminish bacterial vitamin production.[7,8] Thus, alcoholic liver disease may not only be an effect of alcohol on the liver but may also be potentiated by perturbations in the microbiome which contribute to liver inflammation and damage.

Gut Microbiota and NAFLD

The gut microbiome has also been implicated in the pathogenesis of NAFLD. Alterations to the gut microbiome have been linked to the development of obesity, which is the strongest risk factor for NAFLD.[9] Short-chain fatty acids are a major microbial fermentation product of dietary fibre and contribute a large portion of dietary energy.[10] In genetically obese mice and obese patients, perturbations in the gut microbiota have been noted, particularly a decrease in the ratio of the phyla Bacteroidetes to Firmicutes, though this has not consistently been found.[11-14] Some studies have shown that these microbial changes in obesity lead to an increased capa-

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bility of the microbiome to synthesize short chain fatty acids, thereby extracting more energy from the diet, contributing to obesity and NAFLD.[15, 16] Furthermore, the production of alcohol in the gut by the microbiota has been also been suggested as promoting the development of NAFLD. Many alcohol metabolizing enzymes such as alcohol dehydrogenase, aldehyde dehydrogenase and CYP2E1 are elevated in the hepatic parenchyma of patients with non-alcoholic steatohepatitis.[17] Elevated serum alcohol concentration has been found in adult NAFLD patients as well as pediatric patients meaning this finding is likely not due to occasional drinking.[18] In short, the microbial changes associated with NAFLD may contribute to its pathogenesis by promoting obesity and the endogenous production of alcohol.

Gut Microbiota and Cirrhosis

Lastly, there are also alterations in the gut microbiome associated with cirrhosis, advanced liver fibrosis that can result from a multitude of chronic liver diseases. In a metagenomics study, Qin et al. sequenced the genotypes of the microbiota of 98 cirrhotic patients and 83 healthy controls.[19] In both groups, Bacteroidetes was found to be the most abundant phylum, though cirrhotic patient had relatively less. Compared to controls, the bacterial communities in cirrhotic patients were found to be much less rich. A number of enzyme groups were differentially represented by the cirrhotic and control microbiomes. For instance, enzyme pathways for ammonia and GABA metabolism were enriched in cirrhotic patients.[19] This may suggest a role for gut bacteria in the pathogenesis of hepatic encephalopathy, a complication of cirrhosis thought to be at least partially due to hyperammonemia and elevated GABA levels.[20] Using a combination of only 15 microbial genes, Qin et al. were able to discriminate between controls and patients with cirrhosis.[19] These findings suggest that the gut microbiome does play a role in cirrhosis, and that microbial gene signatures may become a useful biomarker.

Conclusion

There is a growing body of evidence for the role of the gut microbiome in the pathogenesis of liver disease including alcoholic liver disease, NAFLD and cirrhosis. The more studies are published, the more firm our understanding of this issue will be. It may be possible, in the near future, to target therapies towards the gut microbiome in addition to current treatments, or utilize microbiome signatures to help identify those at risk of liver disease.

References

1. Cho I, Blaser MJ. The human microbiome: At the interface of health and disease. Nat Rev Genet. 2012 Mar 13;13(4):260-70.
2. Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. Physiol Rev. 2010 Jul;90(3):859-904.
3. Goel A, Gupta M, Aggarwal R. Gut microbiota and liver disease. J Gastroenterol Hepatol. 2014 Jun;29(6):1139-48.
4. Henao-Mejia J, Elinav E, Jin C, Hao L, Mehal WZ, Strowig T, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature. 2012 Feb 1;482(7384):179-85.
5. Wang Y, Tong J, Chang B, Wang B, Zhang D, Wang B. Effects of alcohol on intestinal epithelial barrier permeability and expression of tight junction-associated proteins. Mol Med Rep. 2014 Jun;9(6):2352-6.
6. Yan AW, Schnabl B. Bacterial translocation and changes in the intestinal microbiome associated with alcoholic liver disease. World J Hepatol. 2012 Apr 27;4(4):110-8.
7. Chen P, Schnabl B. Host-microbiome interactions in alcoholic liver disease. Gut Liver. 2014 May;8(3):237-41.
8. Zhong W, Zhou Z. Alterations of the gut microbiome and metabolome in alcoholic liver disease. World J Gastrointest Pathophysiol. 2014 Nov 15;5(4):514-22.
9. DiBaise JK, Frank DN, Mathur R. Impact of the gut microbiota on the development of obesity: Current concepts. Am J Gastroenterol Suppl. 2012;1:22.
10. Schwiertz A, Taras D, Schafer K, Beijer S, Bos NA, Donus C, et al. Microbiota and SCFA in lean and overweight healthy subjects. Obesity (Silver Spring). 2010 Jan;18(1):190-5.
11. Duncan SH, Lobley GE, Holtrop G, Ince J, Johnstone AM, Louis P, et al. Human colonic microbiota associated with diet, obesity and weight loss. Int J Obes (Lond). 2008 Nov;32(11):1720-4.
12. Jumpertz R, Le DS, Turnbaugh PJ, Trinidad C, Bogardus C, Gordon JI, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. Am J Clin Nutr. 2011 Jul;94(1):58-65.
13. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: Fermentation and short chain fatty acids. J Clin Gastroenterol. 2006 Mar;40(3):235-43.
14. Zhang H, DiBaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y, et al. Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci U S A. 2009 Feb 17;106(7):2365-70.
15. Tilg H, Kaser A. Gut microbiome, obesity, and metabolic dysfunction. J Clin Invest. 2011 Jun;121(6):2126-32.
16. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006 Dec 21;444(7122):1027-31.
17. Zhu L, Baker SS, Gill C, Liu W, Alkhouri R, Baker RD, et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: A connection between endogenous alcohol and NASH. Hepatology. 2013 Feb;57(2):601-9.
18. Zhu L, Baker RD, Baker SS. Gut microbiome and nonalcoholic fatty liver diseases. Pediatr Res. 2015 Jan;77(1-2):245-51.
19. Qin N, Yang F, Li A, Prifti E, Chen Y, Shao L, et al. Alterations of the human gut microbiome in liver cirrhosis. Nature. 2014 Sep 4;513(7516):59-64.
20. Felipo V. Hepatic encephalopathy: Effects of liver failure on brain function. Nat Rev Neurosci. 2013 Dec;14(12):851-8.