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The Influence of the microbiome on the innate immune microenvironment of solid tumors ☆

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ABSTRACT

Cancer remains a leading cause of death despite many advances in medical and surgical therapy. In recent decades, the investigation for novel therapeutic strategies with greater efficacy and reduced side effects has led to a deeper understanding of the relationship between the microbiome and the immune system in the context of cancer. The ability of the immune system to detect and kill cancer is now recognized to be greatly influenced by the microbial ecosystem of the host. While most of these studies, as well as currently used immunotherapeutics, focus on the adaptive immune system, this minimizes the impact of the innate immune system in cancer surveillance and its regulation by the host microbiome. In this review, known influences of the microbiome on the innate immune cells in the tumor microenvironment will be discussed in the context of individual innate immune cells. Current and needed areas of investigation will highlight the field and its potential impact in the clinical treatment of solid malignancies.

Introduction

Cancer remains a leading cause of death worldwide. Despite a decline in cancer-related mortality, the annual incidence and mortality in America are still greater than 1.8 million and 600000, respectively [1]. While improvement in cancer screening has played a large part in this decline, the progressive understanding of the tumor microenvironment (TME) has likewise facilitated improved diagnostics and therapeutics [2–4]. The TME is composed of neoplastic cells, extracellular matrix (ECM), and non-neoplastic cells, which include resident mesenchymal cells, endothelial cells, and immune cells [5]. These cells secrete a variety of cytokines, chemokines, and growth factors, that either potentiate or attenuate tumor growth and metastasis [5,6]. The relationship between the immune system and cancer has long been investigated. It was hypothesized by Virchow in 1863 that chronic inflammation is the origin of cancer [7]. Prior research has shown that the immune cells in the TME can influence genomic instability, epigenetic modification, cellular proliferation, anti-apoptotic pathways, angiogenesis, and metastasis through a variety of mechanisms [8]. The host microbiome has been shown to influence immune cells in the TME that direct their pro- or anti-tumor phenotype [9,10].

The microbiota, the collection of microorganisms that include bacteria, virus, fungi, and archaea which live on and within every human, has been shown to play an essential role in physiologic homeostasis [11]. Disruption of the microbial millieau has been shown to contribute to the development of many diseases [11], including cancer [12]. The term “oncobiome” was coined to describe the field of research investigating the role of the microbiome in human cancer development [9]. The microbiome has been shown to influence oncogenesis via direct impact of bacterial toxins/metabolites [13,14], alterations in metabolism [15,16], and importantly, regulation of local and systemic immune responses [17–19]. Exploiting the microbiota through its effect on the immune system has become a potential avenue to develop novel therapeutics and optimize current ones [20,21]. However, most studies have investigated the influence of the microbiome on the adaptive immune system with little information regarding the innate immune component despite extensive cross-talk. Given the ease of study of the bacterial microbiome due to its high abundance [22], this manuscript will focus on the bacterial microbiota acknowledging that much is yet to be discovered regarding the virome [23], fungome [24], and the influence of lesser microbial species. This paper aims to summarize what is known about the influence of the microbiome on individual innate immune cells in carcinogenesis (Fig.1), as excellent and comprehensive reviews on the adaptive immune system as it relates to the microbiome already exist.[25]

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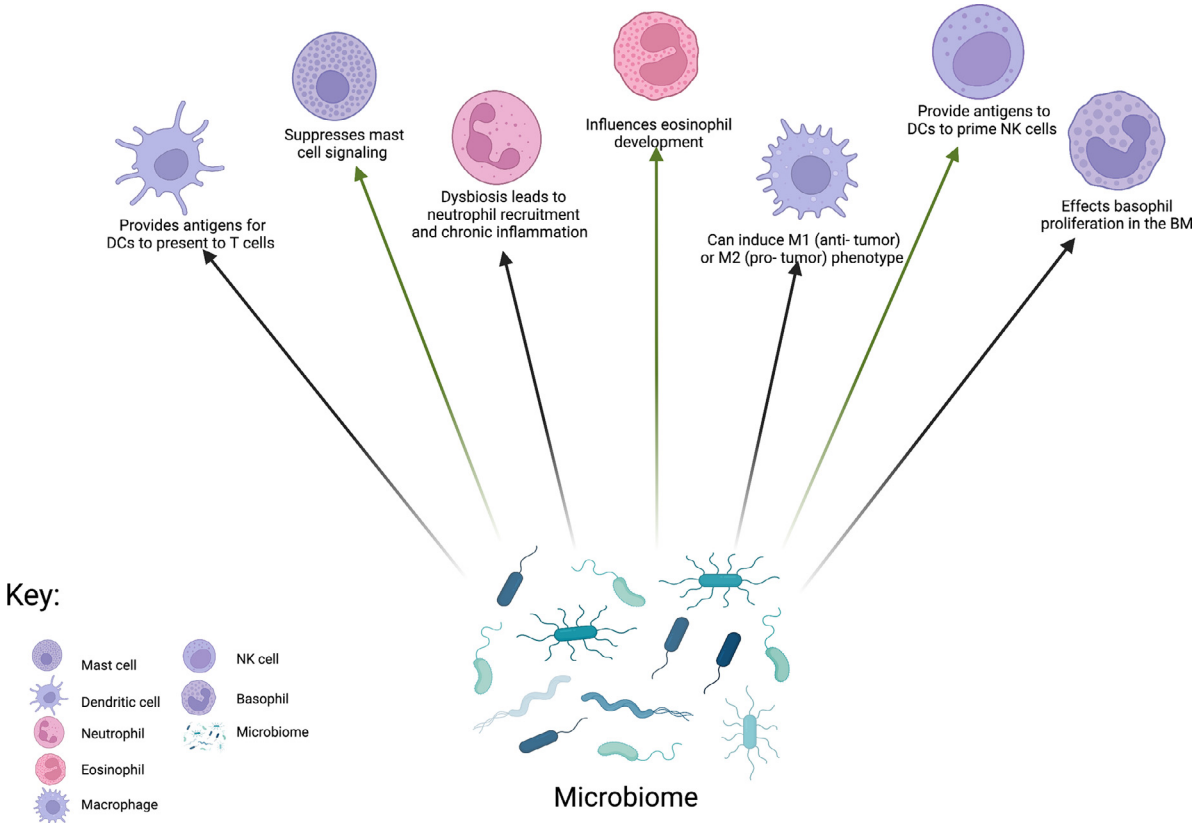

Fig. 1. Interaction of the microbiome with the innate immune system.

The microbiome and innate immune cells in the tumor microenvironment

Macrophages

Macrophages have a multi-faceted immunologic role in that they remove pathogens, cellular debris via phagocytosis, serve to activate T cells through antigen presentation, and release cytokines to facilitate immune cell trafficking and activation [26–28]. Regarding cancer, macrophages provide critical costimulatory support for both immunosuppressive and immune-stimulatory functions within the TME of solid malignancies. Tumor-associated macrophages (TAMs) are the most abundant population of myeloid cells present in the TME [29]. They originate in the circulation and are recruited to the TME by a variety of mechanisms [29,30]. Once recruited, they can promote the growth and survivor of the tumor via tumor production of IL 4, 6, and 10, CSF-1, and TGF-B1, which promotes an M2 or immunosuppressive phenotype, reducing the cytotoxic effects of M1 TAMs [31,32]. The M2 polarized TAMs are tumorigenic, and influence the TME by promoting tumor proliferation, invasion, and migration [33]. Polarization of TAMs into the M2 phenotype have also been shown to facilitate angiogenesis and lymphangiogenesis in a VEGF-dependent manner and mediating immunosuppression [34,35]. M2 TAMs also induce the tumor-permissive Th2 phenotype in T-cells within the TME [31]. TAMs have a high degree of plasticity, and can be converted to an M1 or inflammatory phenotype, characterized by release of TNF-α, IL-1β, IL-12, and IL-23 [26]. These cells facilitate anti-tumor function through antibody-dependent and independent cytotoxicity [29,32]. M1 macrophages release cytokines that inhibit the proliferation of surrounding cells and damage adjacent tissue in response to IFN-gamma [29]. These cells express NO synthase, ROS, IL-12 (a regulatory of Th1 response), and engulf and kill target cells [29]. Controlling the phenotype switch from M2 to M1 in the TME has been shown to enhance adaptive and innate anti-tumor responses [36].

Given the dual-immunologic role of macrophages, much interest in mediators of macrophage polarization in the TME has been generated. The microbiome has been shown to have a regulatory role over this process in variety of disease processes, including solid malignancies [37–39]. A recent study demonstrated the importance of the microbiome in modulating the effect of intratumoral macrophages in pancreatic ductal adenocarcinoma (PDAC) [40]. Specifically, microbiota depletion was associated with immunogenic reprogramming of the PDAC TME, by a) reduction in myeloid-derived suppressor cells and b) an increase in M1 differentiation, promoting Th1 differentiation of $CD4^+$ T cells and $CD8^+$ T-cell activation. Furthermore, splenic-derived macrophages treated with cell-free extract derived from the gut microbiota of *Ptf1a*^{Cre};LSL-*Kras*^{G12D} (KC) mice bearing PDAC tumors was able to reverse this observation with decreased CD4 and CD8 T-cell activation as evidenced by reduced CD44 and PD-1 expression and Th1 differentiation. Finally, macrophages treated with similar cell-free bacterial extract from tumor-bearing KC mice had decreased antigen presenting capability with concomitant reduction in CD4 activation and Th1 differentiation. There is precedent for bacterial product to modulate macrophage activity. Lipopolysaccharide (LPS), a bacterial wall endotoxin of Gram negative bacteria, has been shown to be capable to recruit monocyte-like macrophages (MLM), an immature macrophage population, to the TME via chemokines in a model of colitis-induce colorectal cancer (CRC) [41]. Moreover LPS induced MLMs to produce IL-1β, which stimulated T helper cells to promote inflammation and tumorigenesis [41]. *Fusobacterium nucleatum* has also been shown to modulate the recruitment of M2-like TAMs, leading to the generation of an immunosuppressive TME favorable for colorectal tumor growth and progression (Fig.2)[42]. Mechanistically, *F. nucleatum* triggers TAM activation through the engagement of TLR4 and activation of IL-6/STAT3/c-

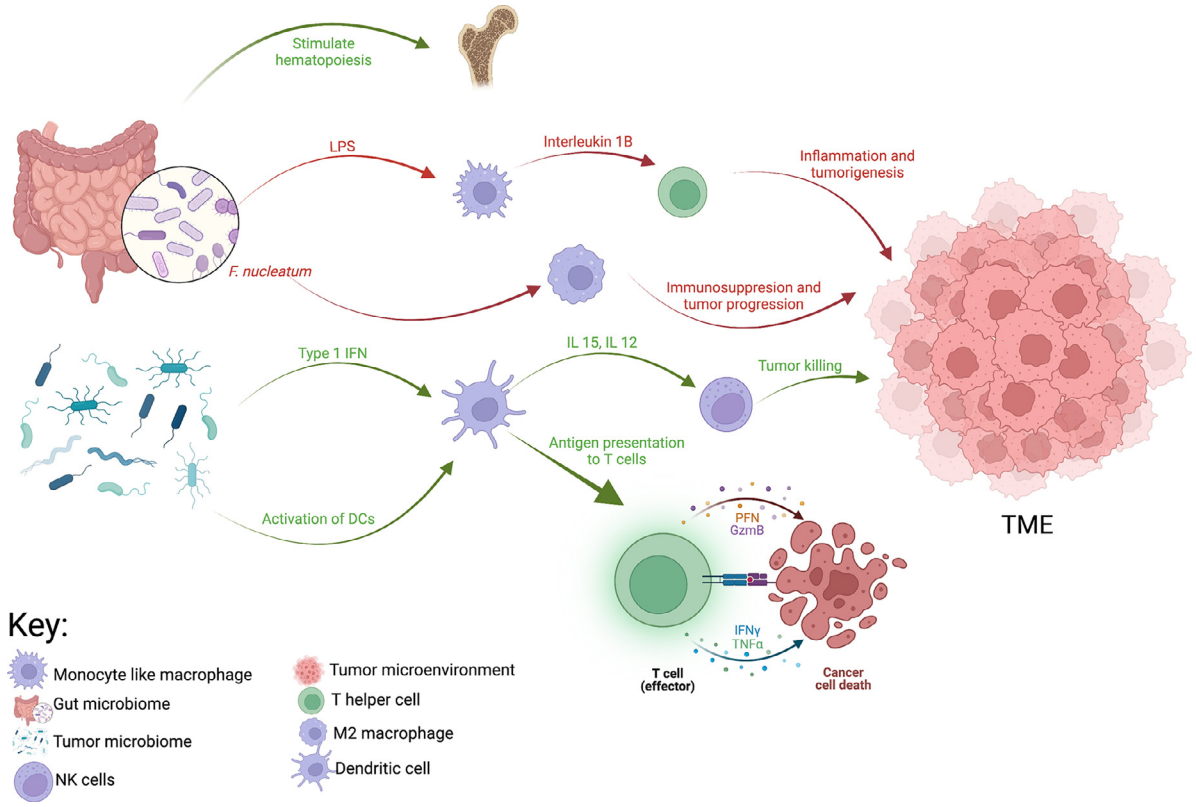

Fig. 2. Interaction of the microbiome with components of the immune system in the tumor microenvironment.

MYC signaling [17]. Furthermore, *F. nucleatum* facilitates infiltration of CD11b^{+} myeloid cells into tumors of the *Apc*$^{Min/+}$ mouse model of intestinal cancer. The monocytic subset of MDSCs (of which macrophages belong) are able to inhibit CD4 T cell activity through arginase-1 and iNOS production with subsequent tumor progression [42,43]. Interestingly, it appears that a microbiome-macrophage axis may be bidirectional in that transient suppression of macrophage function with a liposomal formulation of the bisphosphonate, clondronate, was associated with an increase in the relative abundance of the Lactobacillaceae and Clostridiaceae families and reduced tumor formation in the AOM/DSS mouse model of CRC [44]. Given the commonality of macrophages within the tumor microenvironment and their dual role in cancer progression and suppression, developing therapeutics that control interactions between the microbiome and macrophage polarization has great therapeutic potential and further insight is to be gained on the signaling mechanisms that the microbiome utilizes to influence the function of TAMs in the TME.

Neutrophils

Neutrophils play an essential role in gut homeostasis via elimination of microbes which have translocated across the intestinal mucosal barrier and serves as one of the first defense mechanisms in this capacity. Additionally, through immune cell recruitment and and cytokine release, they play a critical role in the resolution of inflammation and mucosal healing [45,46]. In excess, they can cause dysregulated inflammation and persistent mucosal injury as evidenced by inflammatory bowel disease [45]. They also constitute an important component of the immune interaction in a variety of solid tumors including breast [47], gastric [48], melanoma [49], RCC [50], and CRC [51]. A fair amount of literature supports the role for neutrophils both in circulation and within the TME as being associated with cancer progression and prognosis [51–53]. Intratumoral neutrophil recruitment may enhance CD8 T-cell responsiveness and support anti-tumor immunity in colorectal cancer [54] but not in hepatocellular carcinoma [55]. Given these disparate results, further clarification regarding the recruitment and activation signals of neutrophils in solid malignancies is needed.

Neutrophils are derived from myeloid stem cells that differentiate into a myeloblast and further into promyelocyte, myelocyte, metamyelocyte, band cell, and ultimately segmented neutrophils [56]. These segmented neutrophils then have the capability to be recruited out of the bloodstream into tissue, including cancer, via the influence of chemotactic molecules [57]. Prior studies have shown that neutrophil development and function, as well as clearance of ageing neutrophils, are influenced by the intestinal microbiota [58–60]. Moreover, disrupted microbial communities have the capacity to recruit and activate neutrophils, leading to chronic inflammation and tissue injury via secretion pro-inflammatory chemokines, such as CXCL8 [45]. Therefore, it is not surprising that this crosstalk between the microbiota and neutrophils can play a role in the modulation of cancer growth and the TME. Specifically, it has been shown that the lungs of patients with chronic obstructive lung disease (COPD) harbor non-typeable *Haemophilus influenzae* (NTHi) which has been shown to trigger COPD exacerbations. Pulmonary expression of IL-17C in a murine model of lung cancer was increased in mice exposed to NTHi which resulted in increased recruitment of neutrophils into the TME with concomitant increased growth, suggesting a causal relationship between the two [61]. Long et al demonstrated that *Peptostreptococcus anaerobius*, a bacteria enriched in patients with CRC [62], was able to bind to the $\alpha 2/\beta 1$ integrin on colon cancer cells via its putative cell wall binding repeat 2 (PCWBR2) to activate the PI3K-Akt pathway. This led to increased NF-κB expression with downstream production of cytokines such as IL-10 which promoted neutrophil recruitment into the tumors of *Apc*$^{min/+}$ mice and tumor progression. Given these observations, it appears that the importance of neutrophils in tumor immunity can be regulated by the host microbiome which provides the opportunity to exploit this relationship for therapeutic potential.

Natural Killer cells

Natural killer (NK) cells are often considered the first-line innate immune defense against malignancies and impart direct cytotoxicity to primary and metastatic tumor cells. They have an intimate relationship with the adaptive immune system, given that the cytotoxic role of their interferon-gamma (IFNγ) production also serves to modulate adaptive immune response [63,64]. They mediate killing of target cells via the release of cytotoxic granules containing perforins and granzymes, with subsequent induction of apoptosis via TRAIL and FasL receptors [65]. Classically, there are two subsets of NK cells which are defined by their expression of CD16 and CD56: $CD56^{hi}CD16^{+/-}$ and $CD56^{lo}CD16^{hi}$ [66]. The $CD56^{hi}CD16^{+/-}$ subset is responsible for specialized cytokine production, such as VEGF and IL-8, and exhibit low perforin expression whereas the $CD56^{lo}CD16^{hi}$ subset performs natural and antibody-dependent cytotoxic functions with increased perforin expression for enhanced killing [66]. These cells are extremely plastic and their function can be drastically altered in the TME [67]. For instance, they have been shown to recruit dendritic cells (DC) to the TME via chemokines CCL5 and XCL1, which promote immune control of cancer [68]. Prior research has demonstrated that the cytotoxic activity of peripheral (circulating) NK cells is inversely correlated with cancer risk [69] but the role of NK cells is often heterogenous between cancers [5,65]. This heterogenous effect is likely due to tumor evasion and NK cell inactivation. For example, tumor cells have the ability to coat themselves in collagen to activate NK inhibitory signals, as well as platelets to evade NK detection [70]. Other cells in the TME also release cytokines the blunt NK cell cytotoxic effects and their ability to prime T cells, as is evident by the arrested proliferation and expansion of T cells [5]. Methods to prevent these phenomenon will play an important role in NK cell-mediated tumor killing and already have been used in the adoptive transfer of NK and CAR-NK cells in both preclinical and clinical models [71].

Host-specific factors that influence NK cell cytotoxicity and tumor surveillance prove critical in the initial stages of carcinogenesis. The microbiome provides evidence of host factors that can modulate this activity. For example, priming of NK cells by dendritic cells is necessary in order to become fully functional. This occurs through DC-derived IL-15 activation of resting NK cells after DCs recognize type-I IFN signals [72,73]. Ganal et al demonstrated that the microbiome is important for this process [74]. They demonstrated that mononuclear phagocytes, which include DCs and macrophages, in germ-free mice were unable to prime NK cells through type I IFNs. Moreover, the NK cell-activating receptor, NKp44, has been found to directly bind members of the genus *Mycobacterium, Nocardia farcinica*, and *Pseudomonas aeruginosa* [75]. Elements of which have previously been demonstrated in abundance in the tumor microbiome of several cancers [40,76]. The NK cell-DC axis has proven important in the TME as Lam et al demonstrated that microbial-derived stimulator of interferon genes (STING) agonists can induce type-I IFN production by intratumoral monocytes that can activate NK cells, creating an anti-tumor niche [77]. Our group has recently demonstrated that the microbiota can modulate NK cell infiltration into pancreatic cancer xenografts and regulate their activation and thus cytotoxicity [78]. Finally, dietary modification of the gut microbiota has been shown capable to also alter intratumoral NK cell activity, providing intriguing insight into therapeutic implications. Rizvi and colleagues demonstrated that a high salt diet induced intratumoral NK cell-mediated tumor immunity through inhibition of PD-1 expression in a B16 melanoma mouse model [79]. Depletion of the microbiota attenuated the high salt diet-induced effects but was subsequently restored after fecal microbiota transplant from high salt diet-fed mice. Finally, the high salt diet resulted in an increased abundance of *Bifidobacterium* in the gut with concomitant increase in gut permeability and intratumoral *Bifidobacterium* which activated NK cells and induced regression of the melanoma. These data demonstrate not only the importance of NK cells in the peripheral and intratumoral compartments but also the extensive crosstalk that NK cells have with other components of the immune system.

Dendritic cells

The importance of DCs in relation to NK cells in the TME has been discussed previously but they possess their own independent role in carcinogenesis that is worthy of discussion. Dendritic cells function as antigen presentation cells (APCs) to present non-self-antigens to T lymphocytes and in many ways bridge the innate and adaptive immune systems [80]. After a series of differentiation stages beginning with myeloid precursors, the commitment of DCs to myeloid DCs (mDC) is regulated by several transcription and growth factors, including CCR7, Zbtb46, and Flt3 [80]. Common DC progenitor (CDP) cells then differentiate into plasmacytoid dendritic cells (pDC) or pre-DC progenitors which further differentiate based on CD11b, CD8α, and CD103 expression (conventional DCs; cDC) [81]. A primary function of pDCs is to produce large amounts of type-I IFN in response to infection whereas cDC are potent APCs to naïve T-cells in which different subtypes are more responsive to certain pathogens (for example, $CD8\alpha^+$ cDCs are responsible for mounting an immune response against intracellular pathogens) [80,82]. Additionally, cDCs produce IL-12, which polarizes CD8+ T-cells into their cytotoxic phenotype [83]. The phenotypic response of DCs in the TME is dependent on specific signals encountered and whether an anti-tumor or immunosuppressive effect is produced [84]. For example, pDC evoke T cell anergy or deletion via secretion of tolerogenic factors such as IL-10, TGF-B, or via engagement of co-stimulatory receptors in T cells [85]. Moreover, pDCs in the TME are known to have impaired secretion of type-I IFN [86]. The presence of infiltrative pDC in different tumor types has been shown to be associated with worse outcomes [86–88]. The process whereby pDCs may be modulated in the TME can therefore provide an opportunity for therapeutic intervention.

Accumulating evidence exists for DC activation by native bacteria of the gut microbiota which opens the possibility of modulating the anti-tumor function of the adaptive immune system via innate immunity. Utilizing a B16 melanoma xenograft mouse model, Sivan and colleagues demonstrated that *Bifidobacterium sp*, present either natively or orally reconstituted, resulted in the upregulation of anti-tumor genes in intratumoral DCs, increased ability for DCs to activate T cells, and increased the population of major histocompatibility complex (MHC) class II^{HI} DCs in the TME [89]. Further evidence of the microbial impact on DCs is provided by Ling et al in a cohort of 64 treatment-naïve gastric cancer patients [90]. They found increased abundance of $CD303^+$ DCs in tumor tissue compared to normal and peritumoral. This increase in $CD303^+$ DCs were associated with an increase in the genera *Stenotrophomonas* and decreased *Comamonas*. Although a rare population, $CD303^+$ DCs are a known immunosuppressive subpopulation of pDCs that associate with tumor progression in breast and lung cancer [91,92]. Given the close relationship of DC function to adaptive immunity, microbiota-mediated alterations of DC function may have profound downstream effects on T cell activity and anti-tumor immunity.

Other innate immune cells

Limited knowledge of the role of mast cells, basophils, or eosinophils in the TME as it relates to the microbiome is available. While prior studies have investigated the role of these minor innate immune cells in cancer physiology, the results have not been consistent. For example, while mast cells have been shown to accumulate in the TME and portend a worse prognosis in pancreatic ductal adenocarcinoma [93] and colorectal cancer [94], there is evidence that mast cell infiltration and activation demonstrates improved response to treatment and survival in melanoma [95]. Furthermore, basophils can release molecules such as VEGF-A and VEGF-B, which promote angiogenesis in the TME, but can also secrete granzyme-B and TNFα, which have anti-tumor effects [96].

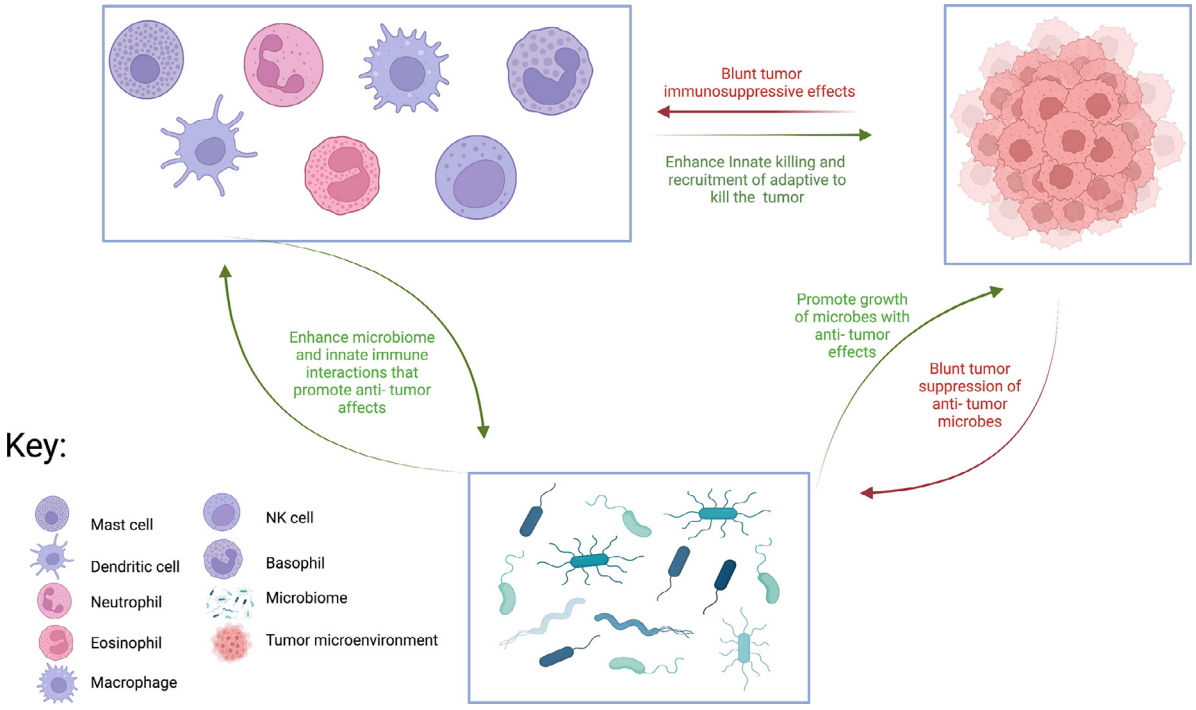

Fig. 3. Future areas of microbiome-innate immune system research for potential clinical interventions.

Furthermore, tumor-associated eosinophils or evidence of eosinophil degranulation has been shown to be associated with a favorable prognosis in solid tumors such as CRC and oral squamous cell carcinoma [97–99]. However, intratumoral eosinophil infiltration has also been shown to inhibit T and NK cell activity in lung cancer [100]. These disparate findings of minor innate cells in various cancers likely represents our limited insight into the crosstalk of these cells with other components of the innate and adaptive immune systems and demand further investigation.

Recognizing factors that mediate the crosstalk of minor cells of the innate immune system with cells in the TME is important to understand the fine tuning needed within the TME to facilitate an anti-tumor response. All three cell types are located at host-environment interfaces such as the intestines, lungs, and skin. Thus, it is not unexpected that the local host microbiome in these locations would have a reciprocal influence on mast cells, eosinophils, and basophils in the context of cancer. However, very little data are available on the influence of the microbiome in the context of these cells and cancer development or progression. Further exploration into this understudied area of research may therefore lead to novel or optimized cancer therapies.

Therapeutic implications of innate immune cells in response to microbiome-influenced immunotherapy

The discovery of the PD-1/PD-L1 and CTLA-4 pathways in tumor immunology coupled with the development of immunotherapy based on these pathways has been one of the greatest breakthroughs in cancer treatment [101,102]. Recent notable studies have illustrated the influence of the host microbiota on response to these immunotherapies. Given that the PD-1/PD-L1 and CTLA-4 pathways are primarily checkpoints of T cell activation, attention has not been as focused on the innate immune system in the microbiome-immunotherapy relationship, although PD-L1 is present on innate cells as well [103]. However, microbial influence on the innate immune system in the TME has repercussions to immunotherapy response in a variety of tumors. In a groundbreaking study, Routy et al demonstrated that resistance to immunotherapy is largely related to gut microbiota composition. In that study, *Akkermansia muciniphila* and *Enterococcus hirae* induced DCs to produce IL-12 which is a potent cytokine for Th1 cells and immunogenicity of PD-1 blockade under normal microbiota conditions [104]. Indirect microbial influence on dendritic cells has also been shown by Vetizou and colleagues whereby recolonization of the gut microbiota in germ-free or antibiotic-mediated microbiota depleted mice with *Bacteroides fragilis* resulted in the induction of a Th1 immune response which resulted in the maturation of intratumoral DCs and a more robust response to CTLA-4 inhibition in a mouse model of melanoma [105]. Finally, a clinical study of patients with non-small cell lung carcinoma (NSCLC) revealed that higher microbiota diversity was associated with a greater number of NK cells in the peripheral blood, and better responses to immunotherapy [106]. There are many emerging immunotherapeutic targets focused on the innate immune system which may provide additional efficacy based on microbiome relationships [107]. This active area of research may enable tumors once thought to be non-immunogenic to be recognized by the innate and adaptive immune systems in the context of the microbiome.

Discussion and future directions

Much interest has rested on the adaptive immune system and its role in the development and progression of solid tumor malignancies. However, one of the greatest influences of this system, and one that should not be underestimated, is that of the innate immune system. This first-line defense against pathogens and cancer has roles in complement cascade activation, elimination of foreign substances, recruitment of other immune cells, and antigen presentation to activate the adaptive immune system. Despite its consideration as the more evolutionarily aged arm of the human immune system, its multifaceted roles and interactions with host physiology and immunity demonstrate the importance of this system. Given its role in initial bacterial recognition and the need to preserve immune tolerance at such locations as the intestinal mucosal barrier, it is not surprising that the host microbiota would play a role in its regulation.

With decreased costs associated with 16S and metagenomic sequencing of the intestinal microbiota, progress in microbiome research has been progressing at a fast pace. This has allowed a myriad of investigations into the role of the microbiome in many human disease processes,

including cancer. As such, we now know many of the intricate relationships that guide cancer progression through immune suppression, much of which has been shown to be at least partly mediated by the microbiota. Future investigations must interrogate both arms of the immune system given the extensive crosstalk and cells types that are involved (Fig. 3). Moreover, insight into individual innate immune cells that trigger an adaptive immune response to cancer based on the status of the microbiota community will be needed. Finally, establishing microbial consortiums that recapitulate host microbiome metabolomic profiles either through bioreactors or artificial intelligence will be critical to understanding and targeting the immune-microbiome-cancer relationship for the therapeutic benefit of patients.

Declaration of Competing Interest

The authors (Angel Charles and Ryan M. Thomas) declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Angel Charles: Conceptualization, Writing – original draft. **Ryan M. Thomas:** Conceptualization, Writing – original draft, Supervision.

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