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The microbiome and cancer for clinicians

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ABSTRACT

The human microbiome is an emerging target in cancer development and therapeutics. It may be directly oncogenic, through promotion of mucosal inflammation or systemic dysregulation, or may alter anti-cancer immunity/therapy. Microorganisms within, adjacent to and distant from tumors may affect cancer progression, and interactions and differences between these populations can influence the course of disease. Here we review the microbiome as it pertains to cancer for clinicians. The microbiota of cancers including colorectal, pancreas, breast and prostate are discussed. We examine "omics" technologies, microbiota associated with tumor tissue and tumor-site fluids such as feces and urine, as well as indirect effects of the gut microbiome. We describe roles of the microbiome in immunotherapy, and how it can be modulated to improve cancer therapeutics. While research is still at an early stage, there is potential to exploit the microbiome, as modulation may increase efficacy of treatments, reduce toxicities and prevent carcinogenesis.

1. The human microbiome

The microbiome of humans contains trillions of organisms distributed throughout the body, with the largest concentration in the genital tract and on other mucosal surfaces (McDonald et al., 2018). These organisms and their collective genomes - the human microbiome - develops from birth, with influence from both the maternal microbiota and the environment, and varies between individuals due to the cumulative effects of host factors and environmental exposures (Dominguez-Bello et al., 2010; Palmer et al., 2007). The composition and complexity of human-associated microbial communities has largely been defined using culture-independent sequencing of microbial 'barcodes' such as the 16S ribosomal RNA (rRNA) gene (for bacteria) (Human Microbiome Project, C., 2012a). However, the microbiome may be described as 'the genes and genomes of the microbiota, as well as the products of the microbiota and the host environment', which includes plasmid DNA and also viruses, archaea and fungi (although these are not generally detected at present) (Whiteside et al., 2015).

Dysbiosis or disruption of the normal human microbiota is associated with a wide range of diseases, including inflammatory bowel disease, multiple sclerosis, obesity, autism, depression, cardiovascular disease and allergy, as well as cancer (Forbes et al., 2016; Mowry and Glenn, 2018; Rodriguez et al., 2016; Sonnenburg and Backhed, 2016; Fung et al., 2017; Tang et al., 2013; Fujimura et al., 2016). The microbiome has been implicated in cancer in a variety of specific ways, including being directly oncogenic, through promotion of oncogenic mucosal inflammation or systemic metabolic/immune dysregulation and through modulation of anti-cancer immunity or the efficacy of anti-cancer therapy (Kau et al., 2011; Dinan and Cryan, 2017; Mitsuhashi and Okuma, 2018; Floch et al., 2017; Uemura et al., 2001; Zhu et al., 2016; Di Domenico et al., 2017; Jackson et al., 2000; Zhan et al., 2011; Rogers, 2011; Rao et al., 2006; Xie et al., 2016; Bhatt et al., 2017; Boursi et al., 2015). Bacterial species are found in tumor tissue itself, normal tissue adjacent to tumor and at tumor sites such as the gut, genitourinary tract and airway, with overlap between these sites. Microorganisms within, adjacent to and distant from the tumor may play a role in cancer development and progression, and interactions and differences between these microbial populations, with their associated molecules and molecular pathways, have the potential to influence the course of disease (Fig. 1).

2. "Omics" analyses for the microbiome

Technologies for analysis of the human microbiome have developed within recent years, with numerous methods for quantification of the microbiome and its effects available, the most common of which are outlined in Table 1. The most frequently used methods are genomic sequencing of bacterial 16 s ribosomal RNA (rRNA) and shotgun sequencing. Sequencing of the 16S rRNA gene provides relative quantitation of bacterial community composition, generally at the level of the

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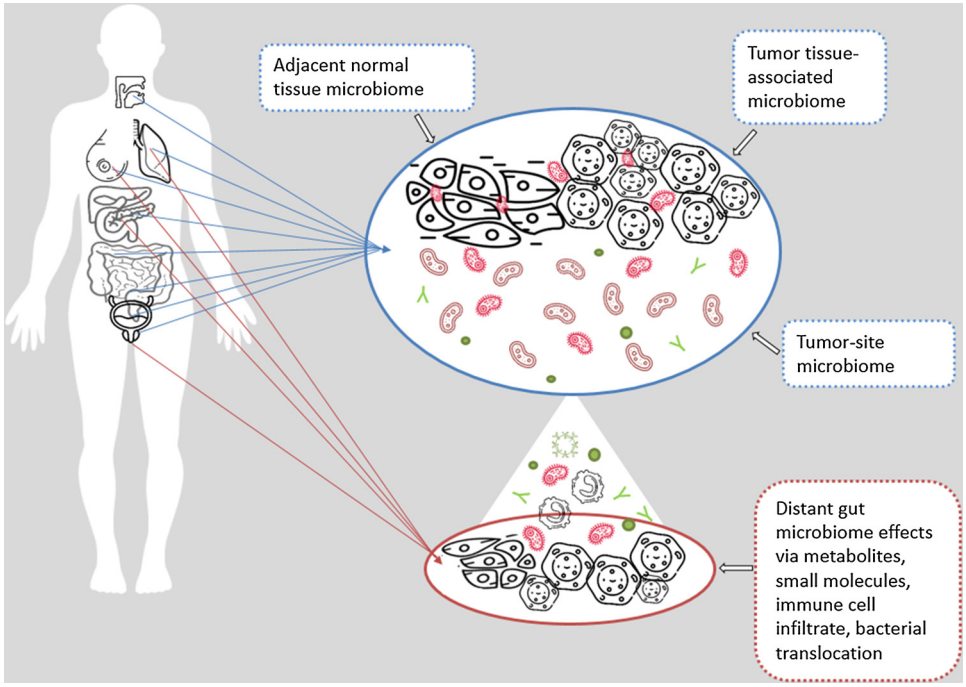

Fig. 1. The relationship between various tumor types and the microbiome. Tumor tissue contains its own microbiome. Adjacent "normal" tissue also contains microbiota which may resemble the microbiome of the tumor, which suggests that alterations in bacterial species may play a causative role in tumor formation. Sites adjacent to the tumor such as feces and urine contain microbes, metabolites, inflammatory molecules and others which may influence tumorigenesis, tumor progression and response to treatment. Finally, bacteria in the gut as well as associated immune cells, cytokines, bacterial metabolites and other molecules may affect remote organs in terms of tumor formation and treatment response.

bacterial genus (Wang and Qian, 2009; Janda and Abbott, 2007; Pei et al., 2010), while shotgun sequencing analyses the entire genomic content of a sample and permits interpretation of the compositional and metagenomic abundance of microbial community members at high genomic resolution (Quince et al., 2017). The IS-pro technique is another method by which bacterial species can be characterized by amplifying 16 S–23 S rRNA gene interspace regions with lengths that are specific for each microbial species (Budding et al., 2016). Analysis of the metatranscriptome, or the mRNA of the microbial community, can reveal which organisms are active and which microbial genes are being expressed (Franzosa et al., 2014), but because of the short half-life of mRNA, represent a single time-point of gene expression that may not reflect longer-term adaptations between the host and microbiota (Bikel et al., 2015). Similarly, proteomics examines the protein content of samples such as feces, and again since protein expression is dynamic, this test gives an analysis of the expressed and functional proteins at a particular time point (Singhal et al., 2015; Jin et al., 2017). Finally, metabolomics is the study of the metabolites found in a sample, regardless of their organism of origin (host or microbial), and can include vitamins, short-chain fatty acids, bile acids, choline derivatives or polysaccharides, among many other compounds (Daliri et al., 2017). Collectively, these tools are used to characterize microbial taxonomic and metagenomic community composition and infer or measure microbial community and aggregate host/microbial metabolism to identify disease associations and novel targets for experimental, diagnostic or therapeutic studies.

3. The tumor-associated microbiome

The microbiome of tumor tissue itself has increasingly come under focus, with the realization that many tissues have their own bacterial, viral and fungal populations. While the microbiome of mucosal or exposed sites such as the gut, skin, mouth and vagina have been examined in more detail, the microbiome of non-mucosal tissues is less well characterized, in particular because controlling for contamination and validating results is challenging in these sample types. Microbial species have been identified in many tissue types with the advent of bacterial RNA sequencing, for example, in breast tissue and gastric tissue (Meng et al., 2018; Urbaniak et al., 2016; Ren et al., 2018). The tumor microenvironment is a hypoxic one which is thought to facilitate the growth of anaerobic and facultative anaerobic bacteria such as Clostridia (Wei et al., 2007), while necrotic areas of the tumor can cause chemotactic compounds to be released, attracting bacterial invasion (Baban et al., 2010). The leaky vasculature of cancerous tissue also allows bacteria to enter, where the absence or low abundance of immune cells may permit growth (Syed Khaja et al., 2017). Indeed, intratumoral administration of non-pathogenic bacteria has been suggested as a mechanism of direct drug or therapeutic delivery (Cronin et al., 2010; Murphy et al., 2017).

Mucosal tumors are in direct contact with bacteria and therefore are susceptible to influence from the microbiome. The microbiome of colorectal cancer (CRC) has been extensively studied, as CRC is exposed to a vast array of bacterial species in the gut. Interestingly, the composition of fecal microbiota is not fully concordant with the composition of the tumor tissue microbiome (Flemer et al., 2017). Bacteria found in tumor tissue from CRC and other cancers are outlined in Table 2. Fusobacteria and Firmicutes are increased in tumor tissue compared to normal colonic tissue, while taxa including Fusobacteria, *Providencia* and *Actinobacter* are altered in abundance between cancerous and adjacent normal tissue (Gao et al., 2017a, 2015; Burns et al., 2015). *Fusobacterium nucleatum* in particular has been found in numerous studies to be enriched in colonic tumor tissue, although whether it is a causative agent or a bystander of some other process remains unclear, with animal models demonstrating conflicting results (Castellarin et al., 2012; Kostic et al., 2012; Tomkovich et al., 2017; Yang et al., 2017; Yu et al., 2015a). The presence of these bacteria are also associated with histologic grade, CpG island methylation phenotype status, CD3 + T cell infiltration, resistance to chemotherapy and poorer overall survival (Koi et al., 2018; Lee et al., 2018; Mima et al., 2015, 2016; Flanagan et al., 2014; Ito et al., 2015; Yu et al., 2017; Tahara et al., 2014). Interestingly, *F. nucleatum* found in CRC may originate in the oral cavity, with identical strains of the bacteria found in matched tumor tissue and saliva (Komiya et al., 2018). The bacteria persists both in metastatic lesions and in tumor xenografts in mice; treatment of mice with these xenografts with metronidazole decreases tumor bacterial load and tumor growth, suggesting that the bacteria may have a role in tumor proliferation, although antibiotics may independently have antineoplastic effects (Bullman et al., 2017). A recent study suggested that

Table 1
"-Omics" techniques for microbiome analysis.

Data type	Data collected	Analysis tools	Pros	Cons	Refs
16S ribosomal RNA sequencing	Sequencing of hypervariable 16S rRNA region allows classification of bacterial composition down to genus level	16S databases, OTU clustering, PICRUSt	Easy to perform, provides information on bacterial composition, large number of databases for analysis	Unreliable for quantification of different bacteria, primer sequences and PCR conditions may differ between analyses	(Wang and Qian, 2009; Janda and Abbott, 2007; Pei et al., 2010)
Shotgun sequencing (metagenomics)	Sequencing of whole genomic content of sample obtained	Various assembly tools	Provides overall composition and abundance of bacteria, can be used for functional analysis	Large amount of data generated requiring analysis and storage, requires high sequencing depth, limited reference databases, expensive	(Quince et al., 2017)
IS-pro	Sequencing of 16S-23S interspace region	Automated software pipeline	Easy to perform, quick assay, identification to species level	Expensive, proprietary technology	(Budding et al., 2016)
Metatranscriptomics	Sequencing of transcribed bacterial RNA content of sample (RNAseq)		Gives snapshot of actual expression profile of bacterial community, may allow inference of functional pathways	Analysis not yet standardized, mRNA has short half-life, technical problems with host RNA contamination	(Franzosa et al., 2014; Bikel et al., 2015)
Metaproteomics	Global analysis of protein content of sample eg feces, tissue, usually by mass spectrometry	Search engines eg SEQUEST, analysis software eg MetaProteome Analyzer	Protein expression analysis may identify potential biomarkers and targets, gives functional data	Contamination and sample collection problems, protein expression is dynamic and changes over time, analysis not yet standardized	(Singhal et al., 2015; Jin et al., 2017)
Metabolomics	Identifies metabolites of microbial and host metabolism in samples eg feces, bodily fluids, usually by mass spectrometry or nuclear magnetic resonance spectrometry	No standardized analysis tools	Can be used dynamically to asses metabolites eg before and after treatment, data on host-microbiome interactions	Complex sample collection problems and analysis, only data on one time point, no data on whether host or microbiome has influenced metabolites	(Daliri et al., 2017)

colonization with *F. nucleatum* may differ between tumors with varying tumor microsatellite instability (MSI) status, and may exert immunosuppressive effects in MSI-high tumors but pro-inflammatory effects in MSI-normal tumors (Hamada et al., 2018; Hale et al., 2018; Kosumi et al., 2018). Infection in the form of bacteremia or endocarditis with *Streptococcus gallolyticus* has long been associated with colorectal cancer, and this species is also found in tumor tissue itself (Abdulamir et al., 2010).

Bacteria have been found in the tissues of upper gastrointestinal cancers such as biliary and esophageal cancers, and in cervical cancer, although their significance remains unclear (de Martel et al., 2009; Murata et al., 2004; Liu et al., 2018a; Lam et al., 2018). In lung cancer patients with a history of heavy smoking, tumor tissue was characterized by significantly lower abundance of Acinetobacter and Acidovorax and higher abundance of Streptococcus and Prevotella compared with tissue from patients with emphysema (Liu et al., 2018b), while the genera Veillonella and Megasphaera may act as biomarkers for lung cancer with good sensitivity and specificity (Lee et al., 2016a).

Non-mucosal tissues have also been shown to contain bacteria, although interpretation of these studies is limited by the potential for contamination and the lack of verification in other work. In pancreatic cancer, bacteria have been shown to migrate from the gut to the pancreas in both murine models, using fluorescent-labelled microbes and 16S sequencing, and in human tumors (Pushalkar et al., 2018). The microbiome can reprogram the immune microenvironment of the pancreas, with ablation of the microbiome allowing decreased myeloid suppressor cells and increased CD4+ and CD8 + T cells. Repopulation of the microbiome restores an immunosuppressive environment in the pancreatic tumor in mice, although this may not reproduce the normal gut microbiome as oral gavage may induce a higher bacterial load and translocation than in non-depleted mice. In a similar study, gut microbiome depletion decreased tumor burden in a pancreatic cancer murine model, an effect which was not seen in mice who lacked mature T and B cells (Sethi et al., 2018; Mitsuhashi et al., 2015). As previously mentioned, human breast cancer tissue has been found to contain its own specific microbiota, which differs from that of the overlying skin or from normal/control tissue (Meng et al., 2018; Hieken et al., 2016; Banerjee et al., 2015). Differences in microbial composition between breast cancer subtypes have been observed, with distinct patterns found in the triple negative and triple positive tumor types (Banerjee et al., 2018). Distinct microbiome profiles have been detected in the ovary, fallopian tubes and cervix, and may be associated with endometrial and ovarian cancers (Walther-Antonio et al., 2016; Brewster et al., 2016). Previous studies have shown bacterial DNA to be present in prostate cancer tissue (Keay et al., 1999; Krieger et al., 2000), identifying *Escherichia*, *Mycoplasma hominis* and *Cutibacterium (*formerly *Propionibacterium*) *acnes* among others (Sfanos et al., 2008; Barykova et al., 2011; Yow et al., 2017; Cohen et al., 2005; Cavarretta et al., 2017). When mice were inoculated via urethral catheterization with *C. acnes* and *E. coli* from prostatectomy specimens, severe inflammation was induced in prostate tissue, along with accelerated development of prostate adenocarcinoma (Shinohara et al., 2013; Simons et al., 2015). Inflammation in the prostate has been shown to merge with intraepithelial neoplasia (Putzi and De Marzo, 2000), while polymorphisms in the promoter regions of the genes of cytokines such as IL-8, IL-10 and VEGF are associated with risk for prostate cancer (McCarron et al., 2002), again suggesting links between inflammation and prostate cancer.

These findings indicate that tumor tissue may have a distinct microbiome – bacteria may enter the necrotic, tumor environment from adjacent body fluids, distant mucosal cavities or elsewhere, and may alter cell infiltrate thereby decreasing immune surveillance. Whether the presence of these bacteria is causative or simply a consequence of the dysfunctional environment of the tumor remains to be elucidated, and results need to be validated to ensure that bacterial species identified are not due to contamination. Some bacteria such as

Table 2
Tumor tissue-associated microbiome.

Tumor type	Bacteria	Associations	Ref
Colorectal	*Fusobacterium nucleatum*	Tumor grade, methylation status, immune cell infiltrate, chemotherapy response, poor prognosis	(Castellarin et al., 2012; Kostic et al., 2012; Tomkovich et al., 2017; Yang et al., 2017; Yu et al., 2015a; Koi et al., 2018; Lee et al., 2018; Mima et al., 2015, 2016; Flanagan et al., 2014; Ito et al., 2015; Yu et al., 2017; Tahara et al., 2014)
	Bifidobacterium	Associated with signet ring cells	(Kosumi et al., 2018)
	Streptococcus gallolyticus	Associated with bacteremia/endocarditis, increased inflammatory markers eg IL-1, IL-8, COX-2	(Abdulamir et al., 2010)
Pancreas	Proteobacteria, Bacteroidetes, Firmicutes	Increased compared to normal tissue, may alter immune microenvironment	(Pushalkar et al., 2018)
	Fusobacterium	Poor prognosis	(Mitsuhashi et al., 2015)
Biliary tract cancers	*Helicobacter bilis*	Found in tumor tissue	(de Martel et al., 2009)
Esophageal cancer	Streptococcus spp., Prevotella spp.	Poor prognosis, nodal status	(Liu et al., 2018a)
Breast cancer	Bacteroidaceae, Agrococcus	Tumor grade	(Meng et al., 2018)
	Fusobacterium, Atopobium, Gluconacetobacter, Hydrogenophaga, Lactobacillus	Malignancy	(Hieken et al., 2016)
	Arcanobacterium, Bifidobacterium, Cardiobacterium, Citrobacter, Escherichia, Bordetella, Campylobacter, Chlamydia, Chlamydophila, Legionella, Pasteurella, Streptococcus, Aerococcus, Arcobacter, Geobacillus, Orientia, Rothia	Differentially abundant between breast cancer subtypes (hormone receptor positive, HER2 positive, triple positive, triple negative)	(Banerjee et al., 2018)
Cervical cancer	Bacillaceae, Halobacteriaceae, Prevotella bivia	Upregulate immune pathways	(Lam et al., 2018)
Prostate cancer	*Cutibacterium acnes*	Induces inflammation, increase in Ki-67 index, decrease in androgen receptor expression	(Cohen et al., 2005; Shinohara et al., 2013)
	Escherischia coli	Accelerated prostate adenocarcinoma development	(Simons et al., 2015)
	Mycoplasma hominis, Enterobacteriaciae*, Escherichia, Acinetobacter, Pseudomonas*	Increased compared to normal tissue	(Sfanos et al., 2008; Barykova et al., 2011; Yow et al., 2017)
Lung cancer	Veillonella, Megasphaera	Biomarker for cancer	(Lee et al., 2016a)
	Acinetobacter, Acidovorax, Streptococcus, Prevotella	Altered compared to emphysematous tissue	(Liu et al., 2018b)

Fusobacterium have been found in numerous studies and do appear to have pro-neoplastic capabilities, although its presence is not consistent, as discussed previously (Repass et al., 2016). As better models of tumorigenesis continue to be developed and with improved detection techniques for bacteria, their proteins and metabolites; the significance of these microbiota will become clearer.

4. The microbiome of tumor-adjacent “normal” tissue

While cancerous tissue itself appears to have an altered microbiome, it is known that many cancers appear to develop in previously inflamed tissues, raising the possibility that bacteria may have a “field effect” promoting the neoplastic process. Tissue adjacent to tumors are likely to be altered compared to true “normal” tissue, due to factors such as immune cell infiltrate, fibrosis and tumor-associated inflammation. Allali et al performed a study examining colorectal cancer and adjacent tissue from patients from the US and Spain (Allali et al., 2015). Tumor and adjacent tissues had very closely related microbiota, with lower diversity seen in tumor tissues, although significant differences were seen between the Spanish and US cohorts, suggesting a role for geographical and environmental factors. Nakatsu et al sampled colorectal tumor and adenomatous tissue and adjacent mucosa, and examined the 16S rRNA gene sequencing profiles of biopsies (Nakatsu et al., 2015). They divided the profiles into five “metacommunities” or clusters with the deepest taxonomic annotations, based on Dirichlet multinomial mixture models (Ding and Schloss, 2014), and found that metacommunity E, containing *Fusobacterium* as well as other Firmicutes, and Proteobacteria were almost always found in both lesion-adjacent mucosa and in lesions themselves; Proteobacteria has also been found in adenoma-adjacent tissue (Lu et al., 2016).

In breast cancer, analysis of the TCGA database found bacteria present in both tumor and normal adjacent breast tissue, with Proteobacteria, Actinobacteria and Firmicutes the main phyla noted in both tissue types (Thompson et al., 2017). Cancerous tissue of the breast contains lower numbers of bacteria compared with adjacent normal tissue, and this is associated with lower expression of antimicrobial response genes including Toll-like receptors and IL-12A; this suggests that alterations in the normal breast microbiome may cause changes in the inflammatory response during carcinogenesis (Xuan et al., 2014). In laryngeal cancer, tumor and adjacent normal tissue were found to have similar microbiota with an increase in the phylum *Fusobacterium* and a decrease in Firmicutes and Actinobacteria compared to the tissue of healthy controls (Gong et al., 2017). Interestingly, in a study of oral cancers, patients with higher T-stage disease had more similarities between tumor and adjacent non-tumor microbiomes than patients with lower T-stage disease; it may be that the bacteria in oral tissue predispose to a more proliferative tumor through a “field” dysbiosis (Mukherjee et al., 2017).

These findings suggest that tumor-adjacent “normal” tissue is in fact similar to tumor tissue, rather than truly normal tissue, in its microbial composition, and that these bacterial communities may form a micronetwork within the tumor environment, causing altered inflammatory signaling. Supporting this hypothesis, transcription factors have been found to be dysregulated in colonic tumor-adjacent mucosa compared to healthy mucosa, suggesting a complex interaction between proteins and receptors on the tumor and the surrounding tissue (Sanz-Pamplona et al., 2014). Further studies incorporating numerous controls including normal tissue from non-cancerous patients are needed to validate these results.

5. The tumor-site microbiome

Many tumors are found at body cavities such as the gastrointestinal tract, airway and genitourinary tract, and these sites have their own

microbiomes, in particular the fecal microbiome. In the colon, *F. nucleatum* has been found in colorectal tumor tissue and is likely to have translocated from feces in the gut into colonic epithelium, inducing pro-inflammatory and oncogenic pathways (Flanagan et al., 2014; Rubinstein et al., 2013; Kostic et al., 2013; Zhou et al., 2018). It expresses a unique adhesion protein called FadA, which can bind to E-cadherin and allow the bacteria to invade CRC cells, causing β-catenin-regulated transcription of the oncogenes Myc and Cyclin D1, and increased cancer cell proliferation. Interestingly, in mouse models, fecal *F. nucleatum* does not appear to induce colitis or inflammation-associated colonic carcinogenesis, but recruits tumor-infiltrating immune cells and increases the number of colonic tumors (Kostic et al., 2013). In the same mouse model, *F. nucleatum* also induced colorectal tumors via the microRNA miR21, inhibitors of which prevented CRC cell line proliferation and invasion (Yang et al., 2017). MicroRNAs have been found to be differentially expressed in normal and tumor tissue in the colon, and to correlate with the microbiome profile of the colon, providing another method by which the gut epithelium can interact with bacteria (Yuan et al., 2018). *Campylobacter jejuni* causes mice to develop more and larger colorectal tumors compared with uninfected mice, an effect which is diminished by administration of the antibiotic rapamycin (He et al., 2018). Other species associated with CRC in the gut include *Escherichia coli* (Arthur et al., 2012), *Bacteroides fragilis* (Wang et al., 2012a), *Streptococcus bovis* (Krishnan and Eslick, 2014) and *Enterococcus fecalis* (Balamurugan et al., 2008). In particular, enterotoxigenic *Bacteroides fragilis* has been shown to induce colonic tumors in mice via IL-17 and possibly via Stat3-driven TH-17 T cell response (Wu et al., 2009; Housseau et al., 2016).

Metabolites produced by the host and by bacteria are increasingly being recognized as modulators of mucosal/epithelial health, cellular homeostasis, metabolism, inflammation and proliferation. Fermentation of fibre into short chain fatty acids (SCFA), and in particular butyrate, is essential for a healthy colonic mucosa (Roediger, 1982). Lower bacterial diversity along with lower SCFAs were associated with colonic tumors in mice, and restoration of the SCFA levels using sterols caused tumor apoptosis (Ma et al., 2018). Bacteria which produce butyrate have been found to be lower in abundance in stool of CRC patients compared with non-CRC patients (Wang et al., 2012a; Balamurugan et al., 2008); butyrate may decrease tumorigenesis and have anti-inflammatory and immunomodulatory effects (O'Keefe, 2016; Vipperla and O'Keefe, 2012). Interestingly, butyrate may also enhance the intestinal barrier function by upregulating the tight junction protein claudin-1 and by increasing mucin production; therefore decreases in butyrate due to dysbiotic changes in the gut bacteria may increase the leakiness of the intestinal epithelium and allow bacteria to enter tissue (Wang et al., 2012b; Willemsen et al., 2003). Deoxycholic acid (DCA) is a secondary bile acid which may be involved in intestinal tumorigenesis. When mice are treated with this bile acid, tumor formation is increased and the microbiota are altered (Cao et al., 2017). When feces from these mice were transplanted into non-treated mice, activation of the Wnt/β -catenin pathway was observed, and inflammation and tumor number was increased.

As with all mucosal surfaces, the airway epithelium has a distinct microbiome which may be altered in many disease states including chronic obstructive pulmonary disease, cystic fibrosis, asthma and lung cancer (Mao et al., 2018). Airway brushings from lung cancer tissue have been shown to have decreased α-diversity (within-sample microbial diversity) and increased abundance of *Streptococcus* spp. compared with brushings from the contralateral non-cancerous lung (Liu et al., 2018c). Paired cancerous and non-cancerous brushings had lower diversity and altered compositions compared with healthy controls, suggesting an overall alteration in the airway microbiome in cancer patients. Enrichment of *Streptococcus* and *Veillonella* in lung cancer brushings was associated with upregulation of the PI3K and ERK pathways, which have been implicated in most lung cancers (Tsay et al., 2018), promoting proliferation, migration, invasion and resistance to therapy (De Marco et al., 2017). *Haemophilus influenza* may promote tumor formation via IL-17C and neutrophil infiltration (Jungnickel et al., 2017), and can increase metastatic growth of lung cancers when inhaled by mice in combination with cigarette smoke (Jungnickel et al., 2015). The bacteria found in bronchial fluid from lung cancer patients may originate in the mouth and provide a link between the oral microbiome and the development of lung tumors (Hasegawa et al., 2014; Hosgood et al., 2014). We know that antibiotic use may reduce the efficacy of immune checkpoint inhibitor treatment in lung cancer, but it is as yet unknown whether this is due to modulation of the gut or the lung microbiome, or a direct anti-neoplastic effect (Derosa et al., 2018).

The urinary tract was long thought to be a completely sterile environment – to such a degree that in the Human Microbiome Project, commenced in 2008, urine was not one of the samples collected for analysis as the urinary tract was not thought to contribute to human microbiota (Human Microbiome Project, C., 2012b). In recent years, it has become apparent that the urinary tract has its own diverse microbiome. Historically, standard urinary culture methods did not detect slower-growing bacteria such as Lactobacillus and Corynebacterium, but these species can now be detected using sequencing of the hypervariable regions of the 16 s rRNA gene (Human Microbiome Project, C., 2012a; Wolfe et al., 2012). The urothelium is continuously exposed to urine and its contents, and it is likely that, similar to the intestinal epithelium, there are reciprocal interactions between the microbes in urine and bladder tissue (Maynard et al., 2012). The link between infection with *Schistosoma haematobium*, a helminth endemic in the Middle East and Africa, and bladder cancer has long been recognized (Humans, I.W.G.o.t.E.o.C.R.t. and C., 2012). It is thought that the helminths release carcinogenic estrogen-like metabolites, nitrosamines and cyclooxygenase-2 which lead to tumorigenesis (Gouveia et al., 2015; Yongvanit et al., 2012), while they can also alter the abundance of *Fusobacterium* and other bacteria found in the urine (Adebayo et al., 2017). Popovic et al have examined the urinary microbiome in bladder cancer (Bucevic Popovic et al., 2018), finding high inter-individual variability but enrichment of Fusobacterium, Campylobacter and Ruminococcaceae in the cancer group. When *F. nucleatum* was further investigated, 16 s rRNA was found in 11 of 42 (26%) bladder tumor tissue samples. Other changes in the urinary microbiome in bladder and prostate cancer patients are shown in Table 3. Interestingly, seminal fluid in mice has also been shown to have its own microbiome, influenced by the presence of a functional *ESR1* gene, which has been implicated in prostate cancer risk (Javurek et al., 2016; Liu et al., 2018d; Hao et al., 2016).

The microbiome of the oral cavity has been studied in the Oral Microbiome Project, which includes 770 microbial species found in the human mouth. The oral microbiome may be influenced by many factors such as oral hygiene, smoking, diet and alcohol consumption (Fan et al., 2018a; Hsiao et al., 2018). In oral cancers, disruption of the normal microbiota has been found, with dynamic changes across the stages of oral squamous cell carcinoma (Yost et al., 2018; Yang et al., 2018a) (Table 3). A biomarker panel of seven genera of bacteria can distinguish oral cavity and oropharyngeal cancers from healthy controls, although whether these bacteria have any prognostic significance is unclear (Lim et al., 2018). The vaginal microbiome has been examined in the context of gynecological cancers; associations have been found between bacteria, the rate of clearance of the oncogenic virus HPV and cervical intraepithelial neoplasia (Brotman et al., 2014; Oh et al., 2015; Seo et al., 2016; Audirac-Chalifour et al., 2016; Champer et al., 2018).

Overall, it appears that the tumor site microbiome differs significantly from that of non-tumor sites within the gut, lung, genitourinary tract and oral cavities, among others. It is possible that either dysbiotic bacteria themselves, or their products such as butyrate and other short-chain fatty acids, cause alterations in the adjacent mucosal surfaces, including direct bacterial invasion, increases in neutrophil and other immune cell infiltrates, expression of cytokines such as IL-17 and upregulation in oncogenic pathways involving genes such as ERK, PI3K,

Table 3
The microbiome of tumor sites in various cancer types.

Sample type	Tumor type	Bacteria	Effect	Ref
Feces	CRC	*Fusobacterium nucleatum*	Induces tumorigenesis via miR21, increases tumor multiplicity, recruits immune cells, induces oncogene expression via E-cadherin binding and B-catenin signaling	(Yang et al., 2017; Rubinstein et al., 2013)
		Campylobacter jejuni	Produces cytolethal distending toxin causing dsDNA breaks, increases tumor growth and multiplicity	(He et al., 2018)
		Escherischia coli	Inflammation and increased tumor formation	(Arthur et al., 2012)
		Bacteroides fragilis	Induces colonic tumors via IL-17, induces Stat3-driven TH-17 T cell response	(Wang et al., 2012a; Wu et al., 2009; Housseau et al., 2016)
		Butyrate-producing bacteria eg *Roseburia. E. rectale and F. prausnitzii*	Decreased in CRC patient feces, associated with decreased butyrate which may cause increased tumorigenesis	(Wang et al., 2012a; Balamurugan et al., 2008)
Airway	Lung	*Haemophilus influenza*	promote tumor formation via IL-17C and neutrophil infiltration, increase metastatic growth	(Jungnickel et al., 2017)
		Streptococcus, Veillonella	Increased in cancer compared with controls	(Tsay et al., 2018)
Urine	Bladder	Fusobacterium, Campylobacter and Ruminococcaceae	Increased in cancer compared with controls, F. nucleatum also found in tissue	(Bucevic Popovic et al., 2018)
		Acinetobacter, Anaerococcus and Sphingobacterium	Increased in cancer compared with controls	(Wu et al., 2018b)
	Prostate	Veillonella, Streptococcus, Bacteroides, E. coli, Anerococcus spp, Proprionibacterium	Increased in cancer compared with controls	(Yu et al., 2015b) (Cavarretta et al., 2017; Shrestha et al., 2018; Alanee et al., 2019)
Oral	Head and neck cancers	*Fusobacterium periodonticum, Parvimonas micra, Streptococcus constellatus, Haemophilus influenza*, and *Filifactor alocis*	Increased with increasing stage of cancer	(Lim et al., 2018)
Vaginal	Cervical cancer	*Lactobacillus gasseri* and *Lactobacillus iners*	Altered clearance of HPV	(Brotman et al., 2014; Oh et al., 2015),
		Atopobium vaginae, G. vaginalis and Fusobacterium	Associated with cervical intraepithelial neoplasia	(Seo et al., 2016; Audirac-Chalifour et al., 2016; Champer et al., 2018)

Wnt/B-catenin and STAT3. The alterations in the immune microenvironment may explain why microbiome composition affects the efficacy of immune checkpoint inhibitors (discussed below), and why antibiotic treatment may also influence these therapies.

The “common ground” hypothesis, postulated by Lynch et al in 2016, proposed that changes in the microbiota, instigated by an environmental factor such as diet or chronic infection, lead to polygenic changes which cause disease, such as cancer, in a host with genetic susceptibility (Lynch and Pedersen, 2016). While this remains a theoretical explanation, many of the studies examined here support this hypothesis. It appears that lower diversity of the microbiota is associated with the presence of tumor – this decrease in diversity may be present in tumor-adjacent normal tissue, suggesting that this change may be a precursor to the development of cancer and may even be a causative factor. The considerable variation in both the microbiota of various body sites and in the genetic susceptibility of hosts leads to the heterogeneity of studies attempting to establish causation by specific bacteria in human diseases. Further studies with adequate controls are needed to validate many of the findings described here.

6. Indirect effects of the gut microbiome in cancer

The microbiome of the gut can vary in patients with non-gastrointestinal tumors such as pancreatic cancer and hepatocellular cancer (HCC) (Table 4) (Grat et al., 2016). In pancreatic cancer, the bacteria found in the tumor microenvironment are similar to those found in the gut. As previously described, bacteria can translocate from the gut to the pancreas (Pushalkar et al., 2018; Geller et al., 2017), while in murine models, ablation of the fecal microbiome protected against development of cancer and altered the immune cell infiltrate, with transfer of feces from cancer-bearing mice reversing this effect (Pushalkar et al., 2018; Sethi et al., 2018). Obese mice demonstrate alterations in their gut microbiota which leads to increased DCA production and induction of a secretory phenotype in hepatic stellate cells which promotes carcinogenesis in the liver, while blocking DCA or reversing the bacterial changes can prevent HCC development (Yoshimoto et al., 2013).

Post-menopausal patients with breast cancer have been shown to have lower gut flora diversity, an oestrogen-independent effect, and altered IgA-associated microbes, compared with post-menopausal controls (Goedert et al., 2015; Zhu et al., 2018), while the composition of the fecal microbiome differs with varying stages of breast cancer (Luu et al., 2017). The feces of lung cancer patients also varies in bacterial composition (Table 4) [30416659], a dysbiosis which was suggested may lead to a low concentration of butyrate and thereby contribute to cancer proliferation. As described in a later section, it has been shown that alterations in the gut microbiome can affect response to immunotherapy in renal cell carcinoma, melanoma and lung cancers. Differences in the gut bacterial composition have been noted between patients with and without prostate cancer, with increased α-diversity and altered composition (Liss et al., 2018; Sfanos et al., 2018; Golombos et al., 2018), while patients on oral anti-androgen therapy for prostate cancer also have alterations in their gut microbiome, although again the significance of these changes are unclear (Sfanos et al., 2018).

Interestingly, in mice in whom the gut microbiome was altered by disinfection by-products in water, metabolomic analysis of the urine revealed significant changes in metabolites in urine, including the polyamine spermine, which has previously been linked to many cancers including prostate, RCC and others (Gao et al., 2017b; Rioux-Leclercq et al., 2004; Sandsmark et al., 2017; Murray-Stewart et al., 2016), suggesting that the microbiota of the gut alters metabolites in remote sites by some mechanism. The composition of the oral microbiome may be associated with non-oral cancers, such as gastric cancer (Wu et al., 2018a), pancreatic cancer (Olson et al., 2017; Maisonneuve et al., 2017; Fan et al., 2018b; Bracci, 2017)and colon cancer (Table 4), with numerous bacterial species found in the mouth involved in biofilm

Table 4
Indirect effects of gut microbiome in various cancer types.

Sample type	Tumor type	Bacteria	Effect	Ref
Feces	Pancreas	Bifidobacterium pseudolongum	Translocates to pancreas, accelerates oncogenesis in murine model	(Pushalkar et al., 2018)
		Proteobacteria, Synergistetes, and *Euryarchaeota*	Increased in feces of PDAC patients compared to controls	(Pushalkar et al., 2018)
	Hepatocellular cancer	*Escherischia coli*	Increased in feces of HCC patients compared to cirrhotic controls	(Grat et al., 2016)
	Breast cancer	*Clostridium coccoides, Faecalibacterium prausnitzii, Blautia*	Lower diversity, variation in fecal microbiota with stage of cancer	(Goedert et al., 2015; Zhu et al., 2018; Luu et al., 2017)
	Lung cancer	Bacteroides, Veillonella, and Fusobacterium	Increased in feces of lung cancer patients compared with controls	(Zhang et al., 2018)
		Escherichia, Shigella, Kluyvera, Fecalibacterium, Enterobacter, and Dialister	Decreased in feces of lung cancer patients compared with controls	(Zhang et al., 2018)
	Prostate cancer	Bacteroides and Streptococcus	Increased compared with controls	(Liss et al., 2018; Sfanos et al., 2018)
		Akkermansia muciniphila and Ruminococcaceae spp	Increased in patients on oral anti-androgen therapy	(Sfanos et al., 2018)
Oral microbiome	Gastric cancer	Increase in Firmicutes and a decrease in Bacteroidetes	Altered compared with controls	(Wu et al., 2018a)
	Pancreatic cancer	*Porphyromonas gingivalis* and*Aggregatibacter actinomycetemcomitans*	Associated with periodontal disease and pancreatic cancer development	(Olson et al., 2017; Maisonneuve et al., 2017; Fan et al., 2018b; Bracci, 2017)
	Colon cancer	*Treponema denticola, Prevotella spp.*, Streptococcus	Increased compared with controls, biofilm formation	(Klimesova et al., 2018; Yang et al., 2018b; Flemer et al., 2018)

formation, pro-inflammatory stimulation and colorectal carcinogenesis (Klimesova et al., 2018; Yang et al., 2018b; Flemer et al., 2018).

The effects of alterations of the microbiome in the gut, and potentially in other sites, may cause long-distance effects in organs such as the liver, breast, lung and prostate. The method by which this modulation occurs remains unexplained – it may be that bacterial metabolites such as bile acids, fatty acids and polyamines induce carcinogenesis in remote organs. Stimulation of the rich immune system of the gut could lead to alterations in immune cell populations and small molecule expression which in turn provoke tumor formation. It may be that oncogenic bacteria translocate directly from one body site to another, as may occur in the pancreas. Once the mechanisms by which this effect occurs are revealed, the microbiome may be exploited to influence the processes of carcinogenesis and tumor progression.

7. Immunotherapy and the microbiome

There is growing evidence that the human microbiome can affect the efficacy of immunotherapy. The advent of checkpoint inhibitors and the widespread use of this type of immunotherapy has uncovered a new interaction between cancer treatment and the microbiome. In patients with metastatic melanoma treated with the anti-CTLA-4 antibody ipilimumab, gut microbiota enriched with Fecalibacterium and other Firmacutes was found to be associated with longer progression-free survival (PFS) and overall survival (OS) than microbiota driven by Bacteroides (Chaput et al., 2017). Interestingly, colitis as an adverse effect of the treatment was also associated with the beneficial microbiota profile, suggesting that this may be a marker of response to treatment. More recently, the gut microbiome profile in melanoma patients was associated with response to treatment with anti-programmed cell death protein-1 (anti-PD-1) antibodies, with abundance of the Ruminococcaceae family in responders (Gopalakrishnan et al., 2018). Transplantation of the feces of responders into germ-free mice enhanced systemic and anti-tumor immunity. In a similar study in metastatic melanoma, patients who responded to immunotherapy had fecal profiles enriched with *Bifidobacterium longum, Collinsella aerofaciens*, and *Enterococcus fecium* (Matson et al., 2018). Mouse models of melanoma have also identified Bifidobacterium as being associated with antitumor immunity; oral administration of Bifidobacterium had similar tumor control rates to administration of anti-PD-1 ligand (anti-PD-L1) therapy, and co-administration of both almost completely abolished tumor growth, suggesting this bacteria as a promising adjunctive therapy to checkpoint inhibitors (Sivan et al., 2015).

In patients with advanced cancers treated with immunotherapy, resistance was associated with an abnormal gut microbiome and with antibiotic therapy (Routy et al., 2018). In this study, abundance of *Akkermansia muciniphila* was associated with response to treatment. When germ-free mice were inoculated with feces from non-responders, their response was restored by oral supplementation with *A. muciniphila*. This bacterial species is enriched in patients with prostate cancer who have been treated with anti-androgen therapy; and may enhance response to subsequent or concurrent immunotherapy in these patients. Antibiotic treatment in patients with advanced RCC and non-small cell lung cancer (NSCLC) decreased the effectiveness of anti-PD-L1 monoclonal antibody treatment. Patients who had recent antibiotic treatment had a higher risk of primary progressive disease, shorter PFS and shorter OS in RCC and NSCLC (Derosa et al., 2018). Prior exposure to antibiotics such as penicillins, cephalosporins and macrolides increased the risk of cancers including lung, gastric, prostate and breast cancers even after adjusting for smoking status and number of infections, suggesting that alterations in the microbiome may predispose to cancer development [26338196].

8. Modulation of the microbiome and its role in cancer therapeutics

Given the significant role that the microbiome appears to play in cancer, modulation of the microbiota may allow alteration of the course of disease. There are many ways in which the microbiome can be modified. Prebiotics are defined as substrates that are selectively used by host micro-organisms conferring a health benefit, with the most studied being oligosaccharides which promote Bifidobacteria and appear to improve conditions such as type 2 diabetes mellitus, metabolic syndrome and allergies among many (Anon., 2019; Roberfroid et al., 2010). Probiotics are live micro-organisms that, when administered in adequate amounts, confer a health benefit, and again have been shown to have wide-ranging effects on various health-related conditions including supporting a health digestive tract (Hill et al., 2014; Ritchie and Romanuk, 2012). Synbiotic treatment involves a combination of pre- and pro-biotics in an attempt to synergize the effects of both bacteria and substrates, and has been used in treatment of many conditions such as pancreatitis, non-alcoholic steatohepatitis and childhood eczema (Markowiak and Slizewska, 2017; Zhang et al., 2010; Eslamparast et al., 2014; Dang et al., 2013). Apart from oral "-biotic" supplementation, fecal microbiota transplantation (FMT) is the most widely recognized technique used to modify the microbiome. FMT has a demonstrated benefit in recurrent or refractory Clostridium difficile infection (van Nood et al., 2013; Cammarota et al., 2015; Lee et al., 2016b), and has also been used in treatment of ulcerative colitis and metabolic syndrome (Vrieze et al., 2012; Moayyedi et al., 2015)

Modulation of the microbiome can be exploited in cancer therapeutics. Firstly, since the microbiome appears to be involved in the process of carcinogenesis, manipulation of microbiota may help in cancer prevention. Recent work in a mouse model of colonic carcinogenesis showed that oral intake of a probiotic supplement containing *Lactobacillus helveticus* could decrease IL-17-producing T cells and suppress hyperplasia and tumor formation, possibly by altering the gut microbiome (Rong et al., 2018). Synbiotic administration can also alter fecal microbiota, reduce colonic proliferation and increase epithelial barrier function in patients with resected colonic polyps or tumours (Rafter et al., 2007). There is also potential to genetically modify microbes, as well as to use antibiotics, drugs targeting bacterial-induced inflammation or genotoxins, to prevent carcinogenesis (Khazaie et al., 2012; Schwabe and Jobin, 2013). An interesting study from the National Institute of Health examined the 21 common laboratory mouse strains and compared their microbiota to that of a closely related wild relative (Rosshart et al., 2017). When laboratory mice were reconstituted with natural "wild-type" microbiota, they had increased resistance to mutagen and inflammation-induced colorectal tumorigenesis. Modulating the microbiome in the pre-cancerous phase of disease may provide a mechanism to prevent cancer development.

Altering the microbiota can affect cancer growth and prevent cancer recurrence. In a mouse model of inflammation-induced colonic tumors, probiotic supplementation decreased tumor cell proliferation and tumor number, downregulated NF-kB activation and promoted beneficial commensal bacteria in the gut (Rong et al., 2018). Another interesting study in a murine melanoma model demonstrated that aerosolized probiotic treatment could promote immunity against lung metastases, representing another delivery method for microbiome modulation (Le Noci et al., 2018). Administration of *Lactobacillus acidophilus* to mice with breast tumors altered cytokine production and reduced tumor growth, possibly altering the microbiome in the gut, tumor or other location (Maroof et al., 2012). A number of trials have shown effectiveness of probiotic supplements in patients with bladder cancer. A double-blind randomized trial in 138 patients with primary bladder cancer reported that daily oral administration of an oral *Lactobacillus casei* preparation prevented recurrence after transurethral resection of tumors compared with placebo (Aso et al., 1995). Another retrospective study demonstrated some possible effect of previous intake of fermented milk products on decreasing risk of bladder cancer [12053032]. A more recent prospective randomized controlled trial in 207 patients demonstrated that 3-year recurrence free survival after transurethral bladder tumor resection was improved with intravesical epirubicin and 1 year of *Lactobacillus casei* compared with intravesical epirubicin alone (Naito et al., 2008). These intriguing results suggest that oral supplementation with bacteria may alter the fecal and/or urinary microbiome and thereby influence neoplastic disease in the bladder.

Microbiome modulation can also be used as an adjunct to standard cancer treatment. In 2013, it was shown in murine models that germ-free or antibiotic-treated animals did not respond to platinum-based chemotherapy, indicating that an intact microbiome was required for modulating the myeloid-derived immune cell responses in the tumor microenvironment (Iida et al., 2013). In the same year, Viaud et al showed that germ-free or antibiotic-treated mice demonstrated decreased translocation of Gram-positive bacteria into lymphoid organs, a reduction in T helper-17 cells and diminished response to cyclophosphamide, while transfer of T helper-17 cells restored the efficacy of cyclophosphamide (Viaud et al., 2013). Oral gavage with Enterococcus hirae also restored tumor responsiveness to cyclophosphamide (Daillere et al., 2016). Cisplatin is a platinum-based chemotherapeutic agent that can cause breaching of the intestinal epithelial barrier and translocation of gut bacteria to the bloodstream. In mice with ovarian tumors, cisplatin damaged the intestinal epithelium and altered the gut commensal flora, an effect which was abrogated by administration of *Ruminococcus gnavus* and fecal pellet gavage (Perales-Puchalt et al., 2018). In a mouse lung cancer model, concurrent antibiotics decreased the effectiveness of cisplatin, while supplementation with Lactobacillus decreased tumor size and improved survival, suggesting that in fact cisplatin-induced intestinal damage and alteration of the microbiome may be a part of its anti-tumoral activity (Gui et al., 2015). In a mouse model of colon cancer, intratumoral Gammaproteobacteria could metabolize gemcitabine into its inactive form, an effect which was abrogated by treatment with the antibiotic ciprofloxacin (Geller et al., 2017); interestingly, this bacteria was found in 76% of human pancreatic cancer tissue samples, suggesting that this may be a mechanism by which these tumors become resistant to treatment with gemcitabine.

There are suggestions from animal models that alterations in the microbiome may affect the response to newer therapies such as adoptive T cell transfer. In mice treated with adoptive T cell therapy, changes were observed in the gut microbiome; when the mice were treated with oral vancomycin (which does not cross the intestinal barrier), changes in abundance of Bacteroidetes and Firmicutes were seen, and tumor progression was reduced, providing evidence that the gut microbiota can influence the efficacy of adoptive T cell therapy (Uribe-Herranz et al., 2018).

Finally, modulation of the microbiome may be useful in treatment of cancer-related and therapy-related effects. Chemotherapy can cause severe imbalances in the gut microbiome which alter metabolic pathways – this has the potential to be modified (Montassier et al., 2015). Treatment with synbiotics containing *Bifidobacterium breve* and *Lactobacillus casei* along with galacto-oligosaccharides decreased complications such as diarrhea, neutropenia and lymphopenia in patients receiving neoadjuvant chemotherapy for esophageal cancer (Motoori et al., 2017). Probiotics have also been used to improve diarrhea associated with 5-fluorouracil chemotherapy and radiation in numerous gynecological and gastrointestinal tumour types (Osterlund et al., 2007; Lalla et al., 2014; Ferreira et al., 2014). Fecal transplantation can be used in treatment of immunotherapy-related colitis (Wang et al., 2018).

The numerous studies described here suggest that pre-/pro-/synbiotic supplementation and fecal transplantation may have cancer preventative effects, and may also be used as adjunct treatments in many cancer types. Used alone or combined with standard chemotherapy or immunotherapy, microbiome modulation may enhance the efficacy and decrease side effects of these treatments, prevent

disease recurrence and decrease metastases.

9. Confounding factors and limitations in microbiome research

Much of the research described here involves small studies with limited data on clinical factors and controls. There are many confounding factors that may influence the microbiome which larger-scale studies need to address in their design. There are differences in microbial composition between males and females, which may be affected by factors such as sex hormones, body size and even mood (Pala et al., 2019; Raju et al., 2019; Taylor et al., 2019). Smoking can influence the lung microbiome (Greathouse et al., 2018; Yu et al., 2016) in addition to the gut microbiome (Vogtmann et al., 2015; Benjamin et al., 2012), while smoking cessation can also induce changes in the intestinal microbiota (Biedermann et al., 2013). The gut microbiome of populations who consume different diets varies dramatically, with large differences in both microbes and metabolites seen between rural Africans and African-Americans, groups who have low and high risk of colon cancer development respectively (Ou et al., 2013); when their diets were reversed, rural Africans who were fed high-fat, low-fibre diets developed increased stool *F. nucleatum* levels, suggesting this as a mechanism for the carcinogenic risk (O'Keefe et al., 2015). Other factors including stent insertion or other instrumentation, bowel preparation and medications such as proton pump inhibitors (PPIs) and metformin can also influence the microbiome (Buhmann et al., 2019; Vaishnavi et al., 2018; Scheufele et al., 2017; Mishiro et al., 2018; Jalanka et al., 2015; Hojo et al., 2018; Wu et al., 2017). Therefore, future investigation into the role of the microbiome in cancer needs to account for all of these potential confounders. Many of the studies described in this review are limited by lack of or inadequate control samples and lack of validation in independent cohorts or further research. This limits our ability to draw conclusions or critically analyze much of the available data on the human microbiome and cancer.

10. Conclusions

From the evidence reviewed here, it is clear that the microbiome plays a complex role in human cancers. We know that the microbiome is influenced by many factors including environmental, dietary and genetic variations. The human microbiome is an emerging target in the field of cancer development and therapeutics. While much of this research is still at an early stage and the technologies used for analysis continue to evolve, there is obvious potential to utilize the microbiota of various sites in the body to predict cancer development and to act as a prognostic biomarker in cancers. A growing body of evidence suggests that the microbiome can influence response to immunotherapy, chemotherapy and newer cell transfer therapies. Modulation of the microbiome may provide methods to increase efficacy of treatments, reduce treatment toxicities and even to prevent carcinogenesis. While work has been done on the fecal microbiome, little research exists examining the role of the microbiota of tissue and of tumor-site fluids such as urine and mucus in tumorigenesis and treatment response, and further work is needed to delineate the influence of confounding factors on bacterial composition. Well-designed, controlled, structured, observational and interventional studies of the microbiome in cancer development and treatment are needed to assess disease associations and the diagnostic and therapeutic potential of the microbiome in human cancers across organ sites.

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