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THE INFLUENCE OF THE COMMENSAL MICROBIOTA ON DISTAL TUMOR-PROMOTING INFLAMMATION

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Abstract

Commensal microbes inhabit barrier surfaces, providing a first line of defense against invading pathogens, aiding in metabolic function of the host, and playing a vital role in immune development and function. Several recent studies have demonstrated that commensal microbes influence systemic immune function and homeostasis. For patients with extramucosal cancers, or cancers occurring distal to barrier surfaces, the role of commensal microbes in influencing tumor progression is beginning to be appreciated. Extrinsic factors such as chronic inflammation, antibiotics, and chemotherapy dysregulate commensal homeostasis, and drive tumor-promoting systemic inflammation through a variety of mechanisms including disruption of barrier function and bacterial translocation, release of soluble inflammatory mediators, and systemic changes in metabolic output. Conversely, it has also been demonstrated that certain immune therapies, immunogenic chemotherapies, and checkpoint inhibitors rely on the commensal microbiota to facilitate anti-tumor immune responses. Thus, it is evident that the mechanisms associated with commensal microbe facilitation of both pro- and anti-tumor immune responses are context dependent and rely upon a variety of factors present within the tumor microenvironment and systemic periphery. The goal of this review is to highlight the various contexts during which commensal microbes orchestrate systemic immune function with a focus on describing possible scenarios where the loss of microbial homeostasis enhances tumor progression.

Keywords

Commensal microbiota; cancer; inflammation; metabolism; dysbiosis

1. Introduction

Commensal microbes, comprised of bacteria, archaea, viruses, and eukaryotes, inhabit all mucosal barrier surfaces, providing a physical barrier in defense against invading pathogens. Additionally, commensal microbes play essential roles in the maintenance of local tissue and immune homeostasis within the gastrointestinal tract [1–5], the skin [6, 7], the urogenital tract [8, 9] and the oral/respiratory tract [10–13]. Colonization with commensal microbes at birth is critical for the postnatal development and function of mucosal immunity [14, 15]. However, commensal-mediated immune conditioning extends beyond mucosal surfaces,

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impacting both systemic immune function and homeostasis. Changes in commensal homeostasis are dynamic and occur gradually during aging or from changes in diet. Acute disturbances resulting from antibiotic usage, infection, or chemotherapy can also drastically alter established commensal equilibrium, rapidly culminating in a loss of immune homeostasis. Loss of commensal homeostasis, or commensal dysbiosis, can lead to increased inflammation and immune pathology that ultimately affects the systemic periphery. In this context, alterations to commensal equilibrium induce pathological inflammation that is supportive of tumor growth. Although we do not yet have a firm understanding of the precise microbial populations that associate with tumor-promoting inflammation, it is evident that commensal microbes influence the outcome of extramucosal tumors.

Over three decades ago, scientists began to observe that certain gram-negative commensal species influence myelopoiesis and the emergence of granulocyte precursors from the bone marrow [16–18], suggesting that commensal microbes influence immune function through undefined interactions with distal sites such as the bone marrow. Germ-free mice have a deficit in the myeloid compartment of bone marrow resulting in increased susceptibility to infection with Listeria. However, restoration of immune function is achieved through recolonization of germ-free mice with fecal contents from conventional mice, enabling clearance of Listeria [19]. Additional studies demonstrated that commensal products, such as lipopolysaccharide (LPS) or peptidoglycan provide a tonic level of stimulation through Toll-like receptors (TLR) and other innate receptors expressed by myeloid cells, driving myelopoiesis [20] and enhancing myeloid clearance of bacterial [21] and viral pathogens [22, 23]. Commensal microbes are also associated with the development of mucosal-associated and peripheral lymphocytes such as Foxp3+ regulatory T cells [24–26], IL-17-producing αβ T cells [27, 28] and γδ T cells [29], and invariant NKT cells [30, 31]. Data from the Human Functional Genomics Project supports much of what has been elucidated in mice, demonstrating that distinct commensal or metabolic signatures are associated with both innate and adaptive cytokine response patterns [32]. These studies underscore the complex immunoregulatory influence that commensal microbes have on local and systemic immune homeostasis in healthy individuals.

Cancer is a systemic disease: inflammatory immune cells, chemokines and cytokines distally influence tumor growth and metastatic progression. Cancer can impact the composition of commensal microbes locally within affected tissues [33–36] or distally within the intestines [37, 38], altering the immune environment in favor of tumor growth and global immune suppression [39]. The relationship between commensal microbes, inflammation, and oncogenesis is well-documented for colorectal cancer [40–42], which is locally influenced by dysregulation of commensal homeostasis as a result of chronic antibiotic exposure, diet, age, infection, and genetic polymorphisms that drive inflammation and oncogenesis. Cancer patients may also have disruptions in commensal homeostasis as a result of chemotherapy, administration of antibiotics, whole body irradiation, cachexia, and/or systemic tumor-promoting inflammation (Figure 1). Several recent studies have begun to link changes within the composition of commensal microbes to global modulation of tumor-promoting inflammatory cytokines [39] and have identified certain microbes that facilitate enhancement of anti-tumor immune responses during immunotherapy [43–45] and chemotherapy [43, 46].

Thus, patients with extramucosal tumors, occurring distal to mucosal surfaces, are also influenced by alterations in commensal composition. In this review, we will highlight mechanisms associated with commensal-induced pathological inflammation with a focus on detailing how microbes, microbial products, and/or disruptions in commensal homeostasis impact extramucosal cancer progression.

2. Alterations to microbiome associated with inflammation and cancer

In healthy adults, the abundance of certain commensal species is associated with the functional ability of both myeloid and lymphoid cells to produce inflammatory cytokines such as TNFα, IL-6, IL-1β, IFNγ, IL-17 and IL-22 [32]. These cytokines are all capable of influencing tumor progression through multiple mechanisms, including the promotion of tumor growth through the recruitment of suppressive immune cells into the tumor microenvironment via TNFα, IL-6, IL-1β or facilitating enhanced tumor immune surveillance via IFNγ and IL-17. However, microbial populations associated with inflammation may be altered during states of dysbiosis, defined as an imbalance of commensal homeostasis and resultant outgrowth of pathological microbial species. It is well-accepted that commensal dysbiosis can drive pathologies within barrier surfaces, but dysbiosis also results in systemic damage to distal organs due to aberrant inflammation and metabolic dysregulation [47]. Dysbiosis can be induced by multiple mechanisms, including diet or genetic-induced dysbiosis, antibiotic-induced dysbiosis, and dysbiosis due to tumor-promoting chronic inflammation, all of which associate with a more unfavorable outcome during cancer.

2.1 Inflammation, dysbiosis, and cancer

There are several studies linking dysbiosis with cancer and inflammation, although it remains relatively undefined whether dysbiosis directly impacts tumor progression or serves as a biomarker of oncogenesis. Dysbiosis has been demonstrated in patients with advanced breast cancer, with breast tumors having reduced microbial diversity compared to normal breast tissue [34]. In these patients, reduced diversity of tumor-associated commensal species corresponds with reduced expression of inflammatory innate signaling receptors such as TLR2, TLR5, and nucleotide-binding oligomerization domain–containing protein (NOD)1 and NOD2 [34]. These innate recognition receptors may serve a protective role in breast tissue, as TLR5 signaling and activation of MAIP1S has been shown to inhibit breast tumor growth through the induction of autophagy and tumor cell death [48, 49]. These studies suggest that dysbiosis within the breast tissue may occur through dysregulation of innate signaling receptors, promoting the outgrowth of inflammatory or DNA-damaging bacterial species. Indeed, Urbaniak et al. determined that *Escherichia coli* and *Staphylococcus epidermidis* isolates from dysbiotic breast tissues are able to directly induce DNA damage in a tumor cell line [50]. Microbial sequencing of an additional cohort of breast tissue specimens found a tumor-specific increase in *Fusobacterium* [51], a genus of bacteria which harbors the species *F. nucleatum*, a bacterium directly associated with driving inflammation and carcinogenesis in colorectal cancer [52, 53].

Changes in the composition of commensal microbes within the reproductive tract are also associated with increased inflammation. Women with endometrial cancer have dysbiosis in the vagina, cervix, and endometrium that is associated with malignant progression [54]. Protein analysis of cervical samples revealed that severe cervical dysbiosis correlates with elevated levels of both proinflammatory cytokines and enzymes associated with proteolysis and alterations to the cervical mucosa and cytoskeleton [55]. Furthermore, alterations in the composition of bacteria within the reproductive tract are associated with increased levels of GM-CSF, TNFα, IFNγ, and IL-1β [56]: cytokines that promote myeloid infiltration within tumor beds. Together, these studies suggest that severe dysbiosis within the reproductive tract leads to an increase in inflammation and pathology, resulting in damage to mucosal surfaces. Importantly, these studies highlight that the location, composition and function of the normal microflora within each unique niche serves a specific homeostatic role.

2.2. Diet-induced dysbiosis and cancer

Diet-induced dysbiosis and obesity are prevalent health issues in developed countries. Morbidities associated with obesity include insulin resistance, cardiovascular disease, and an increased incidence of several types of cancers [57–60]. In a healthy individual, commensal metabolic byproducts help to stabilize commensal equilibrium, preventing the growth of inflammatory species which compete with the host for nutrients. In homeostatic conditions, commensal microbes also salvage potentially toxic nutritional byproducts such as bile, which can accumulate, cause toxicity, and in some instances, induce DNA damage leading to oncogenic transformation [61]. A previous study comparing the bacterial composition of obese and non-obese individuals found that obese individuals have significantly reduced gene richness and compositional diversity within their microbiota, with a predominance of *Bacteroides* spp. occurring within the dysbiotic gastrointestinal tract [62]. Functionally, this study found that commensal bacteria from obese individuals have microbial gene signatures associated with inflammation and mucosal damage, including increased proportions of inflammatory bacterial species, a reduced capacity to produce immune regulatory butyrate, an increase in mucus degrading proteins, and an increased capacity to handle oxidative stress [62]. Diet-induced changes in microbial diversity can therefore result in systemic inflammation and a disruption in homeostasis due to altered metabolite output and/or a disruption in mucosal integrity, leading to bacterial translocation and systemic distribution of shed microbial products (Figure 1), which we will discuss in greater detail below.

In mice, a high-fat diet results in changes within the composition of commensal microbes, promoting decreased production of immunoregulatory metabolites and localized inflammation within the stomach epithelium, leading to cancer [63]. Fecal transplant experiments have demonstrated that transfer of the microbiome from mice fed a high-fat diet was sufficient to increase cancer incidence in recipient animals [63], providing evidence that diet-induced changes to the composition of commensal microbes is sufficient to influence cancer progression independent of the physiologic manifestations associated with obesity. Administration of the immune regulatory short-chain fatty acid butyrate, which was reduced in people and animals with diet-induced changes to commensal equilibrium [62, 63], was also sufficient to reduce histopathology and tumor progression in animals fed a high-fat diet [63]. Butyrate directly inhibits the growth of multiple tumor types through inhibition of

histone deacetylases and potent anti-inflammatory activity [64], suggesting that dietary intervention through consumption of fiber-rich foods could provide therapeutic benefit during tumor progression. The effects of butyrate will be discussed in further detail in section 4.1.

Diets high in fat and low in fiber also result in the accumulation of metabolites associated with increased toxicity. For example, obesity has been linked to increased systemic levels of deoxycholic acid [61]. Mechanistically, circulation of deoxycholic acid through the hepatic portal vein induces an inflammatory and pro-tumorigenic senescence-associated secretory phenotype in hepatic stellate cells, resulting in inflammation-induced damage of adjacent hepatic cells and resultant oncogenesis [65]. Supporting a role for this DNA-damage inducing metabolite, rats fed a diet containing high amounts of deoxycholic acid developed pre-neoplastic liver lesions [66]. Alterations in commensal microbe composition resulting from dietary changes may also influence additional bacterial metabolites as highlighted in Table 1.

2.3 Antibiotic-induced dysbiosis

Although antibiotics have significant health benefits for individuals with microbial infections, excessive antibiotic exposure can negatively impact commensal biodiversity and immune function [67–69]. According to the CDC, greater than 5 out of 6 individuals are prescribed antibiotics annually in the United States [70], often unnecessarily. Additionally, cancer patients are frequently prescribed prophylactic antibiotics due to severe immune suppression and susceptibility to infectious diseases. Several studies have demonstrated associations between chronic/prolonged antibiotic use and increased cancer risk. In one study, women prescribed 11 or more courses of the same antibiotics had an increased association with developing breast cancer [71]. While a large-scale retrospective study of over 2 million women found only a slight increase in hazard risk of breast cancer in women using all classes of antibiotics for more than 101 days, women prescribed 3 or more courses of tetracyclines over a span of more than 101 days have a significantly greater risk of breast cancer than women given other types of antibiotics [72, 73]. Similarly, in a large multi-cancer health database survey, it was found that the risk for lung, esophageal, gastric and renal cancers significantly increases in individuals prescribed penicillins more than 5 times. The risk for lung and renal cancers is significantly associated with multiple courses of macrolides [73]. This study also confirmed that long-term exposure to tetracyclines increases the risk of breast cancer [73]. Overall, these retrospective studies suggest that although a single exposure to antibiotics does not significantly influence cancer risk, multiple and long-term exposures to single classes of antibiotics increase the incidence of numerous cancers. Although the mechanisms linking antibiotic use and cancer development and progression are unknown, one might speculate that chronic antibiotic exposure drives prolonged dysbiosis, inflammation, and tissue damage that leads to an increased risk for oncogenic transformation in susceptible tissues. However, undefined host or environmental factors may result in the need for frequent antibiotic courses and may also be associated with an increased risk of cancer. Further studies are necessary to determine whether there is a direct relationship between antibiotics and cancer.

Antibiotics, especially tetracyclines [74], are also capable of directly influencing tumor progression through the induction of mitochondrial dysfunction, increased production of reactive oxygen species (ROS), and corresponding DNA damage [75]. Antibiotics have been shown to directly influence immune cell function in addition to modulating the composition of commensal microbes, resulting in the attenuation of immune surveillance. Metastatic growth of Lewis lung carcinoma and B16F10 melanoma is enhanced in the lungs of antibiotic-treated mice which is mediated by a reduction in lung-protective IL-17-producing γδ T cells. This increase in metastatic growth was lost upon administration of recombinant IL-17 [76], demonstrating that the systemic influence of commensal microbes on the induction of immunoregulatory IL-17 T cells can serve a protective role in the establishment of anti-tumor immunity. However, other studies have demonstrated that antibiotic treatment induces the production of immune-suppressive and tumor-promoting mediators, through the induction of dysbiosis. Antibiotic-induced dysbiosis promotes the outgrowth of Candida species in the lungs, resulting in an increase in prostaglandin E2 (PGE2) production and polarization of macrophages into an M2 suppressive phenotype [77]. These studies highlight the contextual relationship between commensal microbes and the immune system. By further understanding the functional consequences of alterations to microbial diversity, we may be able to develop unique probiotic cocktails to attenuate various pathological conditions, especially in immune compromised patients that require antibiotic treatment.

2.4 Genetic mutations associated with effects on bacterial composition/tumorigenesis

Analysis of data from the Human Microbiome Project demonstrated a significant association between certain single nucleotide polymorphisms (SNP) and the composition of commensal microbes at several barrier sites [78]. Polymorphisms associated with immunological pathways and commensal-driven diseases significantly impact microbial composition [78]. This human data supports several mouse studies demonstrating that single genes associated with microbial sensing are significantly able to impact the composition of commensal microbes and overall host physiology [79–81].

Approximately 7% of the general population harbors a dominant-negative SNP mutation within the flagellin-binding domain of TLR5, resulting in ablation of TLR5 signaling [82]. This polymorphism was shown to have an influence on the outcome and survival of patients with various extramucosal malignancies [39]. Mechanistically, TLR5 signaling through interactions with commensal microbes results in systemic elevation of IL-6 and the recruitment of myeloid-derived suppressor cells (MDSC) into the tumor microenvironment. MDSCs secreting adenosine induce galectin-1 expression in γδ T cells, resulting in cumulative suppression of tumor-associated immune responses and more rapid progression of ovarian tumors and sarcomas [39]. This study was the first to suggest that genetic polymorphisms present within the human population, mediated through interactions with commensal microbes and the immune system, could influence the outcome of extramucosal cancers.

A recent study has demonstrated that retinoic acid-inducible gene-I (RIG-I), a viral RNA receptor capable of recognizing double-stranded RNA viruses, regulates the composition of commensal microbes through the production of IgA and the downstream induction of

Reg3γ, an antimicrobial peptide important in controlling the composition of commensal microbes [83]. RIG-I-deficient mice have increased dysbiosis and emergence to colorectal cancer upon treatment with AOM/DSS. Clinically, these findings are relevant, as human colorectal cancer specimens have significantly reduced levels of RIG-I, suggesting that downregulation of this receptor results in dysbiosis and susceptibility to colorectal cancer [83]. Expression of NOD2 on the colonic mucosa was also found to influence the composition of commensal microbes and the inflammatory microenvironment within the intestines, leading to an increased incidence of colitis-associated cancer in NOD2-deficient mice [84]. Although most studies have focused upon the role of NOD receptors in modulating intestinal malignancies, a study using NOD-deficient breast tumor cell lines demonstrated that breast tumors lacking NOD were more resistant to TNFα-induced apoptosis and were more sensitive to estrogen-mediated tumor growth [85]. Thus, similar to what has been reported in colorectal cancer, NOD expression on the tumor epithelium may have a protective role in extramucosal cancers, such as breast cancer. However, the attenuation of tumor growth in this model is primarily mediated through NOD-dependent activation of caspase 8, resulting in apoptosis [85, 86]. Because these studies were performed using in vitro models, this mechanism may be mediated independently of commensal microbiota within the breast tissue.

3. Microbial products associated with inflammation and tumor progression

While most bacteria comprising the human microbiota are compartmentalized on the skin and in the gastrointestinal and female reproductive tracts, recent studies have demonstrated that additional sites contain regional microbiota. Organs previously considered to be sterile in healthy individuals, such as lymph nodes [87–89] and the bladder [90–93], are now known to contain bacteria under homeostatic conditions without any observable pathological consequence. Additionally, some bacterial-derived products reach systemic circulation [94, 95], which may influence tumor progression. For example, disruption in the compartmentalization of commensal microbes or enhanced microbial shedding of inflammatory ligands during pathological conditions has the potential to drive systemic tumor-promoting inflammation, induce DNA damage, and promote cellular proliferation; all of which promote the progression of extramucosal tumors.

3.1 Bacterial components circulating in the periphery

Bacterial LPS, also known as endotoxin, is the best-characterized bacterial component found in systemic circulation. A cell wall component of gram negative bacteria, LPS is the major ligand for TLR4 and stimulates proinflammatory cytokine production through binding the receptor. Additionally, LPS has pro-angiogenic effects [96–98]. In the context of wound healing, pro-inflammatory and pro-angiogenic functions of acute LPS exposure are considered beneficial, but chronic LPS-mediated inflammation could be detrimental during tumorigenesis and metastasis. Importantly, though gram negative bacteria shed LPS as a normal part of cell division, antibiotics further promote LPS shedding through their bactericidal effects [99, 100], suggesting that during dysbiosis, LPS levels may be elevated in the periphery.

In addition to promoting proinflammatory cytokine production, LPS also drives myeloid cells to produce ROS [101, 102]. The superoxide radicals produced by this process cause direct DNA damage, potentially contributing to mutations leading to cellular transformation [103]. The resultant inflammation from LPS exposure contributes both to hepatic injury and the induction of acute pancreatitis in mice [104, 105]. This inflammation accelerates the development of pancreatic cancer in mice with a genetic driver mutation in K-ras [106, 107]. As mutated K-ras has been identified in a substantial proportion of healthy individuals, increased levels of circulating endotoxin may synergize with K-ras induced transformation, driving tumorigenesis [108, 109]. Furthermore, systemic exposure to LPS enhances metastasis to both the lungs and liver in several different tumor models [110–112]. LPS may act directly on tumor cells, eliciting production of mediators that influence epithelial mesenchymal transition and promote enhanced metastasis through the induction of cell adhesion molecules that facilitate invasion, as demonstrated using in vitro cell culture spheroid models [113, 114]. Additionally, TLR4 expression associates with metastasis to distal lymph nodes in patients with breast cancer [115]. In vitro stimulation of breast tumor cell lines with LPS induces a significant increase in tumor-specific production of matrix metalloproteinases and cytokines associated with angiogenesis, such as VEGF and IL-6. In immunocompromised mice, this ultimately results in increased metastatic dissemination to the liver [115].

Another bacterial product associated with systemic inflammatory effects is flagellin. The only known ligand for TLR5, flagellin is the main protein component of flagellum on flagellated bacteria. Though it has been reported to be detectable in healthy human serum, systemic concentrations of flagellin in the serum increase in the context of inflammation and injury [116–118]. Flagellin has been reported to have both pro- and anti-tumor effects. Multiple publications have demonstrated immunosuppressive functions of flagellin and TLR5 signaling through the induction of Th2 responses [119, 120]. Dendritic cells stimulated with flagellin secrete low levels of Th1-supportive cytokines, such as IL-12p40 and p70, IL-6 and TNFα, resulting in Th2 polarization of CD4 T cells [119]. Additionally, flagellin stimulation of myeloid precursors induces the generation of CXCR4-expressing MDSCs [120]. These studies suggest that depending upon the cell type (mature DC versus immature myeloid precursor) and the immunological context of flagellin activation, stimulation through TLR5 may have varying immune modulatory effects. Flagellated bacteria are a common commensal type found on murine skin, and the presence of flagellin exacerbates tumor development in a model of skin cancer [7, 121]. In vitro, flagellin enhances proliferation and migration of several types of cancer cell lines, including multiple myeloma, gastric cancer, and salivary gland adenocarcinoma [122–124]. However, other studies have shown that flagellin promotes anti-tumor activity through suppression of cancer cell proliferation and migration [48, 125, 126]. These contrasting findings may depend on several factors, including the antigenicity of the tumor, the timing of the flagellin stimulus [127], the cytokine and immune composition of the tumor microenvironment, and perhaps even the stage of tumor initiation or progression.

Two additional bacterial components, peptidoglycan and polysaccharide A (PSA), affect systemic inflammation through the ligation of TLR2. Peptidoglycan is a bacterial cell wall component that is shed through cell division. Present in human plasma, peptidoglycan has

been shown to promote invasiveness, adhesion, and pro-inflammatory cytokine production of cancer cells in vitro [128, 129]. PSA, a capsule component of *Bacteroides fragilis*, drives the differentiation of immunosuppressive IL-10-producing Foxp3+ regulatory T cells both in mice and humans [130–132]. The broad expression of TLRs 2, 4, and 5 on cells of various human cancer types underline the potential effects of bacteria and/or their components on the tumor microenvironment (reviewed in [133]).

3.2 Bacterial Translocation

While resident bacterial communities are present in extramucosal organs of healthy individuals, intestinal barrier permeability is additionally increased in the context of inflammation, enhancing translocation of bacteria and bacterial components from the gut to distal locations [134]. For example, intestinal permeability and systemic levels of LPS are enhanced in cases of alcohol abuse and are often detected in patients with metabolic disorders influenced by obesity [95, 135–137]. Considering the strong correlations between obesity, alcohol use, and increased cancer risk, bacterial translocation and/or systemic bacterial products likely play a large role in promoting the systemic inflammation seen in these conditions. Cancer treatments such as chemotherapy, radiation, and checkpoint blockade also result in mucosal damage, increasing intestinal permeability [94]. Total body irradiation, used to lymphodeplete recipients of both bone marrow transplants and adoptive T cell therapy, results in elevated serum LPS and proinflammatory cytokines in mice [94, 138]. Thus, while bacteria may play a role in tumorigenesis, cancer treatment may additionally exacerbate this effect by increasing bacterial translocation to extramucosal sites.

Bacterial translocation is not always associated with tumor-promoting inflammation, and may also be associated with the enhancement of anti-tumor immunity. Cyclophosphamide induces immunogenic cell death in cancer cells and promotes the differentiation of Th17 and Th1 cells which enhance therapeutic efficacy [139, 140]. Cyclophosphamide also results in increased intestinal permeability and the translocation of bacteria from the intestines to lymph organs. Unexpectedly, cyclophosphamide-induced bacterial translocation of gram positive bacterial species results in the generation of Th1 memory T cells and the differentiation of IFNγ-producing Th17 cells (Figure 1) which are critical for anti-tumor immune responses during therapy [46]. Because this study demonstrates that antibiotics diminish the efficacy of cyclophosphamide-induced tumor immune surveillance, it is important to consider how antibiotic administration during treatment with certain chemotherapies may impair therapeutic efficacy. Treatment with the checkpoint inhibitor anti-CTLA-4 is also known to induce mucosal pathology and disrupt commensal homeostasis. However, Vetizou et al. demonstrated a clear relationship between colonization with certain *Bacteroides* species, such as *B. fragilis* and *B. thetaiotaomicron,* and reduced mucosal pathology during treatment with a-CTLA-4. Additionally, they showed that T cells recognizing these bacterial species associate with responsiveness to therapy in both murine models and in patients with melanoma [45]. As T cells recognizing specific bacterial species mediate the efficacy of anti-CTLA-4 therapy, it is possible that shared antigens exist between commensal species and tumor neoantigens.

4. Systemic effects of commensal metabolites during cancer

Another mechanism by which bacteria contribute to systemic inflammation is through the production of metabolites. The microbiome, defined as the combined genetic material of all microbes within the human body, outnumbers human genes by roughly 150-fold [141]. This vast quantity of genetic material codes for a wide variety of different proteins that impact bacterial metabolism. Commensal bacteria have key roles in human digestion, including the extraction of nutrients and the synthesis of biologically relevant metabolites (reviewed in [142]). Several groups have shown striking differences in the concentration and composition of circulating metabolites in germ-free compared to conventional mice, demonstrating the contributions of commensal microbes to systemic metabolic products [143, 144]. This could be relevant in the development of immune function as germ-free animals have poorly developed lymphoid structures and a defect in granulopoiesis, as discussed previously [19, 20].

4.1 Short-Chain Fatty Acids

One of the best-studied families of microbial metabolites is the short-chain fatty acids (SCFA), comprised of butyrate, propionate, and acetate. Produced by anaerobic bacterial fermentation of dietary fiber, SCFAs are broadly anti-inflammatory. SCFAs are ligands for G protein-coupled receptors, and butyrate and propionate exert their anti-inflammatory effects through their actions as histone deacetylase inhibitors. These effects include the modulation of NF-κB pathways, leukocyte trafficking, and suppression of various cytokines and chemokines [145–153]. Additionally, SCFAs promote tight junction integrity in the intestines, reducing translocation of bacteria and bacterial products [154–156]. Germ-free mice have very low concentrations of SCFAs in their intestines, demonstrating the importance of commensal microbes in the production of these metabolites [157]. SCFAs have mainly been investigated for their anti-inflammatory effects on colitis [158]. However, as they reach systemic circulation after their derivation in the colon, SCFAs may have effects in the context of extramucosal cancers [159–161].

One well-known function of SCFAs is the effect they exert on populations of T cells. Butyrate promotes both the induction of regulatory T cells and their resultant production of IL-10 in addition to driving the elimination of activated T cells through the upregulation of Fas [162–166]. In the context of intestinal inflammation, these effects would be beneficial to the host. However, in the context of cancer, an increase in Tregs and concurrent decrease in effector T cells would facilitate a reduction in tumor immune surveillance and anti-tumor immunity. This effect of butyrate extends beyond the gut, as mice on a high-fiber or SFCA-supplemented diet showed both suppressed colonic inflammation as well as diminished allergic airway disease as a result of increased suppressive activity of Tregs in the lungs [167]. Additionally, SCFAs induce the production of PGE2, a potent tumor-promoting mediator, from human monocytes. This effect is enhanced in the presence of LPS, demonstrating the complex effects of commensal bacteria on systemic inflammation [168].

However, other studies have shown anti-tumor effects of butyrate and other SCFAs. For example, oral administration of dietary fiber as a prebiotic reduced the incidence of carcinogen-induced mammary cancer [169]. Several potential mechanisms of SCFAs may

account for this effect. Butyrate exerts anti-proliferative and pro-apoptotic effects on several cancer cell lines in vitro [170–175], primarily through the induction of oxidative stress within tumor cells and modulation of the expression of genes associated with cellular proliferation and growth. Additionally, butyrate inhibits angiogenesis through downregulation of VEGF gene expression [176]. Another potential anti-tumor effect of butyrate is its ability to suppress CCL2 production, both in vivo and in vitro from tumor cell lines, through impairment of phosphorylation of the ERK1/2 and Akt inflammatory signaling pathways [177–179]. As CCL2 has been implicated in tumor progression and metastasis through recruitment of tumor-associated macrophages, SCFAs may inhibit this process [180]. Finally, it was demonstrated that butyrate in combination with 5-azacytidine, a DNA methyltransferase inhibitor, reduces the growth of breast cancer stem cells [181], suggesting that using probiotics to enrich for butyrate-producing bacteria or increasing the dietary consumption of fiber may have a protective role against certain types of cancers.

4.2 Metabolites that influence DNA damage

In the context of gastrointestinal cancers, some bacterial metabolites impact tumorigenesis through direct DNA damage. Commensal bacteria convert primary bile acids produced by the liver to secondary bile acids. As previously mentioned, the secondary bile acid deoxycholic acid causes DNA damage through the induction of ROS [182, 183]. Additional bacterial products, such as *Enterococcus faecalis*-derived superoxide and *Escherichia coli*-derived colibactin also induce DNA strand breaks [184–187]. Repetitive DNA damage leads to the acquisition of mutations that can drive cellular transformation and the development of cancer.

Polyamines, such as putrescine, spermidine, and spermine, are additional metabolites that are produced by commensal bacteria. Unlike the metabolites mentioned above, polyamines actively protect against DNA damage by scavenging free radicals and influencing the structure of DNA [188–192]. However, polyamines have also been implicated in the suppression of anti-tumor immune responses. Polyamines are increased in the urine and serum of cancer patients and have been shown to promote cancer cell proliferation [193–195]. Additionally, they suppress lymphocyte proliferation and IL-2 production, presumably through metabolic constraints on activated T cells, eventually resulting in decreased anti-tumor immunity [196]. This effect can be inhibited, as depletion of polyamines restricted tumor growth in a T cell-dependent mechanism [197]. Antibiotic treatment decreases polyamine concentrations, demonstrating the impact of commensal bacteria on this metabolic product [198]. Polyamines can also directly enhance the production of tumor-derived proteases and matrix metalloproteinases, resulting in increased extravasation and invasion of tumor cells. Combined with their function in immune suppression, polyamines promote enhanced tumor progression and metastasis [199].

4.3 Metabolites and hormone production

Microbes also play a significant role in the metabolism of hormones. This is particularly important in the context of hormone-receptor positive cancers. Estrogen, specifically, is one driving factor in the development of hormone-receptor positive breast cancer and promotes tumor growth [200, 201]. Estrogens are conjugated with glucuronic acid in the liver,

allowing them to be excreted. Some bacteria produce an enzyme, β-glucuronidase, that deconjugates estrogen from glucuronic acid, promoting its reabsorption into circulation, thereby enhancing estrogen levels in the host [202]. In humans, differences in estrogen metabolism correlate with variability in gut microbial diversity, and antibiotic treatment associates with an increase in excretion of conjugated estrogens [203–205]. Despite its significance in hormone-receptor positive cancer, estrogen has also recently been shown to affect the progression of different estrogen-insensitive tumor models. Svoronos et al. showed that estrogen drives MDSC mobilization as well as their suppressive activity, enhancing tumor progression [206]. This demonstrates that hormones directly impact both tumor growth and immune function.

Additional bacterial metabolites have potential roles in promoting systemic inflammation and tumor progression. These are described in Table 1.

5. Conclusions and future perspectives

The microbiome is often thought of as the “forgotten organ” [207]. Work from the last twenty years has demonstrated critical roles for commensal microbes in the development and progression of many disease states, including cancer. The widespread use of antibiotics in our society makes this topic relevant in the context of cancer, as cancer patients are frequently prescribed prophylactic antibiotics to combat infections associated with chemotherapy-induced immunosuppression. While chronic antibiotic exposure increases the risk of tumorigenesis in multiple cancer types, antibiotic use also impacts commensal homeostasis, decreasing circulating bacterial components and metabolites and shaping systemic immune function. As discussed previously, many secreted bacterial factors act in context-dependent mechanisms, and depending upon the type and stage of cancer, the class of antibiotics prescribed, the duration of antibiotic exposure, and the initial composition of commensal microorganisms, antibiotic use during cancer therapy has the potential to both promote and to inhibit cancer progression. It was recently hypothesized that the impact of persistent use of antibiotics is compounded across generations, resulting in the gradual loss of diversity and emergence into dysbiotic states [67]. Thus, further understanding of the potential direct effects of antibiotics during tumor progression is required to better inform clinical decisions for the treatment of cancer patients.

In tumor-bearing individuals, antibiotics are not the only factor influencing the composition of commensal microbes. Chemotherapy influences microbial composition and induces translocation of commensal microbes from barrier surfaces due to damage of the proliferating cells within the mucosal epithelium. Depending upon the chemotherapeutic agent and the mechanisms associated with tumor-progression, commensal microbes may facilitate tumor regression or result in toxicity, as discussed previously. Multiple studies have found that certain immune therapies enhance tumor immune surveillance through triggering of innate receptors and inflammasomes with microbial products, such as LPS, complexed DNA, and cellular RNA, whereas inhibition of TLR3 and AIM2 inflammasome activation are protective against radiation-induced cytotoxicity [208]. Thus, it will be critical to understand the relevant contexts in which commensal microbes and the activation of relevant signaling pathways influence tumor progression and anti-tumor immunity.

Commensal disequilibrium results in a range of pathologies, and in the context of cancer can have a direct influence on tumor proliferation and cytokine secretion (Figure 1). Systemically, commensal products and metabolic function provoke changes to immune function that may result in either tumor-promoting inflammation or enhanced anti-tumor immunity. The role of commensal microbes during cancer is dependent upon many factors, demonstrating that a more comprehensive understanding of the responses of individual microbes and the collective ecosystem to the tumor environment is needed. Conversely, it will be important to understand how tumors and the tumor microenvironment are impacted by changes in commensal equilibrium. Several studies have already identified that certain commensal microbes are required to facilitate cancer therapy: through checkpoint inhibition of PD-1 [44] and CTLA-4 [45] and during treatment with immunostimulatory immune therapy [43] or chemotherapy [46]. These and future studies could pave the way for engineering probiotic cocktails associated with the restoration of anti-tumor immune responses.

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Abbreviations:

LPS	lipopolysaccharide
TLR	Toll-like receptor
NKT cells	natural killer T cells
NOD	nucleotide-binding oligomerization domain–containing protein
SNP	single nucleotide polymorphism
MDSC	myeloid-derived suppressor cell
PSA	polysaccharide A
RIG-I	retinoic acid-inducible gene-I
SCFA	short-chain fatty acid
CDC	Centers for Disease Control and Prevention
PGE2	prostaglandin E2

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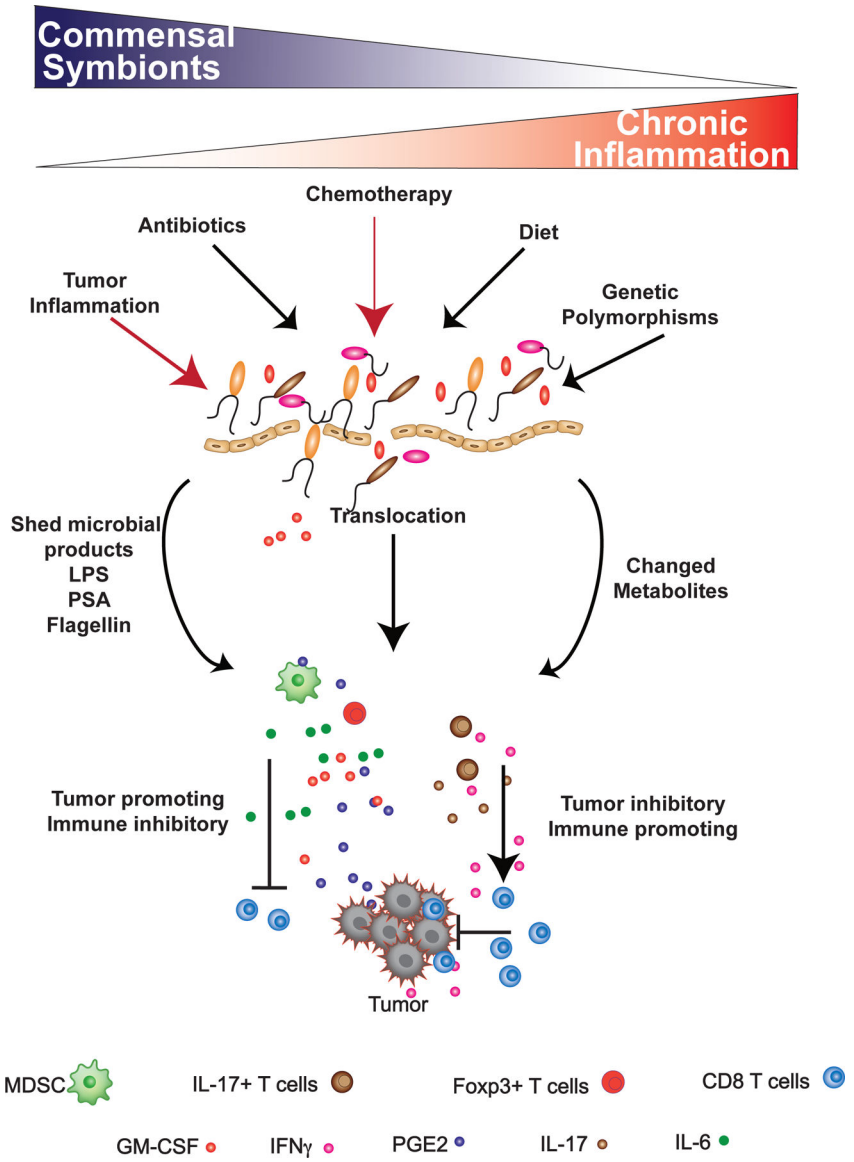

Figure 1: Loss of commensal equilibrium results in systemic inflammation and context-dependent modulation of extramucosal tumor progression.

Factors such as antibiotic usage, diet, or genetics (black arrows) can effectively decrease the biodiversity of the commensal microflora, leading to a higher incidence of chronic inflammation. In tumor-bearing individuals, cancer therapy and tumor-derived inflammation (red arrows) can also modulate the composition of the commensal ecosystem. A reduction in commensal biodiversity (dysbiosis), antibiotics, and chemotherapy can directly damage the integrity of the mucosal epithelium, resulting in bacterial translocation, commensal shedding of inflammatory products, such as LPS, PSA, and flagellin, and a change in metabolic output from the commensal ecosystem. This can lead to an enhancement in tumor-promoting inflammation due to the induction of IL-6, GM-CSF, and TGFβ: factors which enhance the recruitment of immune suppressive myeloid-derived suppressor cells and regulatory T cells into the tumor microenvironment. In the presence of these cells, the ability of T cells to effectively eliminate the tumor are inhibited. Translocation of commensals from mucosal

surfaces can also induce the activation of IFNγ-producing Th-17 cells, which in certain contexts, can facilitate T cell-mediated killing of tumors.

Table 1:

Bacteria and associated metabolites that influence cancer and anti-tumor immunity.

Bacterial metabolite	Bacteria that produces	Function in context of cancer	Reference
Short-chain fatty acids: butyrate, propionate, and acetate	Butyrate: Firmicutes Propionate and acetate: Bacteroidetes.	Pro-tumor: HDAC inhibitors. Suppresses inflammation. Induces Tregs, eliminates activated T cells through upregulation of Fas. Induces production of PGE2. Anti-tumor: anti-proliferative and pro-apoptotic effects on cancer lines. Inhibits angiogenesis. Suppresses CCL2 production.	[146, 148, 151, 163–166, 168, 170–174, 176, 177, 209]
Deoxycholic acid	Many	Pro-tumor: DNA damage	[182, 183, 210]
Superoxide	*E. faecalis*	Pro-tumor: DNA damage	[184]
Colibactin	*E. coli*	Pro-tumor: DNA damage	[186, 187]
Hydrogen sulfide	Sulfate-reducing bacteria	Pro-tumor: DNA damage	[211]
Polyamines	Many	Pro-tumor: suppression of lymphocyte proliferation and IL-2 production. Promote cancer cell proliferation. Anti-tumor: protect against DNA damage.	[188, 189, 191, 195–198, 212]
β-glucuronidase	Many	Pro-tumor: Increases estrogen levels, pro-tumor effects on both estrogen-receptor positive and negative cancers.	[202, 213, 214]
Fragilysin	*B. fragilis*	Pro-tumor: Stimulates cellular proliferation and E-cadherin degradation, degrades intestinal barrier function.	[215, 216]
Heptose-1,7-bisphosphate (HBP)	*Neisseria*	Pro-tumor: Activates NF-κB pathway and promotes inflammation.	[217]
Kynurenine	Indole-positive bacteria	Pro-tumor: Tryptophan catabolite, suppresses T cell function.	[218, 219]