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Mini-review

The microbiome and hepatobiliary-pancreatic cancers

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ABSTRACT

The human intestinal microbiome encompasses at least 100 trillion microorganisms that can influence host immunity and disease conditions, including cancer. Hepatobiliary and pancreatic cancers have been associated with poor prognosis owing to their high level of tumor invasiveness, distant metastasis, and resistance to conventional treatment options, such as chemotherapy. Accumulating evidence from animal models suggests that specific microbes and microbial dysbiosis can potentiate hepatobiliary-pancreatic tumor development by damaging DNA, activating oncogenic signaling pathways, and producing tumor-promoting metabolites. Emerging evidence suggests that the gut microbiota may influence not only the efficacy of cancer chemotherapies and novel targeted immunotherapies such as anti-CTLA4 and anti-CD274 therapies but also the occurrence of postoperative complications after hepatobiliary and pancreatic surgery, which have been associated with tumor recurrence and worse patient survival in hepatobiliary-pancreatic cancers. Hence, a better understanding of roles of the gut microbiota in the development and progression of hepatobiliary-pancreatic tumors may open opportunities to develop new prevention and treatment strategies for patients with hepatobiliary-pancreatic cancer through manipulating the gut microbiota by diet, lifestyle, antibiotics, and pro- and prebiotics.

Introduction

Hepatobiliary and pancreatic cancers have been associated with poor prognosis owing to their high level of tumor invasiveness, distant metastasis, and resistance to conventional treatment options, such as chemotherapy [1–3]. Accumulating evidence indicates that hepatobiliary and pancreatic cancers develop through the accumulation of genetic and epigenetic alterations, which is influenced by host immunity, diet, and environmental and microbial exposures [1–7].

The human intestinal microbiome encompasses at least 100 trillion (10^{14}) microorganisms that can influence host metabolism, the immune system, and disease conditions including obesity and cancer [8]. The liver, biliary tract, and pancreas are exposed to the gut microbiome via blood flow through the portal vein and contain many immune cells, such as T cells and macrophages [9]. Accumulating evidence demonstrates that the gut microbiome can influence hepatobiliary-pancreatic diseases through the gut–liver axis [10,11]. Experimental studies suggest that intestinal microbial dysbiosis (the condition of having imbalances in the microbial communities in the body) potentiate hepatic steatosis and inflammation through increased levels of lipopolysaccharide, the recruitment of macrophages in the liver, and the activation of TLR4 in a mouse model of non-alcoholic steatohepatitis (NASH) [12–15], and that TLR4 can activate hepatic stellate cells and potentiate liver fibrosis through the TGFB signaling pathway [16]. In fact, clinical studies have shown that intestinal microbial dysbiosis is associated with the progression of NASH [17–19] and liver cirrhosis [20–22]. These findings from animal models and human studies suggest that the gut–liver axis may potentiate inflammation and fibrosis in the liver, which have been shown to promote liver tumor development. A growing body of evidence indicates that diet, lifestyle, and drugs can influence the composition of gut microbiota [23,24]. Hence, a better understanding of the roles of microbes in the development of hepatobiliary-pancreatic tumors may open opportunities to develop new

Abbreviations: HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; PDCD1, programmed cell death 1; ROS, reactive oxygen species; RYGB, Roux-en-Y gastric bypass; TLR, Toll-like receptor.

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prevention and treatment strategies for patients with hepatobiliary-pancreatic cancer through targeting microbes and the microbiota.

Here, we review experimental and clinical studies on microbes in relation to hepatobiliary-pancreatic cancers. In addition, we describe emerging evidence supporting roles of microbes in not only the efficacy of chemotherapy and immunotherapy for cancer, but also complications after surgery for hepatobiliary-pancreatic cancers.

Liver cancer

Liver cancer is the second leading cause of cancer-related deaths globally with an incidence of approximately 850,000 new cases per year [25]. Hepatocellular carcinoma (HCC) represents approximately 90% of all cases of primary liver cancer, and the main risk factors for developing HCC include hepatitis B and C virus infection, alcohol intake, ingestion of the fungal metabolite aflatoxin B1, non-alcoholic steatohepatitis, and liver cirrhosis [1].

Experimental and clinical studies suggest associations between microbes and microbial dysbiosis and the development of HCC (Table 1).

Chronic infection with *Helicobacter pylori*, which is a gram-negative bacterial species that selectively colonizes gastric epithelium, has been associated with over a two-fold increased risk of gastric cancer overall [26]. Accumulating evidence demonstrates a possible role of *H. pylori* and other *Helicobacter* species in liver cancer. Experimental studies have shown that *Helicobacter hepaticus* may colonize the hepatic bile canaliculi and the large intestine of mice, and potentiate liver tumor development by increasing tumor cell proliferation, damaging DNA, activating the WNT and NFKB signaling pathways in tumor cells, and suppressing intratumoral immunity in a mouse model of aflatoxin- and hepatitis C virus-induced HCC [27,28]. In human HCC tissue specimens, *Helicobacter* species has been detected [29–31].

Innate immunity is a rapid immune response that recognizes conserved microbial structures in a non-specific manner, typically through the action of pattern recognition receptors expressed on host cells, such as Toll-like receptors (TLRs) [32]. TLRs have been shown to promote the development and progression of gastrointestinal tumors through activation of the NFKB and STAT3 signaling pathways [32]. Experimental studies using a mouse model of diethylnitrosamine-induced HCC suggest that lipopolysaccharide from intestinal Gram-negative microbes can potentiate tumor progression through the activation of TLR4 expressed on hepatocytes and hepatic stellate cells [33,34]. In the mouse model, lipopolysaccharide has been shown to activate TLR4 on hepatocytes and hepatic stellate cells, which leads to up-regulation of hepatomitogen EREG in hepatic stellate cells, enhanced tumor cell proliferation, activation of the NFKB signaling pathway in tumor cells, and inhibition of tumor cell apoptosis.

A growing body of evidence suggests an association of microbial dysbiosis with obesity [35]. Emerging evidence demonstrates an association of the metabolic syndrome due to diabetes and obesity, and the associated liver disease non-alcoholic fatty liver disease and non-alcoholic steatohepatitis with the development HCC [36,37]. Experimental studies using mouse models of obesity-induced HCC have shown that microbial dysbiosis correlates with high levels of bile acids, including deoxycholic acid, in the liver, which can potentiate tumor development by up-regulating the expressions of proinflammation-related genes such as IL6 and TNFA [38,39]. Accumulating evidence suggests that senescent cells produce inflammatory cytokines, chemokines, and proteases, which may contribute to tumor development [40–42]. Yoshimoto et al. have shown that deoxycholic acid produced by gut microbiota can potentiate tumor development by provoking the senescence-associated secretory phenotype in hepatic stellate cells and up-regulation of IL6 in a mouse model of obesity-induced HCC [43]. Among various microbial species, *Clostridium* species were enriched in these mouse models of obesity-induced HCC [38,39,43,44].

Table 1
Experimental and clinical studies on microbes in relation to liver cancers.

	Findings (References)
Experimental studies	· *Helicobacter hepaticus* promotes tumor development by increasing tumor cell proliferation, activating the WNT and NFKB signaling pathways, and suppressing antitumor immunity in a mouse model of aflatoxin- and hepatitis C virus-induced hepatocellular carcinoma (27, 28). · Microbial dysbiosis and lipopolysaccharide activate TLR4 on resident liver cells, which promotes tumor progression by increasing tumor cell proliferation, up-regulating epiregulin, and preventing tumor cell apoptosis in a mouse model of diethylnitrosamine-induced hepatocellular carcinoma (33, 34). · The gut microbiota increase bile acids in the liver, which promote tumor development in a mouse model of obesity-induced hepatocellular carcinoma (38). · Microbial dysbiosis promotes tumor development in a high-fat diet-induced nonalcoholic steatohepatitis-hepatocellular carcinoma mouse model (39). · The gut microbiota produce deoxycholic acid, which promotes tumor development by provoking the senescence-associated secretory phenotype in hepatic stellate cells in a mouse model of obesity-induced hepatocellular carcinoma (43). · A high amount of *Clostridium* cluster XI is associated with tumor development in a mouse model of obesity-induced hepatocellular carcinoma (44). · Probiotics inhibit tumor development from cirrhosis by suppressing tumorigenic inflammation in a rat model of diethylnitrosamine-induced hepatocellular carcinoma (53). · Probiotics change the composition of the gut microbiota, which reduces liver tumor growth by inhibiting angiogenesis and down-regulating IL17 expression in a mouse xenograft model of human hepatocellular carcinoma (54).
Clinical studies	· *Helicobacter* species are detected in human hepatocellular carcinoma tissue specimens (29–31). · The amount of *Escherichia coli* is increased in the stool specimens of patients with hepatocellular carcinoma (47).

Escherichia coli has been shown to induce double-strand DNA breaks and promote colon carcinogenesis in *Il10*$^{-/-}$ mice [45,46]. The increased amount of *E. coli* in the stool specimens is associated with the presence of HCC in patients with liver cirrhosis, suggesting that intestinal overgrowth of *E. coli* may contribute to the development of HCC [47].

Evidence suggests that diet, lifestyle, pharmacological factors (including antibiotics), and pro- and prebiotics can influence the composition of intestinal microbiota [48–52]. Probiotics can change the composition of the gut microbiota and have been shown to inhibit tumor development by inhibiting angiogenesis and down-regulating levels of lipopolysaccharide and IL6 in a mouse xenograft model of human HCC or a rat model of diethylnitrosamine-induced HCC [53,54]. In these animal models, probiotics can increase amounts of microbes that have been shown to reduce the intestinal inflammation, including *Lactobacillus* species, *Bifidobacterium* species, *Parabacteroides* species, and *Oscillibacter* species [55–57], suggesting that these microbes might have a protective role in liver tumor development. Epidemiologic evidence suggests that ever-use of prescription antibiotics is associated with a slightly increased risk of liver cancer, compared to non-use of prescription antibiotics [58].