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The microbiome, genetics, and gastrointestinal neoplasms: the evolving field of molecular pathological epidemiology to analyze the tumor-immune-microbiome interaction

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Abstract

Metagenomic studies using next-generation sequencing technologies have revealed rich human intestinal microbiome, which likely influence host immunity and health conditions including cancer. Evidence indicates a biological link between altered microbiome and cancers in the digestive system. *Escherichia coli* and *Bacteroides fragilis* have been found to be enriched in colorectal mucosal tissues from patients with familial adenomatous polyposis that is caused by

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The MPE approach combined with microbiome research is expected to reveal new risk factors for early-onset colorectal cancer that has been increasing worldwide for uncertain reasons (Akimoto et al. in press), and there is an urgent need for research.

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Use of standardized official symbols: We use HUGO (Human Genome Organization)-approved official symbols (or root symbols) for genes and gene products; all of which are described at www.genenames.org. The official gene symbols are italicized to differentiate from non-italicized gene product symbols.

germline *APC* mutations. In addition, recent studies have found enrichment of certain oral bacteria, viruses, and fungi in tumor tissue and fecal specimens from patients with gastrointestinal cancer. An integrative approach is required to elucidate the role of microorganisms in the pathogenic process of gastrointestinal cancers, which develop through the accumulation of somatic genetic and epigenetic alterations in neoplastic cells, influenced by host genetic variations, immunity, microbiome, and environmental exposures. The transdisciplinary field of molecular pathological epidemiology (MPE) offers research frameworks to link germline genetics and environmental factors (including diet, lifestyle, and pharmacological factors) to pathologic phenotypes. The integration of microbiology into the MPE model (microbiology-MPE) can contribute to better understanding of the interactive role of environment, tumor cells, immune cells, and microbiome in various diseases. We review major clinical and experimental studies on the microbiome, and describe emerging evidence from the microbiology-MPE research in gastrointestinal cancers. Together with basic experimental research, this new research paradigm can help us develop new prevention and treatment strategies for gastrointestinal cancers through targeting of the microbiome.

Keywords

big data; bioinformatics; inflammation; gene-by-environment interaction; omics; population health science

Introduction

Carcinomas that arise in the digestive system, including upper and lower gastrointestinal tract, liver, gallbladder, extrahepatic bile duct, and pancreas, are collectively leading causes of death worldwide (Cortes et al. 2020). The human intestine contains more than 100 trillion microorganisms, which can influence the immune system and health conditions including cancer (Tilg et al. 2020). Emerging longitudinal studies from the Integrative Human Microbiome Project have demonstrated associations of changes in the human microbiome with preterm birth (Fettweis et al. 2019), inflammatory bowel diseases (Lloyd-Price et al. 2019), and prediabetes (Zhou et al. 2019). Accumulating evidence suggests that gastrointestinal cancers develop through the accumulation of somatic mutations and epigenetic alterations in tumor cells with complex influences of host genetic variations, microbiome, immunity, and environmental exposures (Fig. 1). Hence, it has been a challenge to elucidate the role of microbes in the pathogenic process of human gastrointestinal cancers.

The integration of molecular pathology and epidemiology has generated the transdisciplinary field of ‘molecular pathological epidemiology (MPE)’ (Ogino and Stampfer 2010), which aims to link germline genetics and modifiable factors (including environment, diet, lifestyle, and pharmacological factors) to pathologic features, most commonly tumor characteristics (Ogino et al. 2011; Ogino et al. 2019; Ogino et al. 2018). The concept of MPE as a distinct field has been widespread (Carr et al. 2018; Gunter et al. 2019; Hughes et al. 2017; Rescigno et al. 2017; Waluga et al. 2018; Wang et al. 2020). Ogino et al. have shown basic approaches of MPE research in our previous review (Ogino et

al. 2011; Ogino et al. 2016; Ogino et al. 2018). Although an interventional study is a gold standard, to date no interventional MPE studies have been published. Hence, better approach of MPE research is a prospective cohort study, which can reduce potential bias related to case-case and case-control designs. In a prospective cohort study, disease incidence analyses of MPE can compute risk estimates of environmental exposures, including diet, nutrition, and lifestyle, for the incidence of disease with specific subtypes according to phenotypic characteristics (e.g. *KRAS* mutation), and disease consequence (e.g. patient survival) analyses of MPE can examine prognostic associations of environmental exposures according to phenotypic characteristics of diseases. Utilizing colorectal cancer cases in two U.S. nationwide prospective cohort studies (the Nurses' Health Study and the Health Professionals Follow-up Study), MPE studies have shown that cigarette smoking is associated with an increased risk, especially of microsatellite instability (MSI)-high, CpG island methylator phenotype (CIMP)-high, and *BRAF*-mutated colorectal cancers (Limsui et al. 2010; Nishihara et al. 2013a), and that high levels of MSI and CIMP are common features of colorectal cancers arising within 5 years after colonoscopy (Nishihara et al. 2013b). In addition, MPE studies have shown that regular aspirin use after diagnosis is associated with longer survival, especially in patients with PTGS2-overexpressing colorectal cancer (Chan et al. 2009), *PIK3CA*-mutated colorectal cancers (Liao et al. 2012), and CD274-low colorectal cancers (Hamada et al. 2017). These MPE studies demonstrate that the MPE approach can contribute to precision cancer medicine and prevention. In addition to cancer research, MPE approach can be applied to non-neoplastic diseases such as cardiovascular diseases, obesity, diabetes mellitus, drug toxicity, and immunity-related and infectious diseases (Ogino et al. 2016).

Genome-wide association studies (GWAS) suggest interactions of host genetic variations with diet, lifestyle, and other environmental exposures in the development of gastrointestinal cancers (Table 1). There are few gene-environment interaction studies considering microorganisms or immunity in gastrointestinal cancers to date. A gene-environment interaction study has shown a statistically significant interaction of the rs2294008 or rs2976392 single nucleotide polymorphism (SNP) at the *PSCA* gene with *Helicobacter pylori* infection in risk for gastric cancer (Nan et al. 2015). In a study of hepatocellular carcinoma (HCC), the rs7574865 SNP at the *STAT4* gene and the rs9275319 SNP at the *HLA-DQA1* gene showed a statistically significant interaction with hepatitis B virus infection in risk for HCC (Nan et al. 2013). A study using the integration of immunology and MPE into GWAS has revealed that the rs11676348 SNP was associated with colorectal cancer exhibiting Crohn's-like lymphoid reaction or high-level of MSI (Khalili et al. 2015).

The relationship between the complex gut microbiome, tumor cells, and immune cells in humans cannot be completely recapitulated in any *in vivo* or *in vitro* model. Hence, the integration of microbiology into the MPE model (microbiology-MPE) can contribute to better understanding of the complex interactions of environment, tumor cells, immune cells, and microbiome during the development and progression of gastrointestinal cancers (Chen et al. 2019a; Hamada et al. 2019; Luo et al. 2019). Herein, we review major clinical and experimental studies on the microbiome and gastrointestinal cancers, and describe emerging evidence from microbiology-MPE studies.

Gut microbiome and gastrointestinal tract cancer

Esophageal cancer

Esophageal carcinoma largely consists of two histological types, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC is a common type of esophageal cancer worldwide and predominates in certain high-risk areas, such as China and Japan (Stewart et al. 2014). In contrast, EAC is a predominant type in European and North American countries (Ajayi et al. 2018; Baba et al. 2017). Cigarette smoking, alcohol consumption, caustic injury, poor oral health, and poor nutritional status are major risk factors for ESCC; whereas the risk factors of EAC include advanced age, male sex, obesity, gastro-esophageal reflex disease, cigarette smoking, and diet low in vegetables and fruit (Smyth et al. 2017). Genetic polymorphisms of the *GSTM1*, the *ALDH2* and *ADH1B* (alcoholic metabolic enzymes), or the *MTHFR* (folate metabolic enzyme) have been associated with an increased risk of esophageal carcinoma (Tian et al. 2019a). Human studies suggest associations of the microbiome with ESCC and EAC (Table 2).

Low microbial diversity measured by the number of detectable bacterial genera sample in the oral cavity has been associated with the presence of ESCC (Chen et al. 2015; Yu et al. 2014). Peters et al. have performed 16S rRNA gene sequencing in prediagnostic mouthwash specimens, and found that a high amount of *Tannerella forsythia* in the oral cavity may be associated with higher risk of EAC, and that *Porphyromonas gingivalis* may be associated with higher risk of ESCC (Peters et al. 2017). Yamamura et al. have demonstrated that a high amount of *Fusobacterium nucleatum*, which is common species in the oral microbiota, in tumor tissue is associated with shorter patient survival following resection of esophageal cancer, including both ESCC and EAC, and that the amount of *Fusobacterium nucleatum* correlates with tumor expression of chemokine CCL20, which has been shown to promote the accumulation of regulatory T cells (Yamamura et al. 2016). Epidemiological studies have demonstrated an association of indicators of poor oral health, such as high numbers of lost teeth, with an increased risk of ESCC (Chen et al. 2017). These data suggest that dysbiosis in the oral microbiome may play a role in esophageal carcinogenesis.

Other studies have shown that *Escherichia coli* and *Campylobacter concisus*, which have been shown to potentiate carcinogenesis through specific toxins that can induce DNA damage (He et al. 2019; Wilson et al. 2019), are enriched in Barrett's esophagus (Blackett et al. 2013; Zaidi et al. 2016).

Gastric cancer

Gastric cancer remains one of the leading causes of cancer-related mortality worldwide and the most prevalent cancer in Eastern Asia (Ajani et al. 2017). The worldwide incidence of gastric cancer has declined rapidly over the recent few decades due to a decline in *Helicobacter pylori* infection rates. Gastric cancer can be classified according to tumor location as cardia (the upper part of the stomach) and non-cardia (the mid and distal stomach). The incidence of gastric cardia cancer and EAC has increased. Chronic infection with *Helicobacter pylori*, gram-negative species that colonizes gastric epithelium, has been associated with an increased risk of gastric cancer, and *Helicobacter pylori* is categorized as

a class I carcinogen by the World Health Organization (Ajani et al. 2017). Risk factors for cancers arising from cardia and non-cardia regions of the stomach may be different. Common risk factors for both cardia and non-cardia gastric cancer include advanced age, male sex, cigarette smoking, radiation, and family history (Ajani et al. 2017). Factors associated cardia gastric cancer include obesity and gastro-esophageal reflex disease; whereas the risk factors of non-cardia gastric cancer include *Helicobacter pylori* infection, low socioeconomic status, low consumption of fruits and vegetables and high intake of salty and smoked food (Karimi et al. 2014). Genetic polymorphisms of the *APEX1*, *CASP8*, *DNMT1*, *ERCC5*, *GSTT1*, *IL1B*, *IL1RN*, *IL10*, *IL17F*, *MDM2*, *PPARG*, *TLR4*, or *TNF* have been associated with higher risk for and gastric cancer (El-Omar et al. 2000; El-Omar et al. 2003; Tian et al. 2019b). A germline *CDH1* mutation is associated with familial diffuse gastric cancer (Guilford et al. 1998). In addition to the infection with *Helicobacter pylori*, human metagenomic studies suggest a potential link between the gastric microbiome and gastric cancer (Table 2).

A Chinese pilot study showed that low microbial diversity in gastric nontumor tissues was associated with advanced tumor grade in patients with gastric cardia cancer, and that patients with metastatic gastric cardia cancer had lower relative abundance of *Lactobacillales* in gastric nontumor tissues compared to gastric cardia cancer patients without metastasis (Yu et al. 2017). Metagenomic analyses of gastric mucosal microbiota have shown a gradual decrease in microbial diversity from gastritis to intestinal metaplasia to gastric cancer (Aviles-Jimenez et al. 2014), and that lower microbial diversity, lower amount of *Helicobacter*, and higher amounts of certain members of the oral microbiota, including *Parvimonas micra*, *Peptostreptococcus stomatis*, and *Fusobacterium nucleatum*, were observed in both cardia and non-cardia gastric cancer tissues, compared with nontumor tissues (Coker et al. 2018; Ferreira et al. 2018). Dysbiosis in the tongue coating microbiome was observed in patients with gastric cancer (Wu et al. 2018). These findings suggest that oral microbes may play a role in the development of gastric cancer.

Colorectal cancer

Colorectal cancers are a heterogeneous group of diseases that result from the accumulation of genomic and epigenomic alterations, and tumor-host interactions, which is influenced by environmental exposures including, diet, nutrition, and lifestyle, the microbiome, and host immunity (Tilg et al. 2018; Wong and Yu 2019). Modifiable risk factors for colorectal cancer include cigarette smoking, alcohol consumption, overweight and obesity, physical inactivity, high consumption of red and processed meat, and low consumption of dietary fiber, whole grains, and other healthful nutrients (Islami et al. 2018). Genome-wide association studies of colorectal caner have reported that genetic polymorphisms associated with higher risk for colorectal cancer are located either inside or near protein-coding genes that include *ATOH1*, *APOBEC1*, *BMPR1B*, *BMP5*, *CDKN2A*, *CYP17A1*, *EIF3H*, *FKBP5*, *MED13L*, *PDLIM5*, *PTGER4*, *PTPN1*, *RTEL1*, *RPS21*, *SMARCAD1*, *SPSB2*, *TERT*, or *TFEB* (Schmit et al. 2019; Zeng et al. 2016). Germline mutations in the *APC* gene or the DNA mismatch repair genes (*MSH2*, *MLH1*, *PMS1*, *PMS2*, and *MSH6*) have been associated with familial adenomatous polyposis or hereditary nonpolyposis colorectal cancer. Germline mutations of the *MUTYH*, *STK11*, *SMAD4*, *BMPR1A*, or *PTEN* have been associated with other

familial polyposis syndromes (Kuipers et al. 2015). Human metagenomic studies demonstrate associations of the microbiome in mucosal tissue and fecal specimens with colorectal neoplasms (Table 3).

Colorectal mucosal microbiome has been significantly different from the fecal microbiome in patients with colorectal cancer (Chen et al. 2012; Flemer et al. 2017). Metagenomic analyses of the microbiome in human colorectal tumor tissues have demonstrated that the tumor microbiome changes across time periods from adenoma to adenocarcinoma, and that some members of the oral microbiota, including *Fusobacterium*, *Gemella*, *Peptostreptococcus*, *Parvimonas*, and *Leptotrichia*, were enriched in colorectal adenocarcinoma tissues (Nakatsu et al. 2015). Metagenomic analyses of the fecal microbiome in patients with colorectal neoplasms by Yachida et al. identified that *Atopobium parvulum* and *Actinomyces odontolyticus* were significantly increased in patients with adenomas and early stage adenocarcinoma, and that *Parvimonas micra*, *Peptostreptococcus stomatis*, *Fusobacterium nucleatum*, and *Peptostreptococcus anaerobius* were enriched in patients with metastatic colorectal adenocarcinoma (Yachida et al. 2019). Meta-analyses of human metagenomic studies of the fecal microbiome have revealed that oral microbes, including *Fusobacterium nucleatum*, *Parvimonas micra*, and *Peptostreptococcus stomatis*, were enriched in patients with colorectal carcinoma (Thomas et al. 2019; Wirbel et al. 2019). Experimental evidence indicates that *Peptostreptococcus anaerobius* can activate the NFKB signaling pathway in colorectal cancer cell lines and inhibit T-cell-mediated immune responses against colorectal tumors through the recruitment of myeloid-derived suppressor cells and tumor-associated macrophages into the tumor microenvironment in the $Apc^{Min/+}$ mouse model (Long et al. 2019). Epidemiologic studies have demonstrated an association of periodontal disease with colorectal cancer risk (Michaud et al. 2018; Momen-Heravi et al. 2017). These findings demonstrate potential roles of oral and intestinal microbes in the progression of colorectal neoplasm.

In addition to altered composition of the bacteria in colorectal mucosal tissue and fecal specimens, emerging evidence suggests that dysbiosis of the viral microbiome (virome) or the fungal microbiome (mycobiome) is associated with colorectal cancer (Coker et al. 2019; Nakatsu et al. 2018). Nakatsu et al. found that some viral taxa, such as *Orthobunyavirus*, *Inovirus*, or *Tunalikevirus*, were enriched in fecal specimens from patients with colorectal cancer, and that dysbiosis of intestinal virome was associated with worse clinical outcomes in colorectal cancer (Nakatsu et al. 2018). Analyses by Coker et al. found that altered composition of the intestinal mycobiome was associated with colorectal cancer, and that fecal specimens from patients with colorectal cancer had higher amounts of *Malasseziomycetes* and lower amounts of *Saccharomycetes* and *Pneumocystidomycetes* compared to cancer-free individuals (Coker et al. 2019).

Accumulating evidence suggests enrichment of *Fusobacterium nucleatum* in human colorectal adenomas and carcinomas compared with adjacent normal tissue (Mima et al. 2017). Patients with colorectal cancer have identical strains of *Fusobacterium nucleatum* in their colorectal cancer and oral cavity (Komiya et al. 2019). In addition, higher amount of tissue *Fusobacterium nucleatum* has been associated with advanced disease stage (Castellarin et al. 2012; Flanagan et al. 2014; Kostic et al. 2012), a lower density of T cells

in colorectal carcinoma tissue (Mima et al. 2015), and worse patient survival (Mima et al. 2016b). *Fusobacterium nucleatum* has been detected not only in primary tumors, but also in metastatic lymph nodes and liver metastases (Bullman et al. 2017; Yu et al. 2016). In addition to *Fusobacterium nucleatum*, several fusobacterial species, including *Fusobacterium gonidiaformans*, *Fusobacterium periodonticum*, and *Fusobacterium varium* have been enriched in colorectal cancer from southern Chinese populations (Yeoh et al. 2020). Experimental evidence implies potential roles of *Fusobacterium nucleatum* in the development and progression of colorectal cancer. *Fusobacterium nucleatum* may inhibit T-cell-mediated immune responses against colorectal tumors through the recruitment of myeloid-derived suppressor cells into the tumor microenvironment in the $Apc^{Min/+}$ mouse model (Kostic et al. 2013). The Fap2 protein of *Fusobacterium nucleatum* has been shown to interact with T cell immunoglobulin and ITIM domain (TIGIT) receptor, and inhibit activities of NK cells and T cells (Gur et al. 2015). *Fusobacterium nucleatum* expresses the virulence factor FadA on the bacterial cell surface, which has been shown to bind to CDH1, activate the WNT signaling pathway in colorectal carcinoma cells, and promote colorectal tumor growth (Rubinstein et al. 2013). The Fap2 protein has been shown to mediate attachment of *Fusobacterium nucleatum* to colorectal cancers that express host Gal-GalNAc, and be transmitted hematogenously to colorectal carcinoma tissue (Abed et al. 2016). *Fusobacterium nucleatum* has been shown to activate the NFKB signaling pathway and up-regulate MIR21 expression in colorectal cancer cell lines, and promote the development of intestinal tumors in $Apc^{Min/+}$ mouse model (Yang et al. 2017).

Cytolethal distending toxin (CDT) is a well-characterized genotoxin (Ge et al. 2007; Graillot et al. 2016; Guidi et al. 2013; Nesic et al. 2004). Enrichment of *Campylobacter* species has been observed in colorectal cancer tissue and fecal specimens from patients with colorectal cancer (Warren et al. 2013; Wu et al. 2013). In a mouse model, *Campylobacter jejuni* can potentiate the development of intestinal tumors through the genotoxic action of the CDT (He et al. 2019). Colibactin is encoded by the polyketide synthase (*pks*) island present in *Escherichia coli* from phylogroup B2, and has been found to induce DNA damage (Cuevas-Ramos et al. 2010; Nougayrede et al. 2006; Wilson et al. 2019), and promote colon carcinogenesis in $Il10^{-/-}$ mice (Arthur et al. 2014; Arthur et al. 2012). Pleguezuelos-Manzano et al. have demonstrated that *pks*-positive *Escherichia coli* could induce mutations characterized by a specific signature in human intestinal organoids and promote carcinogenesis (Pleguezuelos-Manzano et al. 2020). Clinical studies with a limited sample size suggest that the amount of *Escherichia coli* is higher in colorectal carcinoma tissue than in adjacent normal tissue, and that higher amount of *Escherichia coli* may be associated with advanced disease stage (Bonnet et al. 2014; Kohoutova et al. 2014).

Enterotoxigenic *Bacteroides fragilis* expresses the virulence factor *Bacteroides fragilis* toxin, which has been shown to activate the WNT, NFKB, and STAT3 signaling pathways in colonic epithelial cells, and to potentiate the development of intestinal tumors in $Apc^{Min/+}$ mice (Chung et al. 2018; Wu et al. 2003; Wu et al. 2004; Wu et al. 2007). Accumulating evidence indicates that T helper 17 (T_H17) cells, which produce IL17 and IL22, can promote tumor development and progression in the gastrointestinal tract (Chae et al. 2010; Gaffen et al. 2014; Grivennikov et al. 2012). Enterotoxigenic *Bacteroides fragilis* induces T_H17 cells, which activate the STAT3 signaling pathway in tumor cells in the $Apc^{Min/+}$ mouse model of

colon cancer (Wang et al. 2009; Wu et al. 2009). Some human studies suggest that enterotoxigenic *Bacteroides fragilis* is detected significantly more often in colon mucosa tissue or fecal specimens of colorectal cancer cases than cancer-free individuals, and that higher amount of enterotoxigenic *Bacteroides fragilis* is associated with advanced disease stage (Boleij et al. 2015; Toprak et al. 2006; Wei et al. 2016).

Familial adenomatous polyposis is caused by germline *APC* mutations (Groden et al. 1991; Nishisho et al. 1991). Dejea et al. have identified that *pks*-positive *Escherichia coli* and enterotoxigenic *Bacteroides fragilis* were more commonly found in colorectal tissues from patients with familial adenomatous polyposis (68% and 60%, respectively), compared to those from healthy individuals (22% and 30%, respectively). In mouse models, co-colonization with these two microbes can potentiate intestinal carcinogenesis through increased DNA damage in colonic epithelium and IL17 induction in the colon (Dejea et al. 2018). These findings suggest a potential link between the microbiome and germline genetics in colorectal carcinogenesis.

Enterococcus faecalis has been shown to produce extracellular superoxide that induces DNA damage and genomic instability in colonic epithelial cells (Huycke et al. 2002; Wang et al. 2008; Wang and Huycke 2007), and activates macrophages to produce 4-hydroxy-2-nonenal, which promotes colon carcinogenesis in *Il10*$^{-/-}$ mice (Wang et al. 2013; Wang et al. 2012). One human study showed that *Enterococcus faecalis* was detected more often in fecal specimens of colorectal cancer cases than controls (Balamurugan et al. 2008). Studies demonstrated that the amount of *Streptococcus gallolyticcus* in human colorectal carcinomas was higher than in control tissue, and that the amount of *Streptococcus gallolyticcus* was correlated with PTGS2 (cyclooxygenase-2) expression level in colorectal cancer (Abdulamir et al. 2010; Boleij and Tjalsma 2013; Gupta et al. 2010).

Gut microbiome and hepatobiliary-pancreatic cancer

Hepatocellular carcinoma (HCC)

HCC is the most common primary liver malignancy, and the major risk factors for HCC include hepatitis B and C, alcohol consumption, non-alcoholic fatty liver disease, and liver cirrhosis (Llovet et al. 2016). Numerous polymorphisms in the genes, which are associated with oxidative stress (*GSTM1* and *GSTT1* genes) and detoxifying (*CAT* gene) systems, iron metabolism (*HFE* gene), inflammation (*TNF*, *IL1B*, *TGFB1*, and *NFKB1* genes), DNA repair mechanisms (*MTHFR* gene) cell cycle regulation (*MDM2* and *TP53* genes), growth factors (*EGF* gene), or immune response (*CD24* gene), have been reported as risk factors of HCC (Nahon and Zucman-Rossi 2012). Clinical studies suggest associations of microbes and microbial dysbiosis with the development of HCC (Table 4).

Metagenomic analyses of the fecal microbiome in patients with liver cirrhosis or HCC revealed that *Gemmiger*, *Parabacteroides*, and *Paraprevotella* were enriched in patients with HCC, compared with those with liver cirrhosis (Ren et al. 2019). *Helicobacter pylori* and other *Helicobacter* species have been detected human HCC tissue specimens (Huang et al. 2004; Kruttgen et al. 2012; Rocha et al. 2005). 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 the innate immunity to recognize and eliminate tumor cells in a mouse model of aflatoxin- and hepatitis C virus-induced HCC (Fox et al. 2010; Ward et al. 1994). *Escherichia coli* has been shown to induce double-strand DNA breaks and promote colon carcinogenesis in *Il10*$^{-/-}$ mice (Arthur et al. 2014; Arthur et al. 2012). The increased amount of *Escherichia coli* in the fecal specimens is associated with the presence of HCC in patients with liver cirrhosis, suggesting that intestinal overgrowth of *Escherichia coli* may contribute to the development of HCC (Grat et al. 2016).

Evidence suggests an association of diabetes, obesity, non-alcoholic fatty liver disease, and non-alcoholic steatohepatitis with the development HCC (Anstee et al. 2019). 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 inflammation-related genes such as *IL6* and *TNF* (Xie et al. 2016a; Xie et al. 2016b). 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 (Yoshimoto et al. 2013). Among various microbial species, *Clostridium* species were enriched in these mouse models of obesity-induced HCC (Niwa et al. 2015; Xie et al. 2016a; Xie et al. 2016b; Yoshimoto et al. 2013). Ma and colleagues demonstrate that in multiple mouse models, *Clostridium* species can inhibit the accumulation of hepatic natural killer T (NKT) cells, and suppress antitumor immune response against both primary and secondary liver tumors (Ma et al. 2018). Colonization with a commensal *Clostridium* species, which are gram-positive bacteria and involved in the conversion of primary to secondary bile acids, decreased hepatic NKT cells and increased liver tumor metastases. Analysis of *Clostridium* species in human HCC tissue specimens would be required for clinical application.

Biliary tract cancer

Cholangiocarcinomas are cancers of the intrahepatic or extrahepatic bile ducts (Banales et al. 2016). Primary sclerosing cholangitis, biliary infections with Opisthorchis viverrini and Clonorchis sinensis, biliary malformations such as Caroli's disease and choledochal cysts, hepatolithiasis, recurrent bacterial cholangitis, carcinogens such as thorotrast and dioxins, and hepatitis C and liver cirrhosis are major risk factors for cholangiocarcinomas (Ray 2015). Genetic polymorphisms in *CXCR2* and the drug metabolizing enzyme genes (*CYP1A2*, *NAT1*, *NAT2*, *GSTM1*, *GSTT1*, or *MTHFR*) have been associated with biliary tract cancers (Hsing et al. 2008; Kukongviriyapan 2012). Genetic polymorphisms of the *IL10* and *VEGFA* genes are associated with high risk for gallbladder cancer (Hsing et al. 2008). Although there are a few experimental studies on microbes in relation to biliary tract cancers, clinical studies have shown associations of microbes and microbial dysbiosis with the development of biliary tract cancer (Table 4).

A metagenomic study of the fecal microbiome in patients with intrahepatic cholangiocarcinoma has revealed that amounts of four genera (*Lactobacillus*, *Actinomyces*,

Peptostreptococcaceae, and *Alloscardovia*) were increased in fecal specimens from patients with intrahepatic cholangiocarcinoma, compared with those from healthy individuals (Jia et al. 2019). In preliminary studies of the bile microbiome, dysbiosis in the bile microbiome was associated with biliary mucosal dysplasia or cholangiocarcinoma (Chen et al. 2019b; Pereira et al. 2017).

Epidemiologic studies have demonstrated associations of *Helicobacter* species, including *Helicobacter pylori*, *Helicobacter bilis*, and *Helicobacter hepatics*, with an increased risk of cholangiocarcinoma (Bulajic et al. 2002; Fukuda et al. 2002; Murphy et al. 2014; Segura-Lopez et al. 2015; Shimoyama et al. 2010; Zhou et al. 2013). Experimental evidence suggests that *Helicobacter bilis* can activate the NFKB signaling pathway and increase the production of VEGFA, which leads to enhancement of angiogenesis in human cholangiocarcinoma cell lines (Takayama et al. 2010). Clinical studies using metagenomic analyses have shown that *Bifidobacteriaceae*, *Enterobacteriaceae* and *Enterococcaceae* are enriched in tumor tissue specimens of cholangiocarcinoma (Chng et al. 2016), and that amounts of *Methylophilaceae*, *Fusobacterium*, *Prevotella*, *Actinomyces*, *Novosphingobium* and *Helicobacer pylori* were increased in cholangiocarcinoma tissue specimens compared with nontumor tissue specimens (Aviles-Jimenez et al. 2016).

Epidemiologic studies have shown that chronic *Salmonella typhi* infection is associated with an increased risk of gallbladder cancer (Nagaraja and Eslick 2014). Experimental evidence suggests that *Salmonella typhi* can induce malignant transformation in the $Apc^{Min/+}$ mouse model, murine gallbladder organoids, and fibroblasts that exhibit TP53 inactivation and MYC amplification through activation of the AKT and MAPK signaling pathways (Scanu et al. 2015).

Pancreatic cancer

Pancreatic cancer is associated with an extremely poor prognosis: the 5-year survival rate is 6–10% and approximately 367,000 new cases were diagnosed worldwide in 2015 (Kleeff et al. 2016). Although 10–20% of patients with pancreatic cancer have surgically resectable disease at the time of presentation, only 15–20% of those survive for 5 years or more. Cigarette smoking, a high intake of fat or meat, and diabetes mellitus are major risk factors for pancreatic cancer (Kleeff et al. 2016). Genetic variations as well as environmental exposures have been associated with the development of pancreatic cancer. Genetic polymorphisms associated with an increased risk for pancreatic cancer have been located either inside or near protein-coding genes that include *ABO*, *BCAR1*, *DAB2*, *DPP6*, *FOXQ1*, *HNF1B*, *HNF4G*, *GRP*, *NOC2L*, *NR5A2*, *ETAA1*, *SUGCT*, *PDX1*, *TERT*, *TFF1*, and *TP63* (Klein et al. 2018; Wolpin et al. 2014; Wu et al. 2011). Major germline mutations associated with an increased risk of pancreatic cancer includes mutations in the *STK11*, *CDKN2A*, or *BRCA2*. The pancreas is anatomically connected to the gastrointestinal tract via the pancreatic duct and communicates with the liver via the common bile duct (Thomas and Jobin 2020). An increasing body of evidence suggests possible roles of microbes in the development of pancreatic tumors (Table 4).

Pushalkar et al. have found that *Pseudomonas* and *Elizabethkingia* were enriched in tumor tissue and fecal specimens from patients with pancreatic cancer, and that intestinal microbes can migrate from the gut to the pancreas and inhibit T-cell-mediated immune responses against pancreatic tumors through the recruitment of myeloid-derived suppressor cells into the tumor microenvironment in a mouse model (Pushalkar et al. 2018). Metagenomic analyses of human pancreatic cancer microbiome by Riquelme et al. have found that high amount of *Pseudoxanthomonas*, *Streptomyces*, or *Saccharopolyspora* in pancreatic cancer tissue specimens was associated with high density of $CD8^+$ T-cells in tumor tissues and better overall survival (Riquelme et al. 2019). Analyses of fungal microbiome (mycobiome) in pancreatic cancer tissue specimens by Aykut et al. have revealed that Malassezia was enriched in human pancreatic cancer tissue specimens, and that Malassezia can potentiate the development of pancreatic tumors in a mouse model (Aykut et al. 2019).

Epidemiologic studies have shown positive associations of periodontitis with an increased risk of development of pancreatic cancer (Hujoel et al. 2003; Michaud et al. 2007). Human studies using metagenomic analyses suggest that high amounts of pathogenic periodontal microbes, such as *Neisseria elongata* and *Porphyromonas gingivalis*, in saliva are associated with an increased risk of development of pancreatic cancer (Farrell et al. 2012). Metagenomic analyses of the oral microbiome in patients with pancreatic cancer from a prospective cohort study have revealed that dysbiosis in the oral microbiome was associated with the incidence of pancreatic cancer, and that the presence of *Porphyromonas gingivalis* or *Aggregatibacter actinomycetemcomitans* in the oral cavity was associated with higher incidence of pancreatic cancer (Fan et al. 2018). Gaiser et al. have found enrichment of oral microbes, including *Fusobacterium nucleatum* and *Granulicatella adiacens*, in tumor tissue specimens of intraductal papillary mucinous neoplasms with high-grade dysplasia, which have been precursors to invasive pancreatic cancer (Gaiser et al. 2019). Mitsuhashi et al. have shown that a high amount of *Fusobacterium* species in tumor tissue is associated with worse prognosis in patients with pancreatic cancer (Mitsuhashi et al. 2015).

Emerging findings of the microbiology-MPE research

The concept and study designs of the microbiology-MPE research have been figured and discussed in our previous review (Hamada et al. 2019). Using this approach, we can examine associations of germline genetic variations and environmental exposures, including lifestyle factors, dietary patterns, medications, with specific cancer subtypes according to microbial profile, which are not detectable in conventional epidemiology and microbiology research. If the microbial data before cancer diagnosis are available in prospective studies, we can link microbial profile and the incidence of specific cancer subtypes classified by tumor molecular characteristics (e.g. somatic mutations and epigenetic alterations in tumor cells) or the tumor microenvironment (e.g. antitumor immunity). In patient survival analysis, the microbiology-MPE approach enables us to examine prognostic associations of the environmental exposures according to specific cancer subtypes classified by microbial profile. In addition, we can examine an association of microbial profile with patient survival according to specific cancer subtypes classified by molecular characteristics.

The envirome (or the exposome), which broadly includes dietary and lifestyle factors, have been implicated in the development of colorectal tumors. Smoking, adiposity (body fatness), alcohol drinks, and red and processed meat have been associated with an increased risk of colorectal cancer, whereas regular aspirin use, physical activity, plasma vitamin D level, and high intakes of dietary fiber, whole grains, calcium, and marine omega-3 fatty acid may decrease risk of colorectal cancer (Song et al. 2020). The microbiology-MPE studies have shown that a so-called prudent diet that is rich in whole grains and fiber was associated with a lower risk of colorectal carcinoma with detectable levels of *Fusobacterium nucleatum* but not with a lower risk of carcinoma without *Fusobacterium nucleatum* (Fig. 2A) (Mehta et al. 2017), and that an inflammatory dietary pattern (rich in red and processed meat, refined grains, and sugar) has been associated with a higher risk of *Fusobacterium nucleatum*-positive proximal colon carcinoma, but not with a risk of *Fusobacterium nucleatum*-negative proximal colon carcinoma (Fig. 2B) (Liu et al. 2018b). These findings support a potential role for the gut microbes in mediating the effect of diet on colorectal carcinogenesis. Although mechanistic studies have been a major part of microbiology research on carcinogenesis, insights from microbiology-MPE research would serve as particularly valuable evidence for the microbial etiologies and pathogenesis of human neoplasms.

The proportions of colorectal cancers with specific molecular features such as high-level MSI, high-level CIMP, and *BRAF* and *PIK3CA* mutations have been shown to gradually increase along the bowel subsites from rectum to ascending colon (Yamauchi et al. 2012) and these findings have been replicated in other datasets (Phipps et al. 2012; Phipps et al. 2015; Rosty et al. 2013). These findings led to the colorectal continuum concept that most likely reflected the influence of the gut microbiome on local tissue microenvironment and carcinogenesis. Studies have demonstrated that a high amount of *Fusobacterium nucleatum* in carcinoma tissue is associated with high-level MSI (Ito et al. 2015; Mima et al. 2015; Tahara et al. 2014), autophagy status (Haruki et al. 2019), lower density of T cells in tumor tissue (Mima et al. 2015), and worse patient survival (de Carvalho et al. 2019; Kunzmann et al. 2019; Mima et al. 2016b), and that the proportion of colorectal cancers containing high amounts of *Fusobacterium nucleatum* increased gradually along the bowel subsites from rectum to cecum (Mima et al. 2016a). In addition, our further analyses revealed that *Fusobacterium nucleatum* in tumor tissue was associated with lower-level tumor-infiltrating lymphocytes (TIL) in MSI-high colorectal carcinoma, while it was associated with high-level TIL in non-MSI-high carcinoma; these findings might reflect divergent effects of the bacteria on the tumor-immune microenvironment according to the amount of tumor neoantigens (Hamada et al. 2018). MSI-high colorectal cancers are genetically characterized by a hypermutator phenotype associated with a high number of neoantigens (Giannakis et al. 2016). These data would inform future mechanistic studies to examine the interplay of *Fusobacterium nucleatum* and tumor characteristics in colorectal carcinogenesis.

Future perspectives, challenges, and conclusions

Considering that oral health, diet, lifestyle, pharmacological factors (including antibiotics), probiotics, and prebiotics can influence the composition of intestinal microbiota (Biedermann et al. 2013; O'Keefe et al. 2015; Zitvogel et al. 2015), future investigations need to examine potential influences of those modifiable factors on the gut microflora and

tumorigenic processes. Although to date, no clinical trials demonstrate the efficacy of modulating the microbiome in the development or progression of gastrointestinal cancers, some clinical studies have shown the effect of microbiome modulation in inflammatory bowel diseases and toxicity of cancer chemotherapy. Fecal microbiota transplantation (FMT) has been effective treatment for recurrent or refractory *Clostridium difficile* infection (Costello et al. 2015; van Nood et al. 2013). Ulcerative colitis is a chronic inflammatory bowel disease characterized by colonic mucosal inflammation, and is associated with an increased risk of colorectal cancer (Castano-Milla et al. 2014). FMT has been shown to induce clinical remission and endoscopic improvement in active ulcerative colitis (Moayyedi et al. 2015; Paramsothy et al. 2017; Rossen et al. 2015). Probiotic refers to bacteria or a combination of live bacteria that confer a health benefit to hosts when consumed in adequate amounts (Suez et al. 2019). In 15 patients with colorectal cancer, administration of probiotics may reduce amounts of *Fusobacterium* and *Peptostreptococcus* (Hibberd et al. 2017). Patients with colorectal cancer who received 5-FU and *Lactobacillus rhamnosus* were less like to have diarrhea (Osterlund et al. 2007).

Escherichia coli and *Bacteroides fragilis* have been enriched in colorectal mucosal tissues from patients with familial adenomatous polyposis that is caused by germline *APC* mutations, suggesting a potential link between the microbiome and germline genetics in carcinogenesis. Further investigations need to examine potential combined influences of germline mutations and the microbiome on carcinogenesis in hereditary neoplasms. The integrative approach of microbiology-MPE can be a novel tool that potentially expands our knowledge of the etiologies and pathogenesis of cancers not only in the digestive system but also in other body sites. Future microbiology-MPE analyses can reveal additional links of host genetic variations and modifiable lifestyle factors with specific subtypes of neoplasms, which will contribute to the development of precision prevention and treatment strategies. With the advances in next-generation sequencing technologies, large population-based research on genomics, metagenomics, and other omics (epigenomics, transcriptomics, proteomics, and metabolomics) has become reality, but necessitates our efforts to new transdisciplinary frameworks of our science and research enterprise, including interdisciplinary education system (Ogino et al. 2012). Successful microbiology-MPE studies may be among research examples that can inform such efforts.

Although clinical studies have linked specific microbes and microbial dysbiosis to gastrointestinal cancers, there are considerable study-to-study differences in reported specific microbes and microbial dysbiosis, which may be due to limitations including small sample sizes, undefined tissue sampling sites, procedures for biospecimen collection, processing, and storage, methods for microbiome analysis, and limited data on clinical features and tumor molecular features. Challenges exist in the microbiology-MPE research, as previously discussed (Hamada et al. 2019; Ogino et al. 2011). Sample size is generally limited based on biospecimen availability, which can also lead to selection bias. Hence MPE investigators should make efforts to maximize the number of cases available for research. Statistical analysis methods to test hypothesis on etiological heterogeneity between disease subtypes (Lu et al. 2018; Wang et al. 2015b; Wang et al. 2016) and to address missing data (Liu et al. 2018a; Nevo et al. 2018) in MPE research have been validated in various study designs. Standardized procedures for collecting, processing, and storing biospecimens, and

methods of microbiome analyses are required for collaborative projects on microbiology-MPE. In addition, transdisciplinary education and transdisciplinary research teams are also important to perform the MPE research due to the nature of microbiology-MPE. We have started training programs of molecular pathology, epidemiology, microbiology, and immunology for physicians and researchers (e.g. Lectures and/or hands-on training of epidemiology and biostatistics in departments of pathology).

In conclusion, accumulating evidence supports the influential role of the microbiome in cancers of the digestive system and likely neoplasms of other organs and tissues. The microbiology-MPE research can provide a novel methodological framework to integrate data on host genetic variations and modifiable factors into analyses of the microbiome and tumor characteristics, to generate novel insights into tumor-immune-microbiome interactions. This new type of research effort can inform cancer prevention and treatment strategies targeting the microbiome.

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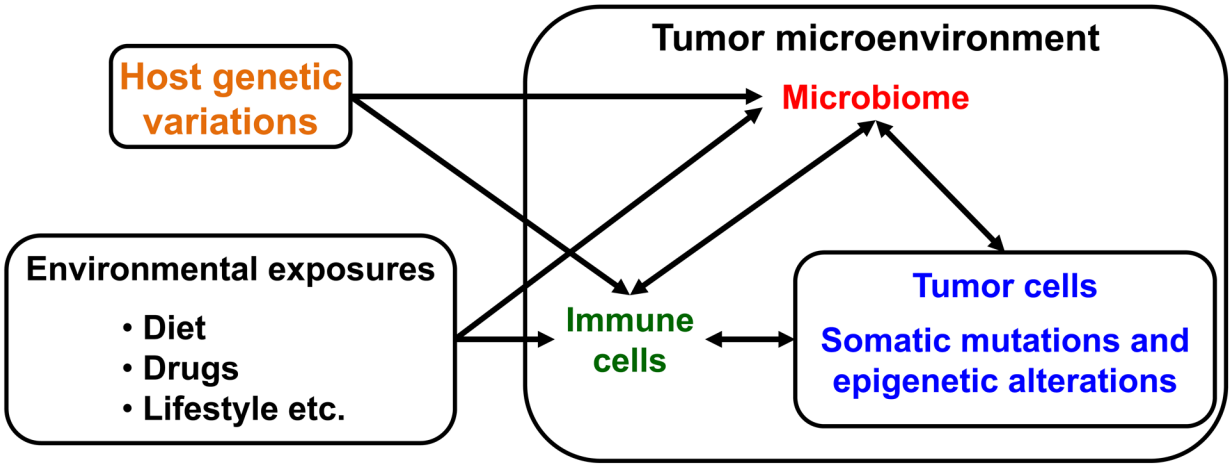

Fig. 1.

Influences of host genetic variations, microbiome, immunity, and environmental exposures on tumor genetic and epigenetic alterations. Gastrointestinal cancers develop through the accumulation of somatic mutations and epigenetic alterations in tumor cells with complex influences of microbiome and immunity in the tumor microenvironment, host genetic variations, and environmental exposures.

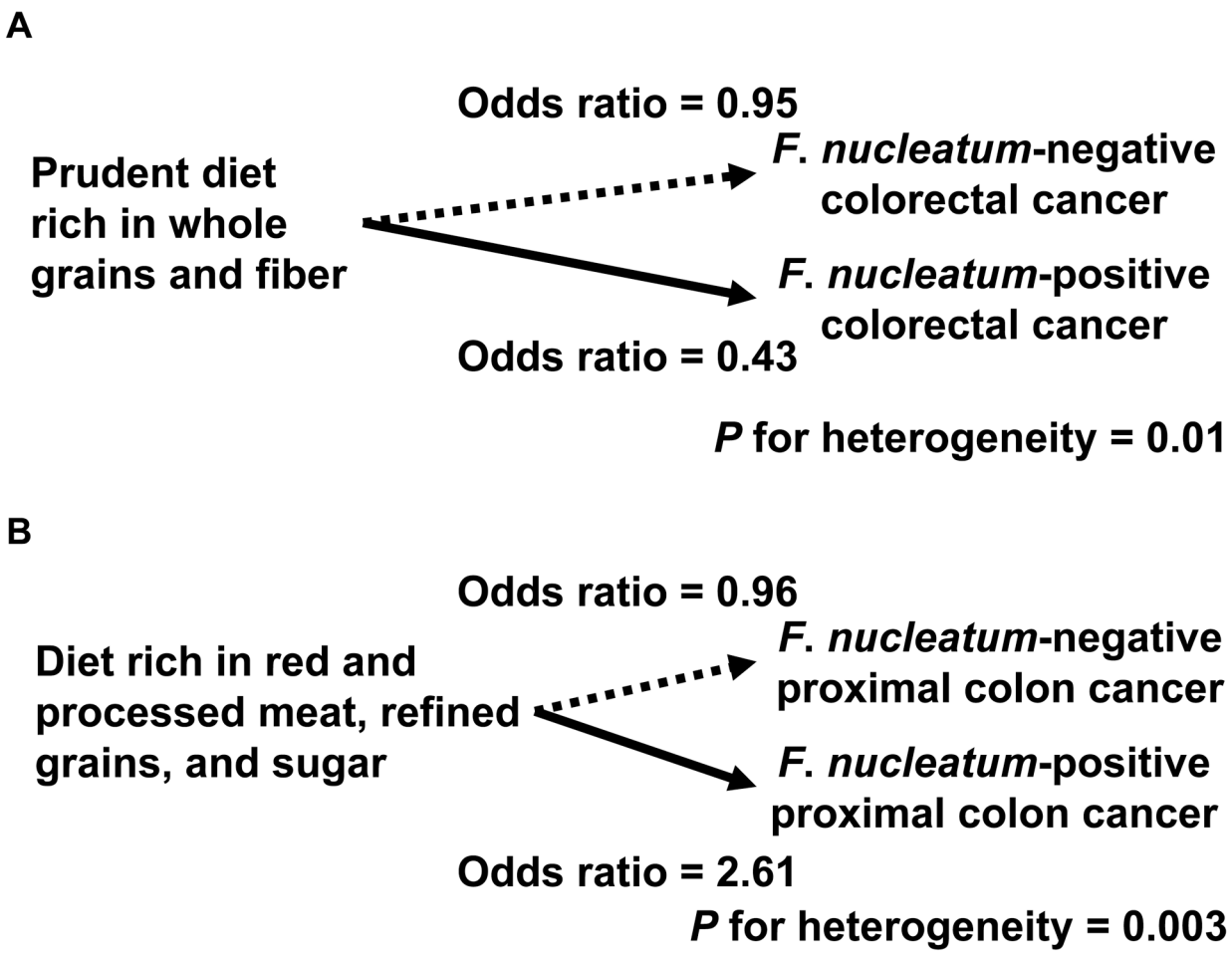

Fig. 2.

Illustration of the microbiome-MPE approach using tumor microbial status. *Fusobacterium nucleatum* can inhibit antitumor immune response and potentiate colonic neoplasia development in animal models. Using data on colorectal cancer cases and tumor microbial profile in two U.S. nationwide prospective cohort studies (the Nurses' Health Study and the Health Professionals Follow-up Study), the microbiome-MPE studies have revealed that a so-called prudent diet that is rich in whole grains and fiber was associated with a lower risk of colorectal carcinoma with detectable levels of *Fusobacterium nucleatum* but not with a lower risk of carcinoma without *Fusobacterium nucleatum* (A), and that an inflammatory dietary pattern (rich in red and processed meat, refined grains, and sugar) was associated with a higher risk of *Fusobacterium nucleatum*-positive colorectal carcinoma, but not with a risk of *Fusobacterium nucleatum*-negative carcinoma (B).

Table 1.

Major studies of interactions between host genetic variations and environmental exposures in gastrointestinal cancers

Environmental exposure	Gene (References)
Esophageal adenocarcinoma	
Smoking	*ADH1B* and *ALDH2* (Tanaka et al. 2010) *RNF144A* (Dong et al. 2018)
Recurrent gastroesophageal reflux disease symptoms	*RND3* (Dong et al. 2018).
Gastric adenocarcinoma	
Helicobacter pylori infection	*PSCA* (Cai et al. 2017)
Alcohol drinking	*SLC52A3* (Cai et al. 2017)
Colorectal carcinoma	
Processed meat or total red meat	*NAT2* (Wang et al. 2015a)
Vegetables	*EIF3H* (Hutter et al. 2012)
Smoking	*SMAD7* and *TGFBR1* (Zhong et al. 2013)
Alcohol drinking	*MFSD14B* (Gong et al. 2016) *DUSP10* (Song et al. 2018)
Aspirin and/or anti-inflammatory drugs use	*MGST1, IL16* (Nan et al. 2015; Nan et al. 2013).
Use of estrogen plus progesterone therapy	*CYP24A1* (Garcia-Albeniz et al. 2016)
Hepatocellular carcinoma	
Hepatitis B virus infection	*STAT4, HLA-DQA1* (Jiang et al. 2013)
Pancreatic cancer	
Smoking	*XRCC3* (Duell et al. 2008) *EPHX1* (Jang et al. 2012)
Obesity	*IGF1* (Nakao et al. 2011) *FTO* and *ADIPOQ* (Tang et al. 2011)
Alcohol drinking	*IGF2R, IRS1* (Dong et al. 2012)
Diabetes mellitus	*PTGS1* (Tang et al. 2014)

Table 2.

Specific microorganism or dysbiosis of microbiome in esophageal and gastric cancers

Specific microorganism or dysbiosis of the microbiome	Findings (References)
	Esophageal cancer
Oral microbiome	• Low microbial diversity in the oral cavity was associated with the presence of esophageal squamous cell carcinoma (Chen et al. 2015; Yu et al. 2014).
	• High amount of *Tannerella forsythia* in the oral cavity was associated with the presence of esophageal adenocarcinoma (Peters et al. 2017).
Fusobacterium nucleatum	• The amount of *Fusobacterium nucleatum* was higher in esophageal carcinoma tissue than in adjacent nontumor tissue. High amount of *Fusobacterium nucleatum* in esophageal carcinoma tissue was associated with shorter patient survival, and the amount of *Fusobacterium nucleatum* correlated with tumor expression of the chemokine CCL20, which has been shown to promote the accumulation of regulatory T cells (Yamamura et al. 2016).
Escherichia coli	• High amount of *Escherichia coli* in esophageal tissue was associated with Barrett's esophagus and esophageal adenocarcinoma (Zaidi et al. 2016).
Campylobacter concisus	• High amount of *Campylobacter concisus* in esophageal tissue was associated with Barrett's esophagus (Blackett et al. 2013).
	Gastric cancer
Helicobacter pylori	• The infection with *Helicobacter pylori* in gastric tissue is associated with increased risk of gastric cancer, and *Helicobacter pylori* is categorized as a class I carcinogen by the World Health Organization (Ajani et al. 2017).
Gastric mucosal microbiome	• Microbial diversity decreased gradually from gastritis to intestinal metaplasia to gastric cancer (Aviles-Jimenez et al. 2014).
	• Microbial diversity and the amount of *Helicobacter* were decreased in gastric cancer tissue, and oral microbes, including *Parvimonas micra*, *Peptostreptococcus stomatis*, and *Fusobacterium nucleatum*, were significantly increased in both cardia and non-cardia gastric cancer tissue (Coker et al. 2018; Ferreira et al. 2018; Liu et al. 2019).
	• Low amount of *Lactobacillales* in gastric nontumor tissue was associated with metastatic gastric cardia adenocarcinoma (Yu et al. 2017).
Tongue-coating microbiome	• High amount of *Firmicutes* and low amount of *Bacteroidetes* in the tongue coating microbiome were associated with gastric cancer (Wu et al. 2018).

Table 3.

Specific microorganism or dysbiosis of microbiome in colorectal cancer

Specific microorganism or dysbiosis of the microbiome	Findings (References)
	Colorectal cancer
Oral microbes	• Members of oral microbes, including *Gemella*, *Peptostreptococcus*, *Parvimonas*, and *Leptotrichia*, were enriched in colorectal adenocarcinoma tissue (Nakatsu et al. 2015).
	• Members of oral microbes, including *Parvimonas micra*, *Peptostreptococcus stomatis*, and *Peptostreptococcus anaerobius*, were enriched in fecal specimens from patients with metastatic colorectal adenocarcinoma (Thomas et al. 2019; Wirbel et al. 2019; Yachida et al. 2019).
	• *Peptostreptococcus anaerobius* can activate the NFKB signaling pathway in colorectal cancer cell lines and inhibit T-cell-mediated immune responses against colorectal tumors through the recruitment of myeloid-derived suppressor cells and tumor-associated macrophages into the tumor microenvironment in the $Apc^{Min/+}$ mouse model (Long et al. 2019).
Viral microbiome	• Some specific viral taxa, such as *Orthobunyavirus*, *Inovirus*, or *Tunalikevirus*, were enriched in fecal specimens from patients with colorectal cancer, and dysbiosis of intestinal viral microbiome was associated with worse clinical outcomes in colorectal cancer (Nakatsu et al. 2018).
Fungal microbiome	• The amount of Malasseziomycetes was increased, while the amounts of Saccharomycetes and Pneumocystidomycetes were decreased in fecal specimens from patients with colorectal cancer compared to cancer-free individuals (Coker et al. 2019).
Fusobacterium nucleatum	• The amount of *Fusobacterium nucleatum* was increased in tumor tissue and fecal specimens from patients with colorectal cancer (Mima et al. 2017).
	• *Fusobacterium nucleatum* was detected not only in primary colorectal tumors, but also in metastatic lymph nodes and liver metastases (Bullman et al. 2017; Yu et al. 2016).
	• *Fusobacterium nucleatum* can inhibit T-cell-mediated immune responses against colorectal tumors through the recruitment of myeloid-derived suppressor cells into the tumor microenvironment in the $Apc^{Min/+}$ mouse model (Kostic et al. 2013). The Fap2 protein of *Fusobacterium nucleatum* has been shown to interact with T cell immunoglobulin and ITIM domain receptor and inhibit activities of NK cells and T cells (Gur et al. 2015).
Campylobacter species	• The amount of *Campylobacter* species was enriched in colorectal cancer tissue and fecal specimens from patients with colorectal cancer (Warren et al. 2013; Wu et al. 2013).
Escherichia coli	• *Escherichia coli* was enriched in colorectal cancer tissue (Bonnet et al. 2014; Kohoutova et al. 2014).
Bacteroides fragilis	• *Bacteroides fragilis* was enriched in colorectal cancer tissue (Boleij et al. 2015; Toprak et al. 2006; Wei et al. 2016).
	• Enterotoxigenic *Bacteroides fragilis* induces T helper 17 cells, which activate the STAT3 signaling pathway in tumor cells in the $Apc^{Min/+}$ mouse model (Wang et al. 2009; Wu et al. 2009).
Enterococcus faecalis	• *Enterococcus faecalis* was detected significantly more often in fecal specimens from colorectal cancer cases than controls (Balamurugan et al. 2008).
Streptococcus gallolyticcus	• The amount of *Streptococcus gallolyticcus* in human colorectal carcinomas was higher than in control tissue (Abdulamir et al. 2010; Boleij and Tjalsma 2013; Gupta et al. 2010).

Table 4.

Specific microorganism or dysbiosis of microbiome in hepatobiliary-pancreatic cancers

Specific microorganism or dysbiosis of the microbiome	Findings (References)
	Hepatocellular carcinoma
Fecal microbiome	• The amount of *Gemmiger*, *Parabacteroides*, and *Paraprevotella* were increased in fecal specimens from patients with hepatocellular carcinoma, compared with those with liver cirrhosis (Ren et al. 2019).
Helicobacter species	• *Helicobacter* species were detected in hepatocellular carcinoma tissue specimens (Huang et al. 2004; Kruttgen et al. 2012; Rocha et al. 2005). • *Helicobacter hepaticus* can suppress the innate immunity to recognize and eliminate tumor cells in a mouse model of hepatocellular carcinoma (Fox et al. 2010).
Escherichia coli	• The amount of *Escherichia coli* was increased in fecal specimens from patients with hepatocellular carcinoma (Grat et al. 2016).
Clostridium species	• *Clostridium* species can inhibit the accumulation of hepatic natural killer T cells and suppress antitumor immune response in mouse models of both primary and secondary liver tumors (Ma et al. 2018)
	Biliary tract cancer
Fecal microbiome	• The amounts of *Lactobacillus*, *Actinomyces*, *Peptostreptococcaceae*, and *Alloscardovia* were increased in fecal specimens from patients with intrahepatic cholangiocarcinoma compared with healthy individuals (Jia et al. 2019).
Bile microbiome	• Dysbiosis in the bile microbiome was associated with biliary mucosal dysplasia or cholangiocarcinoma (Chen et al. 2019b; Pereira et al. 2017).
Helicobacter species	• The presence of *Helicobacter pylori*, *Helicobacter bilis*, or *Helicobacter hepaticus* in tumor tissue was associated with increased risk of biliary tract cancers (Bulajic et al. 2002; Fukuda et al. 2002; Murphy et al. 2014; Segura-Lopez et al. 2015; Shimoyama et al. 2010; Zhou et al. 2013).
Biliary mucosal microbiome	• *Bifidobacteriaceae*, *Enterobacteriaceae* and *Enterococcaceae* were enriched in cholangiocarcinoma tissue (Chng et al. 2016). • The amount of *Nesterenkoni*a was decreased, whereas the amounts of *Methylophilaceae*, *Fusobacterium*, *Prevotella*, *Actinomyces*, *Novosphingobium* and *Helicobacter pylori* were increased in extrahepatic cholangiocarcinoma tissue (Aviles-Jimenez et al. 2016).
Salmonella typhi	• Chronic *Salmonella typhi* infection was associated with gallbladder cancer (Nagaraja and Eslick 2014).
	Pancreatic cancer
Pancreatic tissue microbiome	• *Pseudomonas* and *Elizabethkingia* were enriched in pancreatic cancer tissue. Intestinal microbes can migrate from the gut to the pancreas and inhibit T-cell-mediated immune responses against pancreatic tumors through the recruitment of myeloid-derived suppressor cells into the tumor microenvironment in a mouse model (Pushalkar et al. 2018). • The presence of *Pseudoxanthomonas*, *Streptomyces*, or *Saccharopolyspora* in pancreatic cancer tissue was associated with high density of $CD8^+$ T-cells in tumor tissue and better overall survival (Riquelme et al. 2019).

Specific microorganism or dysbiosis of the microbiome	Findings (References)
Fungal microbiome	• Malassezia was enriched in pancreatic carcinoma tissue (Aykut et al. 2019).
Oral microbiome	• High amounts of *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Neisseria elongata*, and *Streptococcus mitis* in the oral cavity were associated with pancreatic cancer (Farrell et al. 2012). • High amounts of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* in the oral cavity were associated with pancreatic cancer (Fan et al. 2018).
Fusobacterium	• *Fusobacterium nucleatum* was detected in tumor tissue of intraductal papillary mucinous neoplasms with high-grade dysplasia (Gaiser et al. 2019). • High amount of *Fusobacterium* species in tumor tissue was associated with worse prognosis in pancreatic cancer (Mitsuhashi et al. 2015).