Minireview

The Human Microbiome and Cancer

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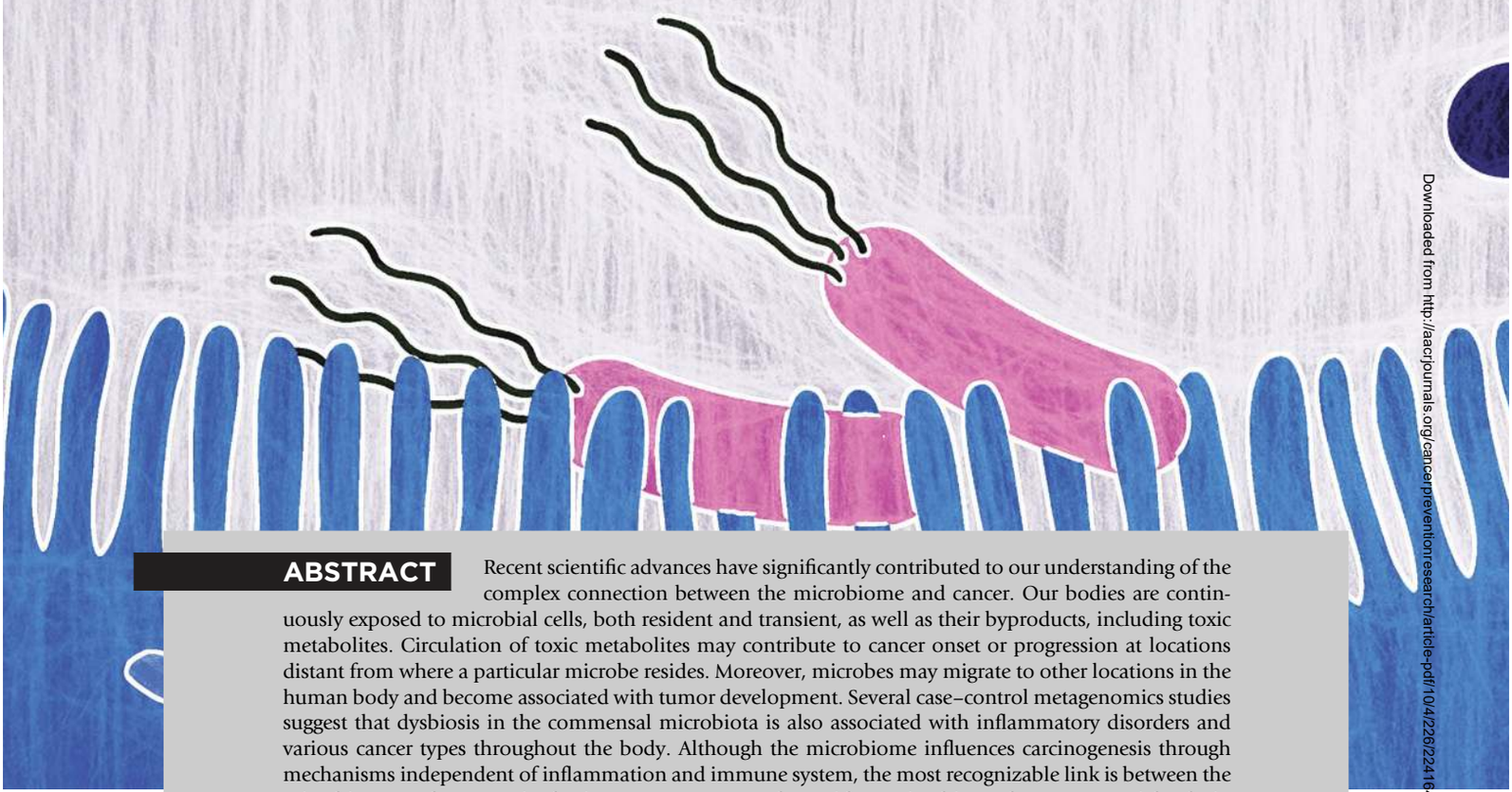

ABSTRACT

Recent scientific advances have significantly contributed to our understanding of the complex connection between the microbiome and cancer. Our bodies are continuously exposed to microbial cells, both resident and transient, as well as their byproducts, including toxic metabolites. Circulation of toxic metabolites may contribute to cancer onset or progression at locations distant from where a particular microbe resides. Moreover, microbes may migrate to other locations in the human body and become associated with tumor development. Several case–control metagenomics studies suggest that dysbiosis in the commensal microbiota is also associated with inflammatory disorders and various cancer types throughout the body. Although the microbiome influences carcinogenesis through mechanisms independent of inflammation and immune system, the most recognizable link is between the microbiome and cancer via the immune system, as the resident microbiota plays an essential role in activating, training, and modulating the host immune response. Immunologic dysregulation is likely to provide mechanistic explanations as to how our microbiome influences cancer development and cancer therapies. In this review, we discuss recent developments in understanding the human gut microbiome's relationship with cancer and the feasibility of developing novel cancer diagnostics based on microbiome profiles. *Cancer Prev Res; 10(4); 226–34. ©2017 AACR.*

An Overview of the Human Microbiome, Immunity, and Cancer

Obtaining a comprehensive view of the microbial ecosystems that are associated with the human body (the human microbiome) has become possible with advances in culture-independent "omics" analyses using next-generation sequencing (NGS) techniques (1, 2). Several studies have suggested a correlation between our microbiome and various diseases, including metabolic disorders, gastrointestinal complexities, and infectious diseases (3–6), and to date, thousands of articles focused on the human microbiome in health and disease conditions have been published. The estimated trillions of microbes that inhabit the human body establish a beneficial relationship with the host, but it is clear that dysbiotic relationships can develop, some of which are thought to result in the development of inflammatory diseases and cancers. Several animal models have provided insight on possible mechanisms

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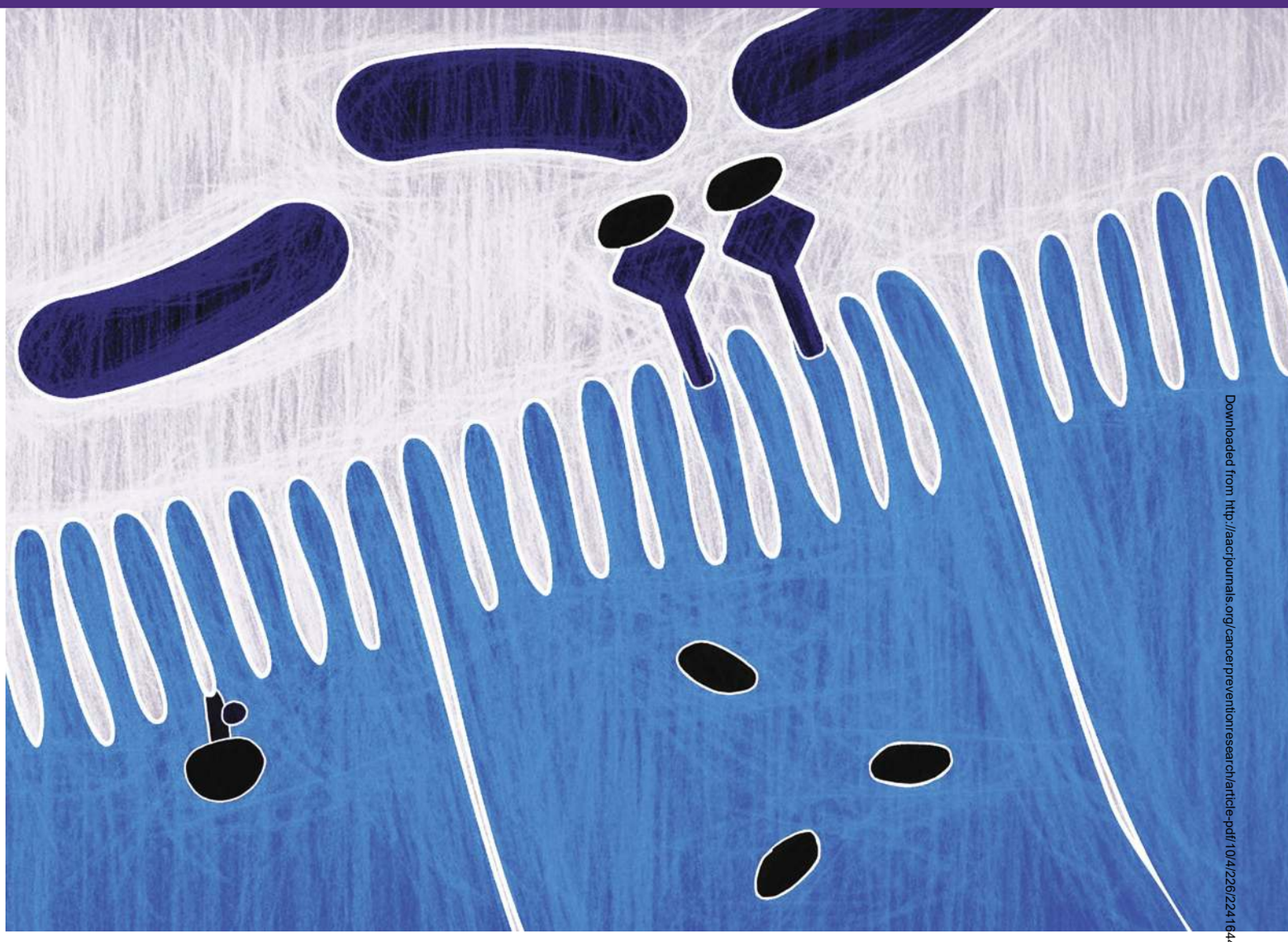

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for microbial cancer triggers, although the situation is complex as both tumor-promoting and antitumor effects have been observed in the presence or absence of particular microbial species (7–11). The microbiota may also induce carcinogenesis through the release of genotoxins that can damage host DNA. This can directly promote carcinogenesis. Bacterial toxins and tumor-promoting metabolites may also lead to chronic inflammation, which in turn may trigger damage to host cells and tissue linings (12, 13). In addition, immunologic dysregulation in response to the resident microbiome may lead to tumor growth (7). There is also an increasing understanding of the composition of the human virome (viruses and bacteriophages), particularly in the gut and oral cavity (14–17). The normal gut virome is proposed to have a role in protective immunity during gut inflammation (18).

The variability of microbial populations and physiologic environments at different sites of the human body suggests that microbial mechanisms and species that are involved in cancer onset will also vary depending on the location. Impaired microbiota can facilitate carcinogenesis through a variety of mechanisms that have been reported in the literature (12, 13). This minireview focuses on cancers promoted by pathogens and immune system–mediated mechanisms.

Cancers triggered or promoted by specific pathogens

Pathogens promote cancer development through well-described genetic mechanisms (13). There are 10 specific biological agents that have been designated by the International Agency for Cancer Research as carcinogenic to humans (19). One of them, *Helicobacter pylori* (*H. pylori*) colonizes the gastric mucosa of half of the world's population (20) and induces chronic gastric inflammation, which can progress toward gastric carcinoma. Although only about 1% to 3% of *H. pylori*–colonized individuals develop gastric cancer, it substantially contributes to global cancer mortality (21–23). The mechanism by which *H. pylori* induces onset of gastric cancer is largely attributed to the presence of cytotoxin-associated gene A (CagA) and secretion of virulence factors, such as VacA, urease, and NapA2, to promote chronic inflammation, oxidative stress, and host DNA damage, which can contribute to carcinogenesis (24–26). The pathogen uses the type IV secretion system to translocate CagA to gastric epithelial cells, which aberrantly modulates β-catenin to increase propensity for gastric

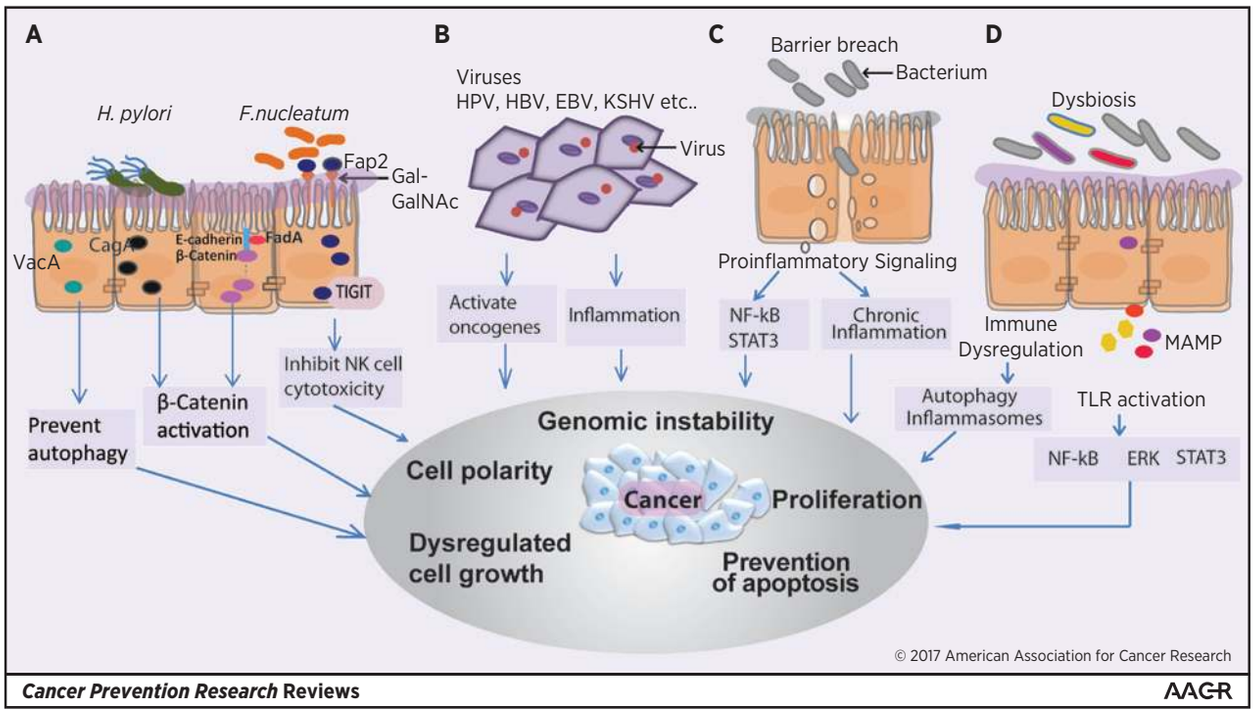

Figure 1.

Mechanisms by which microbes promote carcinogenesis. **A,** Microbes inject effectors into the host cells. These effectors modulate the Wnt/β-catenin signaling by activating β-catenin. For example, *H. pylori* effector protein CagA interacts with E-cadherin and disassociates the E-cadherin/β-catenin protein complex, which leads to increased accumulation of cytoplasmic and nuclear β-catenin. β-Catenin complexes with TCF/LEF transcription factors and activates target gene expression. *F. nucleatum* modulates β-catenin signaling via its FadA protein. Aberrant β-catenin signaling is associated with tumorigenesis and progression. Prolonged exposure to *H. pylori* protein VacA prevents autophagy. The interaction between *F. nucleatum* Fap2 protein and host polysaccharide (Gal-GalNAc) mediates *F. nucleatum* colonization in colorectal cancer. *F. nucleatum* mediates tumor-immune evasion via TIGIT. The Fap2 protein secreted by *F. nucleatum* interacts with TIGIT and inhibits natural killer (NK) cell–mediated immunosurveillance of cancer. **B,** Several human viruses, including HPV, HBV, HCV, HTLV, EBV, and KSHV, are known to cause various cancers. They encode oncoproteins and pathways that have been shown to transform nonpermissive cell types and induce tumors in animal models. During active infection and latent phase, these cancer-causing viruses modify epigenetic programs and impair DNA repair mechanisms in various ways. These subversions lead to host genome instability, a hallmark of carcinogenesis. **C,** Proinflammatory signaling, as a result of barrier failure, induces genomic instability and chronic inflammation, hallmarks for carcinogenesis. **D,** Dysbiosis and altered microbiota–host interaction can induce carcinogenesis through various mechanisms; increased bacterial translocation and immune dysregulation are shown as examples. Microorganism-associated molecular patterns (MAMP) are recognized by TLRs in several cell types. Activation of TLRs by MAMPs and other microbial products contributes to carcinogenesis. For example, TLR4, the receptor for LPS component of the Gram-negative bacterial cell wall, promotes hepatocellular and pancreatic cancer colon cancer. TLR-induced NF-κB and STAT3 activation are key cancer-promoting signaling pathways. Microbiota-induced immune dysregulation can initiate inflammasomes-associated immune response and TLR-activated autophagy.

cancer (27) (Fig. 1A). Chronic bacterial infections can also promote host genetic instability (28). For example, mice chronically infected with *H. pylori* show a 4-fold increase in mutation frequency compared with uninfected mice (29). However, studies in germ-free mice have shown that *H. pylori* alone is less likely to induce gastric cancer. The germ-free mice co-colonized with complex intestinal flora and *H. pylori* synergistically promote invasive gastrointestinal intraepithelial neoplasia (GIN) in 80% of mice, whereas only 10% of *H. pylori* only–colonized males developed GIN, with less severe gastric lesions and significantly delayed onset of GIN (30). The mice co-colonized with complex intestinal flora and *H. pylori* developed more severe gastric pathology, and the mice co-colonized with *H. pylori* and restricted altered Schaedler flora (*Clostridium* species, *Lactobacillus murinus*, and Bacteriodes species) were only slightly less severe (31). Interestingly *H. pylori* infection is also associated with decreased risk of esophageal adenocarcinoma, highlighting the complexity of microbial effects on tissue-specific carcinogenesis (32).

Metagenomics and transcriptomics studies provide insights into the relationship between *Fusobacterium nucleatum* (*F. nucleatum*) and colorectal cancer. Several case–control human cohort studies found higher abundance of *Fusobacterium* spp. in colorectal adenomas compared with controls (33, 34). *F. nucleatum* introduction to a mouse model of intestinal tumorigenesis accelerated tumor development and modulated the tumor microenvironment through an NF-κB–driven proinflammatory response without inducing more widespread inflammation (35). Rubinstein and colleagues demonstrated that *F. nucleatum* promotes colorectal cancer by modulating E-cadherin/β-catenin signaling via its FadA protein (Fig. 1A; ref. 36), FadA binding to E-cadherin inhibits the latter's tumor-suppressive activity. Conversely, inhibition of FadA binding to E-cadherin using an inhibitory peptide abolishes the host inflammatory response and tumor growth (36). A recent study by Abed and colleagues investigated mechanisms underlying fusobacterial attachment to and invasion of colonic adenomas and colorectal cancer (37). The investigators observed that a host

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polysaccharide, Gal-GalNAc, is overexpressed in colorectal cancer and readily recognized by fusobacterial protein Fap2 to mediate *F. nucleatum* attachment to colorectal cancer (37) (Fig. 1A). *F. nucleatum* also mediates tumor-immune evasion via the T-cell immunoreceptor with Ig and ITIM domains (TIGIT). The Fap2 proteins, secreted by *F. nucleatum*, interact with TIGIT and inhibit the natural killer cell-mediated immunosurveillance of cancer (Fig. 1A; ref. 78).

Cancers promoted by viruses

The composition and role of the human virome in health is not well understood. However, there are viruses that are known to cause various cancers, some of which are sufficiently prevalent in the population to be considered part of the human virome. Recognized associations include human papillomaviruses (HPV) causing cervical carcinoma, hepatitis B (HBV) and C viruses (HCV) being the causative agents of hepatocellular carcinomas, human T-cell leukemia virus-1 (HTLV) being involved in T-cell leukemia, Epstein–Barr virus (EBV) being involved in B-cell lymphoproliferative diseases and nasopharyngeal carcinoma, and Kaposi sarcoma–associated herpesvirus (KSHV) being the etiologic factor for Kaposi sarcoma and primary effusion lymphomas (38–40). Human polyomaviruses such as Merkel cell polyomavirus (MCV) and Simian Virus 40 (SV40) are implicated in Merkel cell carcinoma (MCC) and mesothelioma, respectively (38, 39). In addition, MCV, which is highly prevalent virus in the general population, can lead to an aggressive form of skin cancer in the elderly and immunosuppressed individuals (41). These viruses contributed to about 1.3 million new cancer cases worldwide in 2008, demonstrating the importance of fully understanding their biology (19). The mechanisms by which these viruses cause cancer are quite complex. They encode oncoproteins and pathways that have been shown to transform nonpermissive cell types and induce tumors in animal models (38–40). During active infection, these cancer-causing viruses exploit host cell machinery to perform their own replication, including altering cellular structures, manipulating signaling pathways, modifying epigenetic programs, and impairing DNA repair mechanisms in various ways. Together, these subversions ultimately lead to genome instability, a hallmark of cancer (Fig. 1B; ref. 39). There is the added complication in that many of these viruses either integrate into the host genome (HPV, HTLV-1, and HBV among others) or are maintained as latent episomal genomes (EBV and KSHV), resulting in lifetime infections. For HPV, integration of its genome into the host is a central mechanism of oncogenesis because it results in the overexpression of the viral E6 and E7 genes, which synergistically act to immortalize host cells (38). The MCV genome is clonally integrated in the majority of MCC tumors and its regulatory small T antigen acts as a potent oncogene capable of inducing cell transformation (42, 43). For the latent viruses, even though almost all the viral gene expression is silenced, certain viral genes, including oncogenes, are expressed and manipulate pathways that can lead to genome instability (38, 39).

The epidemiologic association of these viruses with cancer is complicated by the fact that several viruses are highly prevalent in the human population. However, the malignancies that they are associated with are relatively rare and require genetic and/or environmental cofactors to develop. For example, seroprevalence of EBV is >80% in the United States (44). EBV is the causative agent of, and is associated with, all cases of nasopharyngeal cancer, which has particularly high incidence in specific geographic locations, suggesting that there are additional important cofactors for the development of disease (38). The virus may also act as a cofactor, as with Burkitt lymphoma where EBV is present in nearly 100% of Burkitt lymphoma cancers, but is not itself the causative agent (45). Burkitt lymphoma is caused by chromosomal translocations that deregulate the proto-oncogenic c-*myc* gene. There is evidence that Burkitt lymphoma cofactors EBV and malaria protect cells from c-*myc*–induced apoptosis and expand the number of EBV^+ germinal center cells from which the lymphoma arises, respectively (46, 47). EBV is also associated with a subset of cases of Hodgkin disease and gastric cancers but is not causative (38). Interestingly, EBV viral gene expression is distinct in each of these malignancies because they arise at different stages of the viral life cycle (45). The varied interactions of EBV and other cofactors in a number of cancer types demonstrate the complicated interplay of contributing factors in cancer genesis and progression.

Barrier failure and microbial toxins

Anatomic separation of intestinal microbiota from the host epithelial cells is critical for regulating immune activation and upholding mutualistic host–microbial associations (12, 48). The goblet cells produce intestinal mucus and Paneth cells produce antimicrobial peptides, which contribute to the separation of host and microbial compartments across the mucosal interface, which limits interaction between the microbiome and immune system (49, 50). Disrupted barrier function may trigger inflammation and carcinogenesis. Ulcerative colitis and Crohn disease are well-known examples of intestinal barrier dysfunction and contribute to the risk of colon cancers (51–53) (Fig. 1C). A genome-wide association study suggests an association between colorectal tumor risk and polymorphisms in crucial barrier proteins, such as laminins (13, 54). Experiments in laboratory animals have shown that reduction of mucus or induced barrier failure increase the circulation of carcinogens through a disrupted gut, leading to the development of intestinal adenocarcinoma as well as tumors in distant organs (55, 56).

Impaired barrier function allows bacterial access to intestinal epithelium, which enables delivery of toxins. Bacterial toxins, such as colibactin-expressing *Escherichia coli* (encoded within the *pks* genomic island), potentiate colorectal cancer in azoxymethane-exposed mice (57). Toxins produced by enterotoxigenic *Bacteroides fragilis* (*B. fragilis*) have been associated with acute inflammatory bowel disease (58), and colorectal neoplasia, especially in late-stage colorectal cancer (59). Similarly, several Gram-negative bacteria produce cytolethal distending toxin (CDT) that together with colibactin can cause DNA damage in mammalian cells. Chronic exposure to CDT promotes genomic instability in fibroblasts and colon epithelial cells (60). As stated earlier, genome instability is a hallmark of cancer.

Intestinal microbiota and their metabolites impact the development of cancer in sites distant from the intestine. For example, the liver does not contain a known microbiome. Yet, intestinal bacteria promote hepatocellular carcinoma (also caused by HBV and HCV) via inflammatory microorganism-associated molecular patterns and bacterial metabolites, which can circulate to distant sites (8, 13, 61). Sustained accumulation of lipopolysaccharide (LPS), a component of the Gram-negative bacterial cell wall, also promotes inflammation-associated hepatocarcinogenesis in animal models (61). Although mouse models have shown that gut commensal microflora and dietary fiber may protect against

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colonic inflammation and colon cancer through the microbe-produced metabolite butyrate (62–64), data from another study show the opposite effect (65). These studies, which are outside of the scope of the current review, highlight the issues when comparing microbiome studies across different research groups, as well as challenges in translating research data to consensus guidelines for dietary interventions to prevent cancer risks. Further investigation is required to delineate the role of butyrate and other diet-induced metabolites in carcinogenesis.

Gut microbiome and cancer

Although findings that associate the human microbiome with cancers are preliminary in nature, some hint at possible new microbe–cancer relationships that were not observed before the advent of high-throughput sequencing. This is likely due to the difficulty associated with cultivating microbial species, with an estimated less than 30% of human microbial species being culturable in the laboratory, and recent studies have suggested in some cases polymicrobial disease causation. In addition to human studies, there have been many studies performed in animal models, and some of these observations are outlined below.

One of the most deadly cancers is esophageal cancer. This is a disease that evolves from inflammation due to reflux esophagitis to metaplasia (Barrett esophagus; refs. 66, 67). The disease is possibly the result of several complicating factors, including antibiotics usage, diet, and smoking. Recent studies have shown a potential role of the microbiome in the esophagus in healthy and disease conditions (68). Microbiome analyses of the normal and esophagitis or Barrett esophagus biopsy samples reveal a significant difference between the microbiome of normal esophagus, which is dominated by the genus *Streptococcus* and the microbiome of esophagitis and Barrett esophagus with an increase in the relative abundance of Gram-negative anaerobic species (69). Similarly, Gall and colleagues observed that *Streptococcus* was the most prevalent genus in normal esophagus or reflux esophagitis versus *Veillonella* in Barrett esophagus; *Fusobacterium* was found only in patients with reflux esophagitis or Barrett esophagus but not in a normal esophagus (70). Another study in Barrett esophagus cohort found an association between the ratio of *Streptococcus* to *Prevotella* species and abdominal obesity as well as hiatal hernia length, which are two known esophageal adenocarcinoma risk factors in Barrett esophagus (70). To address a role for infectious disease species and the human microbiome in this disease etiology, our team recently performed NGS on gastroesophageal reflux disease samples derived from 121 subjects in different phenotypic groups (unpublished data). Samples for NGS were collected from the mouth, esophagus, stomach, and colon, and the resulting sequences clustered into 1,607 operational taxonomic units. We observed that the overall community composition was affected by body site and disease phenotype. Several bacterial phyla had significant correlations with disease stage. In the esophagus, *Firmicutes* was the only phylum with a significant positive correlation to disease.

Expression of pattern recognition receptors, such as Toll-like receptors (TLR), is known to be progressively increased in different stages of gastric cancer (Fig. 1D; refs. 71, 72). Whereas TLRs are localized to the apical and basolateral compartments in normal gastric epithelial cells, they become homogeneously distributed in tumor cells (73, 74). Interestingly, a similar paradigm has recently been observed in esophageal cancer. When the expression of TLR1, TLR2, TLR4, and TLR6 was examined in esophageal specimens from patients using IHC, expression for all of these TLRs was found to increase in Barrett mucosa and dysplasia and remain high in adenocarcinoma (75). Moreover, high expression of TLR4 in the nucleus and the cytoplasm was associated with metastasis and poor prognosis (75). Various cancer cells, including cells of an esophageal cancer cell line, demonstrated cellular invasion in an *in vitro* Matrigel assay when stimulated with DNA, a TLR9 ligand (76). A future challenge will be to define microbial interactions involving TLRs in an effort to understand cancer progression in the esophagus.

Although imbalances in the gut microbiota have been linked to colorectal adenomas and cancer, only *Fusobacterium* has been identified as a risk factor. *Fusobacterium* has been found to be associated with colorectal tumor tissue in several different studies (33, 77), but the presence of *Porphyromonas* species as well suggests the possibility of a polymicrobial disease trigger. In addition, other studies have identified *Peptostreptococcus*, *Prevotella*, *Parvimonas*, *Leptotrichia*, *Campylobacter*, and *Gemella* as additional genera that are associated with the detection of colorectal cancer (79). In studies of colon cancer, Zackular and colleagues used 16S rRNA gene signatures from the stool samples of healthy, precancerous adenomas, and colon cancer in humans to demonstrate that the feces of people with cancer tended to have an altered composition of bacteria, with an excess of the common mouth microbes, *Fusobacterium* or *Porphyromonas* (80). Similarly, Zeller his colleagues showed that the metagenomic profiling of fecal samples from colorectal cancer patients in comparison with tumorfree controls reveals associations between the gut microbiota and cancer, distinguishing sample types with similar accuracy as the fecal occult blood test, used for clinical screening. Two *Fusobacterium* species, *Porphyromonas asaccharolytica* and *Peptostreptococcus stomatis*, were enriched in colorectal cancer patients (81). In addition, metatranscriptome data revealed a significant overrepresentation and cooccurrence of *Fusobacterium*, *Campylobacter*, and *Leptotrichia* genera in colorectal cancer tumor samples. These are Gram-negative anaerobes that are generally considered to be oral bacteria, but the tumor isolates of *Fusobacterium* and *Campylobacter* are genetically diverged from their oral complements (79). The *Campylobacter* isolate *Campylobacter showae* from the colorectal tumor was substantially diverged from their oral isolate (79). Other cancer-associated microbiome studies exist, although the cohorts used have invariably been relatively small. For example, to evaluate microbial association in oral cancers, Schmidt and colleagues (82) sequenced microbial DNA derived from cancer and normal tissues (matched) in patients. Comparison of 16S rRNA gene V4 data from these samples revealed changes in the abundance of *Actinobacteria* and *Firmicutes* between oral cancer and normal tissues (82).

Experiments with germ-free animals have helped to clarify causality between dysbiosis and cancer. For example, T-cell receptor β-chain and p53 knockout mice have the propensity to develop malignant tumors. When germ-free mice with the knockouts were colonized with gut microbiota, 70% of the animals developed adenocarcinomas in the colon, as expected. However, control germ-free animals did not develop adenocarcinomas in the same timeframe (83). Similarly, mice with a mutation in the tumor suppressor gene *APC* (adenomatous polyposis coli) had reduced occurrence of intestinal tumors when they were rendered

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germ free, as opposed to specific pathogen free, suggesting that commensal bacteria play a pathogenic role in this system (84). Tumors in the specific pathogen-free mice showed profiles of inflammation, signs of barrier damage, and activation of c-Jun/JNK and STAT3 pathways (84). An inflammation-based murine model can be generated by treating a normal mouse with the chemical carcinogen azoxymethane, followed by dextran sodium sulfate (85). When an antibiotic cocktail was administered in this model, the rate of colon tumors was reduced, although the total number of bacteria appeared to be unchanged, suggesting that specific species contribute to tumorigenesis (86). When germ-free mice were colonized with microbiota from cancer-bearing mice, the rate of tumors was higher than with microbiota from healthy mice (86). The demonstration of reduced frequencies of tumors in germ-free mice provides support for studies in which specific microbes added to conventional mice resulted in increased frequencies of cancer. Examples of specific microbes are *F. nucleatum* and enterotoxigenic *B. fragilis* as discussed above. Reconstitution of specific microbiotas in germ-free mice is an exciting approach for dissecting the network of microbial and host interactions involved in dysbiosis, inflammation, and cancer.

Immunoregulation and microbiome

Microbiota plays a significant, albeit incompletely mapped, role in the shaping of innate and acquired immunity (87). This process starts during the constitution of the microbial flora at birth, influencing the maturation of the immune system and the development of tolerance and containment of the microbiome (87–89). It continues throughout life via signaling by innate immunity receptors, through sampling of the microbiota by the acquired immune response, and by the generation of metabolic products (90, 91). The central role of immunity in the biology of cancer calls for attention to the exact contribution of microbiota in oncogenesis. For example, data from germ-free and antibiotic-treated mice suggest a diminished response to CpG stimulation in the setting of cancer immunotherapy (92). Upregulation of TLRs by LPS and other microbial products can activate the NF-κB, c-Jun/JNK, and JAK/STAT3 pathways that have well-defined roles in cell proliferation and immunosuppression (Fig. 1D; refs. 12, 93). More generally, the use of antibiotics in the clinical care of individuals with cancer, particularly during periods of immunosuppression, may interfere with effective anticancer immune responses (94).

Microbiome, autophagy, and cancer

Autophagy is a membrane-trafficking mechanism that delivers cytoplasmic constituents into the lysosome for protein degradation. Autophagy plays a significant role in the maintenance of cellular homeostasis. The role of autophagy in cancer is complex and context dependent. In preclinical models of carcinogenesis, autophagy prevents malignant transformation by degrading potentially harmful entities inside the cell but, later, promotes the growth of established tumors (95). One function of autophagy is to prevent intracellular viral and bacterial infection and control inflammation through innate immune signaling pathways (Fig. 1D; ref. 96). Many bacteria have evolved mechanisms to prevent degradation by autophagy, including *H. pylori* (97). Prolonged exposure to *H. pylori* protein VacA prevents autophagosome maturation, and the bacteria are able to persist in these compartments (98). This promotes an environment that favors carcinogenesis by the accumulation of damaged organelles and protein aggregates, persistent *H. pylori* infection, and chronic inflammation. The effect of autophagy on carcinogenesis also appears to be tissue specific, and its effects can be mediated through the microbiome. In the pancreas and lung, inhibition of autophagy predisposes the tissue to lesions (95). However, in models of colorectal cancer, the inhibition of autophagy prevents the development of precancerous lesions (99). The antitumor effects of this inhibition are mediated through the gut microbiome, as autophagy deficiency led to changes in the intestinal microbial community, and treatment with broad-spectrum antibiotics impairs the protective $CD8^+$ antitumoral responses, and induced intestinal lesions (99).

The Future of the Microbiome in Cancer Therapy: Development of Novel Diagnostics and Preventative Measures Based on Microbiome Profiles

As the scientific community continues to generate more microbiome data, and integrate other "omics" types such as transcriptomics, proteomics, and metabolomics from well-phenotyped cohorts, we will identify novel microbial signatures that are associated with disease onset and progression in many diseases, including cancer. These microbiome signatures (including circulating metabolites) have the potential to be developed into diagnostics and therapeutics. Our team, for example, recently studied the microbiome in childhood leukemia patients (an estimated 15,000 children under the age of 19 are diagnosed with leukemia, lymphoma, and other tumors in the United States every year) with the goal of measuring microbiome changes associated with disease onset (100). Our other goal was to identify novel therapies that could be developed for compromises associated with chemotherapy treatment. Known side effects of chemotherapeutic treatments often include drug-induced gastrointestinal mucositis with diarrhea, constipation, and increased risk of gastrointestinal infections. In our study, the gastrointestinal microbiomes of pediatric and adolescent patients with acute lymphoblastic leukemia were profiled by 16S rDNA gene sequencing before and during a chemotherapy course and compared with equivalent 16S rDNA data from their healthy siblings. The microbiome profiles of patients before chemotherapy and the control group were dominated by members of the genera *Bacteroides, Prevotella*, and *Faecalibacterium*, with these having mean relative abundances of 62.2%, 7.3%, and 6.4% respectively, in the patient group, and 40.2%, 12.2%, and 8.3% respectively, in the control group. Microbiome diversity, measured as the Shannon diversity index, of the patient group was significantly lower than that of the sibling control group, and discriminatory taxa included *Anaerostipes, Coprococcus, Roseburia*, and *Ruminococcus*, all of which had lower relative abundance in the disease group. This study is another example illustrating the potential for use of microbiome signatures that are associated with disease onset and progression to develop noninvasive approaches in cancer diagnosis.

Continued evaluation of the mechanisms used by microbes to trigger diseases will also enable the identification of therapeutic approaches, including the use of pre- and probiotics to restore a healthy microbiome and possibly to offset some of the

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impacts of toxic therapies. It has also been shown in murine models that commensal microbiota modulate the efficacy of anticancer therapy through the immune response. Loss of the microbiome decreased TNF expression, decreased proinflammatory cytokines, and reduced the production of reactive oxygen species, leading to impaired tumor regression and survival (92). Loss of the microbiome was also shown to reduce the stimulation of pathogenic Th 17 cells and eliminate chemotherapy effectiveness. Therefore, the efficacy of treatment may be improved through combined anticancer therapy with probiotics. When combined with novel approaches to vaccine design through synthetic biology, there are several opportunities for decreasing cancer incidence as a result of understanding our microbiome.

In this minireview, we presented a brief overview of recent history and advances that have been made with respect to understanding our microbiome and the development or correlation with cancer and future avenues of research that will be beneficial to this space, including the development of novel diagnostics, vaccines, and other therapeutic approaches to treatment.

Disclosure of Potential Conflicts of Interest

J.C. Venter is the co-founder, executive chairman, at Human Longevity, Inc., the founder, chairman, and chief executive officer at J. Craig Venter Institute, has received speakers bureau honoraria from The Harry Walker Agency, and has ownership interest (including patents) in Human Longevity, Inc., Synthetic Genomics, Inc., and J. Craig Venter Institute. A. Telenti is the chief data scientist at Human Longevity, Inc. No potential conflicts of interest were disclosed by the other authors.

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