Editorial on Nutrition

Gut bacteria may control development of hepatocellular carcinoma

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The gut continually encounters many environmental factors, including pathogens and foods. Therefore, the gut requires specialized mechanisms to protect it from the adverse effects of these factors while maintaining gut homeostasis. It has been estimated that more than 10^{14} microorganisms live in the gastrointestinal (GI) tract, with the numbers and species of these microbes differing by site within the GI tract (1). Gut bacteria have been shown to digest complex carbohydrates and plant polysaccharides, neither of which may be metabolized by human enzymes, and to produce short-chain fatty acids (SCFAs) that regulate cell differentiation and proliferation and have anti-inflammatory or immunomodulatory effects. These bacteria also produce a variety of essential vitamins, including vitamin B12, vitamin K, folate and biotin, which are not produced by host cells. Moreover, gut microbiota play an important role in the regulation of systemic immunity, by stimulating intestinal epithelial cells to produce transforming growth factor-β which regulates the development of FoxP3+ regulatory T (Treg) cells and type 17 helper (Th17) cells (2). Taken together, these findings indicate that gut microbiota are greatly involved in the maintenance of host health, which in turn implies that dysbiosis of gut flora could cause various diseases. Because blood from the intestines flows into the liver, the liver is directly affected by metabolites, cytokines and bacteria (via bacterial translocation) present in the intestines. Therefore, the liver is the organ most affected by the intestinal environment created by microbiota.

Several human diseases, including allergies, autism, dementia, obesity, coronary arterial disease, and type 2 diabetes, have been reported associated with alterations in the composition of microbiota (1). Changes in the composition of gut microbiota have also been shown associated with the development of malignancies, including colorectal, hepatobiliary and breast cancer.

The pathogenesis of several liver diseases has been associated with gut microbiota. In principal, dysbiosis or malnutrition, such as a high fat diet, alcohol consumption or low dietary fiber, can alter the gut-liver barrier, leading to an influx into the liver of pathogen-associated molecular patterns (PAMPs), including bacterial proteins and bacterial DNA. This, in turn, can alter the production of bioactive lipids or the formation of inflammasomes in the liver, as well as affect innate immune responses. Gut microbiota can also contribute to changes in the metabolism of SCFAs, bile acids and vitamins, which can modify the pathogenesis of various liver diseases (3). The role of gut microbiota in the pathogenesis of nonalcoholic fatty liver disease (NAFLD) has been widely analyzed, and clinical trials have investigated the treatment of NAFLD with probiotics. Fat deposition in the liver, followed by necro-inflammation, contributes to the pathogenesis of NAFLD, and gut microbiota has been shown to be involved in both processes. Alterations in the composition of gut microbiota have been associated with the progression of NAFLD to nonalcoholic steatohepatitis (NASH) by increasing the production of endotoxins and

activating Kupffer cells (4). Randomized control trials of probiotics for the treatment of NASH have shown that probiotics significantly reduced intrahepatic fat deposition, from 22.6%±8.2% to 14.9%±7.0% (5), and improved liver fibrosis (6).

Alcoholic liver disease is characterized by gut dysbiosis, including a decrease in *Bacteroidaceae* and an increase in *Prevotellaceae* (7). Furthermore, increased gut permeability resulting from ethanol- or acetaldehyde-induced impairment of tight junctions could increase the entry into the liver of endotoxins and bacterial DNA, leading to liver inflammation (8).

As liver disease progresses to liver cirrhosis, both portal hypertension and a decrease in bile acid secretion could affect the composition of gut microbiota (9). For example, alterations in gut microbiota observed in patients with cirrhosis include an increase in pathogenic bacteria including *Enterobacteriaceae* and *Streptococcaceae* and a decrease in beneficial bacteria including *Bifidobacteria* and *Lachnospiraceae*, although the significance of these changes remains unclear (10). Alterations in the composition of gut microbiota found in liver diseases may be associated with the pathogenesis or pathophysiology of those diseases. These analyses may inform new strategies to treat these diseases with probiotics.

Steps thought to be involved in the pathogenesis of hepatocellular carcinoma (HCC) include obesity-induced dysbiosis, which has been found to increase deoxycholic acid, a gut bacterial metabolite that can induce DNA damage. This can induce a senescence-associated secretory phenotype in hepatic stellate cells, thereby promoting hepatic carcinogenesis (11). Furthermore, the interactions of PAMPs from gut microbiota with toll-like receptors can also promote hepatic carcinogenesis (12).

Recently, Li *et al.* reported that probiotics could suppress tumor growth in a mouse model of HCC (13). In this model, C57BL6/N mice were subcutaneously injected with tumor cells, and were fed ad libitum with a diet containing Prohep, a new probiotic mixture composed of *Lactobacillus rhamnosus* GG, viable *Escherichia coli* Nissle 1917 and heat-inactivated VSL#3 (1:1:1), or control (normal) diet. Prohep significantly suppressed tumor growth especially when the probiotics were administrated before the tumor injection, reducing tumor size and weight by 40% compared with the control. This study also assessed changes in the composition of gut microbiota by shotgun metagenomics and analyzed the mechanism of tumor suppression, mainly by focusing on alterations in angiogenesis and the immune response. The levels of expression of proangiogenic genes, including *FLT-1*, *ANG2*, *KDR*, *VEGFA*, and *TEK*, were lower in the Prohep-fed than in the control group, reductions thought to induce tumor hypoxia and suppressing the growth of highly vascularized HCC. Analyses of gut microbiota revealed that seven genera, *Alistipes*, *Butyricimonas*, *Mucispirillum*, *Oscillibacter*, *Parabacteroides*, *Paraprevotella*, and *Prevotella*, were significantly enriched in Prohep-fed mice. These genera have been associated with the production of SCFAs, induction of the anti-inflammatory cytokine interleukin (IL)-10 and suppression of the secretion of the inflammatory cytokines IL-17, IL-6, and interferon (IFN)-γ, and the differentiation of IL-10 producing Tregs. Increases in *Prevotella* and *Oscillibacter* were also shown to reduce the tumor populations of migratory Th17 cells; which are thought to migrate from the intestines and peripheral blood. Moreover, increases in *Prevotella* and *Oscillibacter* were found to promote the differentiation of type 1 regulatory T (Tr1) cells in the gut. Intratumoral Th17 cells, which produce the pro-angiogenic cytokine IL-17 and are derived from the gut mucosa through their interactions with gut-residing segmented filamentous bacteria, have also been shown to be associated with poor prognosis in patients with HCC (14). Therefore, reductions of Th17 cells in tumors could result in the inhibition of angiogenesis. The role of IL-17 in the growth of tumors in this model was confirmed by showing that antibody to IL-17 reduced tumor growth. Because Tr1 cells suppress immune responses by producing IL-10, their differentiation in response to altered gut microbiota may modulate anti-tumor immune responses. All of these changes induced by alterations in gut microbiota may lead to suppressed tumor growth in this model. Although the antitumor effect of Prohep was not comparable to that of cisplatin, the results clearly demonstrated that probiotic-induced alterations in the composition of gut microbiota could suppress the growth of HCCs. The prognosis of patients with HCC is generally dismal, especially when the tumor is diagnosed at an advanced stage. However, the results observed in the mouse model suggest that administration of probiotics may be a novel and promising approach for the treatment of HCC. Because the immunogenicity and biological characteristics of HCC differ in humans and mice, as do their repertoire of gut microbiota, studies in humans are required to confirm these results.

In summary, advances in methods of analyzing gut microbiota have revealed that their total composition plays an important role in the homeostasis of metabolism or

systemic immunity. Changes in gut microbiota have been found associated with the pathogenesis or pathophysiology of various liver diseases, including HCC. These findings have led to the development of several approaches using probiotics for the treatment of these diseases, with some of these approaches showing promising results. However, it is uncertain whether these effects are due to key bacteria or the entire balance of the bacterial repertoire. A recent report suggested that gut microbiota are associated with the efficacy of cancer chemotherapy (15). Studies are needed to assess the role of gut microbiota in modulating the anti-cancer effects of chemotherapy, immunotherapy and radiotherapy, or the possible synergistic anti-cancer effects of combinations of probiotics with these conventional treatments.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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