HHS Public Access

Author manuscript

Semin Immunol. Author manuscript; available in PMC 2020 March 20.

Published in final edited form as:

Semin Immunol. 2019 February ; 41: 101271. doi:10.1016/j.smim.2019.03.003.

Innate lymphoid cells: a potential link between microbiota and immune responses against cancer

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Abstract

The adaptive immune system plays a crucial role in anti-tumor immune responses. Enhancement of T cell responses through checkpoint blockade has become a major therapeutic avenue of intervention for several tumors. Because it shapes immune responses and regulates their amplitude and duration, the microbiota has a substantial impact on anti-tumor immunity. Innate lymphoid cells (ILCs) comprise a heterogeneous population of lymphocytes devoid of antigen-specific receptors that mirror T helper cells in their ability to secrete cytokines that activate immune responses. Ongoing studies suggest that ILCs contribute to anti-tumor responses. Moreover, since ILCs are present at barrier surfaces, they are stimulated by the microbiota and, reciprocally, influence the composition of the microbiota by regulating the surface barrier microenvironment. Thus, ILC-microbiota cross-talk may in part underpin the effects of the microbiota on anti-tumor responses. In this article, we review current evidence linking ILCs to cancer and discuss the potential impact of ILC-microbiota cross-talk in anti-tumor immune responses.

1. Introduction

In the last twenty years, it has become accepted that the immune system plays a crucial role in tumor editing. The immune system can eliminate immunogenic tumors, confine them in a dormant state, or allow the escape of non-immunogenic variants that grow unrestrained [1]. Enhancement of anti-tumor immune responses through checkpoint blockade has become a major therapeutic avenue of intervention for several tumors [2].

Because of its role in shaping immune responses, the microbiota has become the focus of much attention in anti-tumor immunity and immunotherapy. The microbiota consists of a symbiotic ecological community of trillions of microorganisms that reside in the skin, gastrointestinal, respiratory and urinogenital tracts [3]. The microbiota regulates

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Author Contributions

SKP wrote the manuscript draft. MC participated in the conception, interpretation, and writing of the manuscript.

Conflict of Interest Statement

The authors declare no commercial or financial conflict of interest.

physiological functions, such as metabolism of nutrient components and generation of key bioactive molecules like vitamins [4–6]. By occupying surfaces that are access points for pathogens, the microbiota outcompetes pathogens for space and food, thereby protecting the host from infections. Importantly, the microbiota also plays a major role in shaping the immune system and regulating quality, magnitude and duration of immune responses, including anti-tumor responses [7–12].

Barrier surfaces are also the home of innate lymphoid cells (ILCs), a group of heterogenous lymphocytes that lack recombinant associated gene (RAG)-dependent antigen-specific receptors and specialize in the production of effector cytokines and chemokines in response to various stimuli in the microenvironment [13]. Since ILCs are important components of the immune system and extensively cross-talk with the microbiota, there is increasing interest in how ILCs modulate tumor initiation and progression, as well as their ability to impact immunotherapy. Here, we review the current studies on the role of ILCs in cancer, the impact of microbiota in cancer immunotherapy and discuss the plausible pro-tumorigenic and anti-tumorigenic implications of microbiota-ILC cross-talk.

2. ILCs and Natural Killer cells

ILCs develop in the fetal liver and bone marrow from the common lymphoid progenitor but, in contrast to T cells and B cells, are devoid of antigen-specific receptors. Based on the signature cytokines they secrete, their unique arrays of cell surface markers, and the transcription factors that relegate their fate, ILCs are broadly classified into 3 types: ILC1s, ILC2s, and ILC3s, which are considered the innate counterparts of Th1, Th2 and Th17 cells [13, 14]. Natural killer (NK) cells are cytolytic innate lymphocytes and therefore deemed the innate counterparts of CD8 T cells [13].

ILC1s overlap significantly with conventional NK cells, such that distinguishing the two is often problematic. Both cell types produce IFN-γ in response to IL-12, IL-18 and IL-15 and express shared cell surface markers including NKp46 and NK1.1in C57BL/6 mice and other strains carrying a similar *Nkrp1c* allele [15]. However, they do differ in some respects, for instance, ILC1s and NK cells reside in distinct locations. ILC1s are tissue resident cells and hence are largely confined to tissues, including the gut mucosa, salivary glands, liver, and adipose tissue, whereas NK cells are found in the blood and can recirculate between the blood and lymphoid or non-lymphoid tissues [16, 17]. Another criteria frequently used to distinguish ILC1s from NK cells, especially in mice, is based on the transcription factors that drive their development. Hobit [18] and T-bet [19] govern ILC1 development, whereas NK cells rely on EOMES and T-bet [20–22]. A third criteria for distinguishing between the two is based on their differing cytolytic potential; NK cells generate more cytolytic mediators, like perforin and granzymes, than do ILC1s [23]. Finally, although ILC1s and NK cells express a very similar panoply of surface markers, differential expression of CD49a, CD73 and CD61 can help segregate the two cell types [19, 24, 25]. Both ILC1s and NK cells play crucial roles in combating intracellular pathogens through secretion of IFN-γ. ILC1s provide an immediate tissue source of IFN-γ during infections, which is sustained by the subsequent migration of NK cells from the blood into the tissue [19, 25, 26]. NK cells

also lyse virally infected cells and tumor cells, whereas the lytic function of ILC1s is thought to be limited, although this concept has not been experimentally demonstrated.

ILC2s populate adipose tissue, lungs, gut, liver, and skin in the steady state. They lack lineage markers and typically express KLRG1, Sca-1, CD25, CD127 and IL1RL1 (also known as IL-33R or ST2) on the cell surface [27]. The transcription factors GATA3 and RORα drive ILC2 differentiation [28, 29] and mature ILC2s secrete IL-5, IL-9, IL-13 and amphiregulin upon stimulation with IL-33, IL-25 and/or TSLP. Collectively, these characteristics render ILC2s the innate counterparts of Th2 [30]. ILC2s play a role in host response against helminths, but their sustained activation can be detrimental in allergies and asthma [31, 32].

ILC3s are primarily found in the intestine and secondary lymphoid organs in the steady state. They express IL-23R on the surface and depend on the transcription factor RORγT for their differentiation [13, 33]. ILC3s produce IL-22 and IL-17 in response to IL-23 and IL-1 and hence are considered the innate counterparts of Th17. IL-22 stimulates epithelial cell antimicrobial and repair mechanisms [34, 35], whereas IL-17 promotes granulopoiesis and recruitment of neutrophils [36, 37]. ILC3s help maintain intestinal homeostasis and provide host defense against extracellular bacteria and fungi [38–40]. In mouse, three subsets of ILC3s have been identified that have unique features but share overlapping developmental pathways and functions. $CCR6^{+}NKp46^{-}$ ILC3s produce more IL-17 than IL-22 and express MHC class II, which induces the generation of a tolerogenic $CD4^{+}$ T cell response against commensal microbes that buttresses intestinal homeostasis [41]. In the fetus, $CCR6^{+}NKp46^{-}$ ILC3s correspond to lymphoid tissue inducers (LTi) cells, which drive the generation of lymphoid tissues during development [42, 43]. $CCR6^{-}$ $NKp46^{+}$ ILC3s and their immediate $CCR6^{-}NKp46^{-}$ precursors specialize in the production of IL-22.

3. The emerging role of ILCs in cancer immunoediting

The role of NK cells in cancer immunosurveillance has been extensively studied over the years and has recently drawn even more attention because NK cell-based therapies have such marked potential for treating cancer [44, 45]. A number of studies have provided evidence for this. Antibody-mediated depletion of NK cells results in increased tumor growth in various experimental models [46–48]. Enhanced tumor growth has been observed in mice with defects in NK cell receptors and functions [49–52]. In humans, early studies reported fewer NK cells and/or activity in patients with tumors than in healthy individuals and noted that NK cell infiltration into solid tumors is quite infrequent [53]. Lower frequency or impaired function of NK cells positively correlates with poor prognosis of head and neck [54, 55], pharyngeal [56] and colorectal cancers [57, 58]. NK cell activating receptors, such as NKp30 and NKp46, are expressed at lower levels in patients with acute myeloid leukemia than healthy individuals [59]. Recently, activation of NK cells through blockade of the inhibitory receptor NKG2A was shown to enhance anti-tumor responses elicited by checkpoint blockade or cancer vaccines in both experimental and clinical cancer [60]. Moreover, NK cells have been shown to effectively control experimental tumors that have been treated with drugs capable of inducing senescence, suggesting a potential synergism between NK cells and chemotherapy [61].

Moving beyond the established role of NK cells in cancer immunosurveillance and immunotherapy, the impact of ILCs in cancer is now being fully explored. ILC1s expressing granzyme B and TRAIL were detected in a MMTV-PyMT mammary tumor model, where they lysed tumor cells [62]. These unconventional ILC1s were IL-15-dependent but Nfil3-independent, in contrast to NK cells and conventional ILCs that depend on Nfil3 [62]. Since tumor growth was accelerated in *Il15*$^{-/-}$ mice but remained unaltered in *Nfil3*$^{-/-}$ mice, unconventional ILC1s rather than NK cells seemed to dominate the anti-tumor response in this model [62]. Recently, it was shown that human ILC1s and NK cells express an activating receptor, NKp44, which endows them with the ability to recognize tumor cells that secrete platelet derived growth factor (PDGF)-D. Detection of PDGFD triggers the secretion of IFN-γ and TNF-α that, together, slow the proliferation of tumor cells and promote increased expression of MHC class I and adhesion molecules, which facilitates their elimination by the immune system. Moreover, NKp44-PDGF-D interaction potentiates immune checkpoint blockade [63].

Given that IFN-γ hinders proliferation [64, 65], promotes MHC expression, and induces the release of proinflammatory chemokines that attract CD8 T cells [66, 67], NK cells and ILC1s are generally viewed as anti-tumorigenic (Fig.1). However, IFN-γ has been shown to foster tumor development in some situations. IFN-γ induces colonization, boosts proliferation and renders various tumor cells more aggressive [68–70]. In addition, IFN-γ promotes the expression of enzyme indoleamine 2,3–dioxygenase (IDO), which has immunomodulatory functions and facilitates the recruitment of myeloid derived suppressor cells (MDSC), which inhibit T cell response against tumors [71, 72]. Moreover, under certain conditions, such as SMAD4-deficiency, IFN-γ becomes somewhat irrelevant as NK cells and ILC1s alter their phenotype and express molecules implicated in immunoregulation, including the inhibitory receptor TIGIT and the ectonucleotidase CD73, which generates the inhibitory mediator adenosine [73]. A regulatory and poorly cytotoxic ILC population resembling NK cells and ILC1s was reported in human high grade serous tumors. These regulatory ILCs inhibited expansion and function of tumor infiltrating T cells in vitro [74]. Thus, anti-tumor and pro-tumor activities of ILC1s are probably context dependent.

The roles of ILC2s and ILC3s in cancer have also been investigated. Since type-2 responses are generally associated with tumor progression, ILC2s may be pro-tumorigenic. Supporting this notion, the frequency of peripheral ILC2s was increased in patients with gastric cancer [75]. In mice, an increase in ILC2 number by IL-33 favored tumor progression in an experimental model of breast cancer [76]. Furthermore, IL-13 secretion by ILC2s activated MDSCs and triggered the differentiation of M2 macrophages, which are pro-tumorigenic (Fig.1) [76, 77]. ILC2s constitutively express Arginase-1 [78, 79], which may inhibit T cell responses [80, 81] by depriving L-arginine. Moreover, ILC2s secrete amphiregulin, which enhances the suppressive function of regulatory T cells (Tregs), thereby facilitating immunosuppression [82]. However, there is some evidence that IL-5 and IL-9 secreted by ILC2s may induce an anti-tumorigenic response. In the absence of either IL-5 or IL-9, increased tumor metastasis was observed in several different mouse models [83–85]. Thus, more studies are necessary to define the role of ILC2s in cancer.

Most reports suggest that ILC3s are pro-tumorigenic. Consistent with this proposal, the major activator of ILC3s, IL-23 was found to be highly expressed in human and mice colon tumors [86–88]. Mice deficient for IL-23R are resistant to B16F10 melanoma tumor growth [87]. Furthermore, colonic tumor growth was blunted in IL-23- and IL-23R-deficient mice undergoing spontaneous development of colon cancer [88]. ILC3 effector cytokines, IL-22 and IL-17, have also been shown to promote tumorigenesis (Fig.1) [89–91]. IL-22 promotes colorectal cancer in a *Helicobacter hepaticus*-induced model [91]. IL- 22 binding protein is a decoy receptor produced by dendritic cells that controls the bioavailability of IL-22 in the steady state. Lack of IL-22 binding protein and subsequent increase of IL-22 activity facilitated cancer development in a model of spontaneous colorectal cancer [92]. Overall, these reports suggest that sustained activation of ILC3s by IL-23 and inappropriate secretion of IL-17 and IL-22 may result in chronic intestinal inflammation that facilitates cancer. This condition may occur in patients with inflammatory bowel disease, in which sustained IL-23-mediated inflammation increases the risk of colon cancer [93]. However, an anti-tumorigenic role of ILC3s has also been reported in both experimental and clinical cancers. $NKp46^+$ LTi cells inhibited tumor growth in a B16F10 subcutaneous melanoma model [94]. Upon activation by IL-12, these cells induced expression of adhesion molecules such as ICAM and VCAM on the tumor vasculature, which might facilitate infiltration of effector cells into the tumor tissue. ILC3s also enhanced the anti-tumorigenic effect of combined immune-chemotherapy by facilitating macrophage infiltration into the tumor and growth arrest in the B16F10 melanoma model [95]. Moreover, the presence of ILC3s was associated with a beneficial prognosis in human non-small cell lung cancer (NSCLC) [96]. Significant infiltration of ILC3s was evident in early stage tumors, whereas very few infiltrating ILC3s were detected in advanced stage-III tumors. ILC3s accumulated at the edge of tertiary lymphoid structures (TLS) and positively correlated with the density of TLS. Since these infiltrating ILC3s secrete lymphotoxins, they may contribute to the formation of denser TLS, which is predictive of a favorable prognosis [96].

In conclusion, ILC1s together with NK cells are viewed as anti-tumorigenic, whereas ILC2s are considered pro-tumorigenic. Depending on the context, ILC3s can assert both anti- and pro-tumorigenic effects. While the anti-tumor activity of NK cells can be harnessed for therapeutic purposes, ongoing studies in both mouse experimental models and human patients are needed to clarify whether ILCs are a viable target for tumor immunotherapy.

4. The impact of microbiota in immune responses against cancer

The microbiome can play both pro- and anti-carcinogenic roles. Bacteria like *E. coli*, *Bacteroides fragilis* and ε and γ proteobacteria secrete colibactin, *B. fragilis* toxin (BFT) and cytolethal distending toxin (CDT), respectively, which can damage host DNA either directly or indirectly by inducing reactive oxygen species [97–99]. These toxins have been associated with both clinical and experimental colon cancer [100, 101]. Other components of the microbiome, like *H. pylori* and *B. fragilis* secrete toxins like CagA and BFT respectively, which disrupt the β-catenin signaling pathway and drive cancer pathogenesis in the colon [102, 103]. By digesting or modifying the dietary components, gut bacteria also produce metabolites, such as hydrogen sulfide and secondary bile acids, that are carcinogenic (Fig.1) [104–106].

Given the role of healthy microbiota in controlling metabolism and inflammation, perturbations of the microbiota, known as dysbiosis, may increase the risk of cancer by causing dysregulated metabolism and chronic inflammation. Mechanistically, dysbiosis and inflammation can lead to increased expression of TLRs and other pattern recognition receptors in the gut mucosa, thereby enhancing gut responsiveness to bacterial products and generating a feed forward loop that exacerbates inflammation and favors tumor growth (Fig. 1) [12, 107, 108].

A major impact of the microbiota on chemotherapy and immunotherapy for cancer has been recently demonstrated. By damaging the mucosal epithelium, chemotherapy facilitates the translocation of microbiota species into mesenteric lymph node and spleen [109]. In the case of cyclophosphamide treatment, leakage of microbiota through the intestinal barrier resulted in a beneficial enhancement of Th1 and Th17 response against cancer [109, 110]. Accordingly, mice depleted of microbiota by antibiotics treatment and germ-free mice both responded more poorly to this chemotherapy than did mice with normal microflora [109, 110].

Immunotherapy can also be potentiated by the presence of gut microflora. Mice with healthy gut flora responded more favorably to anti-CTLA-4 and anti-PD-1 treatment than did germ-free mice or mice with disturbed microbiota [111–113]. These observations were further corroborated by studies with cancer patients. A negative correlation between antibiotic use and a positive response to anti-PD-1 therapy was observed in patients with non-small cell lung cancer, metastatic melanoma and urothelial carcinoma. Furthermore, the fecal microbiota profiles of poor responders and non-responders to anti-PD-1 therapy differed from those of the responders [11, 12, 114]. Similarly, the efficacy of adjuvant therapies based on anti-IL-10 or CpG-oligodeoxyribonucleotides depends on the gut microbiota, as untreated mice responded better to these therapies than did antibiotic treated mice [115]. Altogether, these studies suggest that a healthy microbiota lowers the risk for cancer and can actually potentiate the effects of cancer chemotherapy and immunotherapy by enhancing anti-cancer immune responses (Fig.1). In contrast, dysbiosis or expansion of toxin-producing species can facilitate a chronic inflammation and epithelial damage that increase the risk of cancer.

5. The cross-talk between ILCs and microbiota

Because of their location at the barrier surfaces, ILC3s and the microbiota continuously cross-talk. ILC3s from germ-free mice produce less IL-22 than do mice with microflora [116]. Indeed, certain components of the microbiota, such as *Lactobacillus reuteri*, degrade nutritional tryptophan generating indol-derivatives that activate the aryl hydrocarbon receptor, a transcription factor expressed in ILC3s, which promotes the secretion of IL-22 [10, 117]. Similarly, segmented filamentous bacteria that colonize the gut induce IL-22 production in intestinal ILC3s by an IL-23-dependent mechanism [118]. Components of the microbiota induce macrophage production of IL-1β that, in turn, stimulates ILC3 secretion of GM-CSF, which promotes the maintenance of oral tolerance [119]. Similarly, the microbiota induces secretion of TNF-like ligand 1A by mononuclear phagocytes, which potentiates IL-22 production by ILC3s [120]. Commensal microbes also impact the

metabolism of vitamin-A [121, 122], which promotes the generation of ILC3s. Vitamin-A deficiency resulted in diminished ILC3 numbers as well as defective gut homing and impaired ILC3 responses to *C. rodentium* infection [123, 124]. Signals from commensal microbes can stimulate mononuclear phagocytes and/or intestinal epithelial cells to secrete IL-1β, IL-23, IL-25 and TSLP [119, 125–128], which have been implicated in either blocking or promoting ILC3 functions [119, 125, 127, 129–131]. Furthermore, commensal microflora facilitates trafficking of ILC3s into the lungs of newborn mice, where they thwart pneumonia infection by secreting IL-22 [132]. Whether the microbiota affects ILC3 numbers is controversial. Adult germ-free mice have normal ILC3 numbers in the intestine [133, 134]. However, while the development of fetal NKp46^{-}CCR6^{+} LTi cells may be microbiota-independent, the intestinal flora may at least promote the development of post-natal NKp46^{+}CCR6^{-}ILC3s [33]. Reciprocally, ILC3s can shape the microbiota through multiple mechanisms. By producing IL-22 that elicits the secretion of antimicrobial molecules by epithelial cells, ILC3s limit intestinal colonization by segmented filamentous bacteria [135–137] and perhaps other pathobionts [135, 136]. Corroborating the role of IL-22 in maintaining intestinal homeostasis, Zenewicz et al. reported that the microbiota of *Il22*$^{-/-}$ mice significantly differs from that of wild type mice in that it encompasses fewer members of some genera, including *Lactobacillus*, which is considered beneficial, and more of others like *Helicobacter*, which can be pathogenic. Moreover, wild type mice cohoused with *Il22*$^{-/-}$ mice long enough to adopt their altered microbiota suffered from exacerbated DSS-induced colitis, though the symptoms were more severe in the *Il22*$^{-/-}$ mice, reflecting both the protective role of IL-22 itself and the detrimentally altered microbiota [138]. It has been shown that ILC3s can also regulate the adaptive immune response against microbiota, thus promoting tolerance. Accordingly, mice that lack ILC3s had elevated levels of IgG and a heightened CD4^{+} T cell response against commensal microflora [139]. In addition, ILC3s can induce apoptosis of CD4^{+} T cells directed against commensal microbes in an MHC class II dependent manner [41]. Selective genetic ablation of MHC class II expression in ILC3s resulted in increased generation of commensal specific T cell and colonic inflammation, which was attenuated by administration of antibiotics. An inverse correlation between MHC class II expression in intestinal ILC3s and expansion of pathogenic Th17 cells in pediatric IBD patients further supports a role for ILC3s in regulating T cell responses against commensal microflora [41]. Collectively, these studies highlight the interdependency of ILC3s and the intestinal microbiota (Fig.1). While the microbiota dictates the function and the development of ILCs, ILCs contribute to the containment of various microbiota species and calibrate the tone of immune response against microbiota.

Emerging studies suggest a link between NK cells, ILC1s and the microbiota. The human fetal intestine has very few ILC1s, which only develop a few weeks after birth, suggesting that the microbiota supports ILC1 development [140, 141]. Moreover, NK cells from germ free mice produce very little IFN-γ and granzyme B in response to poly I:C stimulation. As a result, germ free mice fail to control murine cytomegalovirus infection as well as do specific pathogen free mice, although they harbor comparable numbers of NK cells [142]. Future studies are necessary to identify the microbiota species and/or their metabolites that impact ILC1s and NK cells. While intestinal and lung ILC2 numbers and functions are clearly induced by helminth infections [143, 144], a direct impact of the microbiota on ILC2

development has been controversial. While numbers and expression of surface receptors on lung ILC2s are similar between germ-free and specific pathogen free mice [145], expansion of ILC2s in the intestine of germ-free mice has been observed [146]. Further, infection of germ-free mice with norovirus attenuated the expansion of ILC2s and led to an increase in the ratio of ILC3s to ILC2s, suggesting trans-differentiation of ILC2s into ILC3s [146]. Moreover, elimination of microbiota by antibiotic treatment induced differentiation of ILC2s and ILC1s towards an ILC3 phenotype, revealing a crucial role for the microbiota in maintaining ILC1s and ILC2s [147]. Additionally, commensals maintain the fitness and functionality of ILC2s. Production of TSLP and IL-25 is regulated by commensals; in synergy with IL-33, TSLP and IL-25 play important roles in activating ILC2s. [126–128]. Altogether, these studies demonstrate the importance of the microflora in the development and maintenance of ILCs.

6. Concluding remarks

Relationships between ILCs and cancer, the microbiota and cancer, and ILCs and the microbiota have been established (Fig.2). These studies raise the possibility of complex interactions between ILCs, the microbiota and cancer that should be further explored. Several scenarios can be envisioned. In homeostatic settings, ILCs may be crucial to maintain a balance between pro- and anti-tumorigenic commensal bacteria; ILC- secreted cytokines may support a normal microflora, thereby preventing chronic inflammation and cancer. Concomitantly, ILCs may restrict the niche for commensal bacteria like *E. coli* and *H. pylori* that have been shown to be promote cancer development [101, 103]. ILC-secreted cytokines may also support particular bacteria, such as *E. hirae*, *B. intestinihomini*, *B. fragilis*, *B. thetaiotamicron*, *B. breve* and B*. longum* that have been shown to enhance cancer therapies [112, 113]. In pathologic settings, dysbiosis caused by antibiotic treatment or other factors may induce inappropriate release of cytokines by ILCs, particularly IL-17 and IL-22, which may contribute to chronic inflammation and predispose to cancer. Additionally, given the role of ILCs in recruiting immune cells and shaping adaptive immune responses, abnormal ILC responses to dysbiosis may also impact T cell responses, further contributing to chronic inflammation and cancer. In therapeutic settings, chemotherapy-induced damage of epithelial cells may induce ILC responses that, in turn, impact bacterial translocation and chemotherapy effectiveness. For example, it has been shown that methotrexate-induced epithelial damage elicits ILC3 production of IL-22, which limits damage of the epithelial barrier [148]. Whether ILC3s impact the effectiveness of methotrexate treatment remains unknown. Checkpoint blockade and other immunotherapies may also impact ILCs directly or indirectly, generating feedback loops that may impact microbiota and therapeutic efficacy. Thus, it is important to obtain a complete picture of ILCs profile in clinical cancer. Further research considering the interactions between ILCs, the microbiota and tumors may help delineate as yet undefined crucial steps in cancer progression and pave the way for therapeutic strategies that target ILCs.

Acknowledgments

This work is supported by the US National Institutes of Health (UO1 AI095542, RO1 DE025884, and R01 AI134236.

We would like to thank Susan Gilfillan for critical comments

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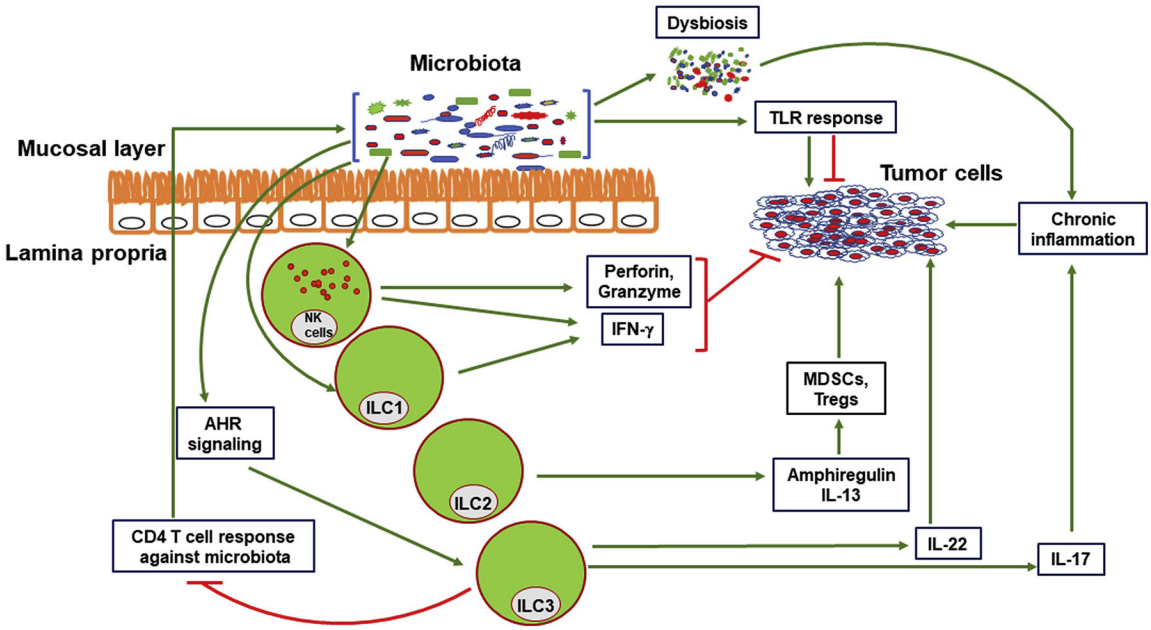

Figure 1. Direct and indirect effects of ILCs on cancer.

ILCs have both pro and anti-tumorigenic effect. ILC1s and NK cells block tumor cell growth through IFN-γ secretion. NK cells also lyse tumor cells through secretion of perforin and granzymes. IL-13 and amphiregulin secreted by ILC2s enhance MDSC and Treg functions respectively, facilitating immune evasion of tumors. ILC3 help maintaining a diverse microbiota and induce CD4 T cell tolerance for commensal bacteria, preventing dysbiosis and chronic inflammation that create a pro-tumorigenic microenvironment. Species in a healthy microbiota can also augment anti-cancer therapy. However, ILC3s can promote tumor growth by excessive secretion of IL-22. Through inappropriate release of IL-17, ILC3s also contribute to chronic inflammation that promotes tumorigenesis. Products from microbiota enhance TLR activation, which can promote or inhibit tumors depending on the context.

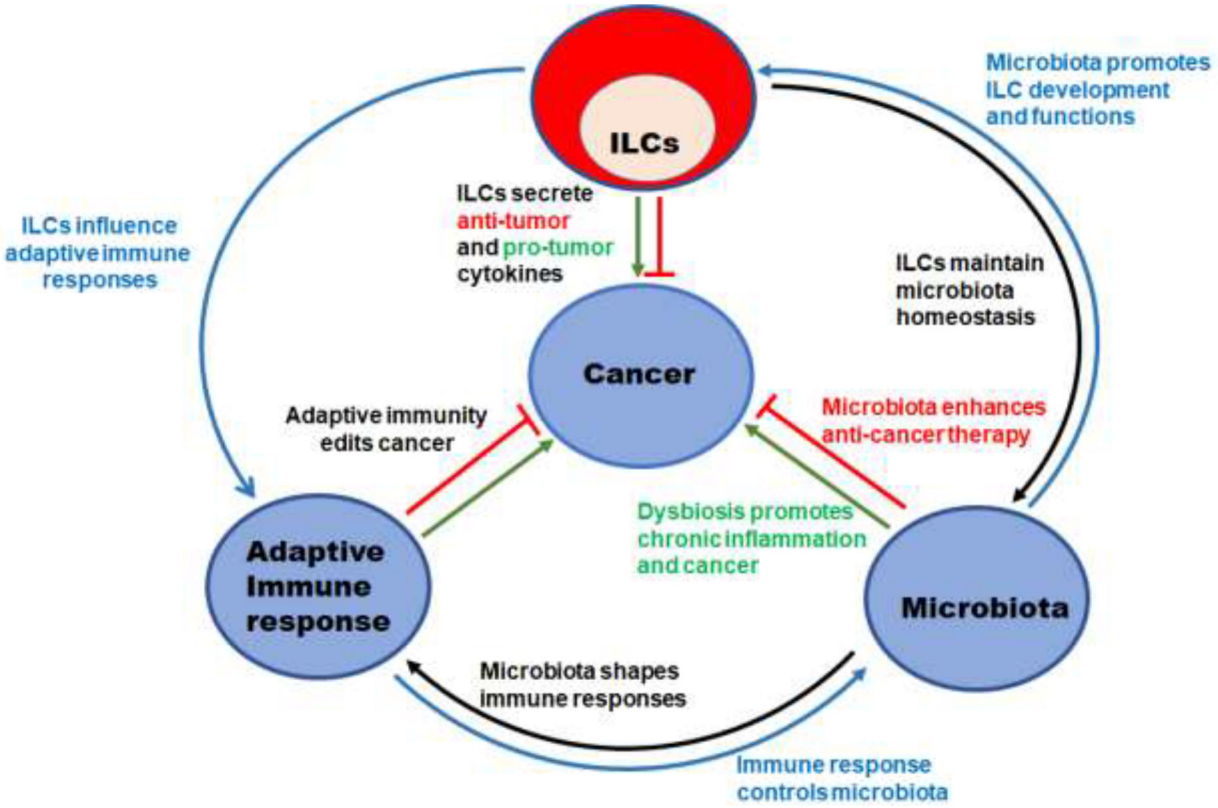

Figure 2. Schematic representation of the interactions between ILCs, adaptive immunity, microbiota and cancer.

ILCs can secrete pro- and anti-tumorigenic cytokines. ILCs can also impact anti-tumor adaptive immune response by secreting effector cytokines. ILCs contribute to the maintenance of a normal commensal microflora which reduces the risk of cancer and may potentiate anti-cancer chemotherapy and immune therapy. Reciprocally, microbiota drives ILCs development and function. Dysfunction of ILCs-microbiota interactions can lead to dysbiosis and chronic inflammation, resulting in a pro-tumorigenic microenvironment. Abnormal interactions between ILCs and adaptive immune responses may also induce a pro-tumorigenic environment through chronic inflammation and dysbiosis.