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Review

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.

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, 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

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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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/or 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 (Fig. 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 the 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