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Interplay between Gut Microbiota and T Lymphocytes in Colorectal Cancer

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Abstract

Colorectal cancer is one of the third leading causes of cancer mortality worldwide. There is increasing evidences about the involvement of gut microbiota in colorectal carcinogenesis. Several recent studies have shed light on the cross talk between gut microbiota and mucosal T cell subsets, specifically intraepithelial lymphocytes and lamina propria CD4⁺ T cells including T-helper cells and T-regulatory (Treg) cells which may be responsible for development of colorectal cancer through creating imbalance between proinflammatory and anti-inflammatory immune cells and their cytokines. In this review, we will focus on the influence gut microbiota on the development of mucosal T cells and their role in promoting colorectal cancer.

Keywords: Gut microbiota; CRC; T lymphocytes

CRC is usually associated with alteration in gut microbiota composition and shift in distribution of bacterial communities. However, these studies neither answer the cause or consequence question of dysbiosis in CRC, nor do they provide mechanistic insights by which the intestinal microbiota influences the development of CRC [4]. Also, several studies found that gut microbiota have a strong impact on regulation and development of immune system which could in turn initiate regulation of immune cells within the lamina propria of the intestine as well as mediating the inflammatory process [5].

In this review, we will focus on how gut microbiotas could regulate the development mucosal T cell subsets, specifically intraepithelial lymphocytes and LP CD4⁺ T cells including T-helper cells and Treg cells. The result of the cross talk between gut microbiota and different T lymphocytes is the imbalance between proinflammatory and inflammatory immune response which in turn will provide suggested mechanisms of promoting colorectal cancer as shown in **Figure 1**.

PSA (polysaccharide A) is a symbiosis factor that promotes antitumor activity by enhancement of development of regulatory T cells to produce IL10 and correct imbalance of T-helper 2 toward T-helper 1 which produce IFN-gamma and TNF- α .

On the other hand, segmented filamentous bacteria (SFB) enhance production of serum amyloid A (SAA) which promote Th17 development which has cancer promoting activity. (IEL) intraepithelial lymphocytes ($\gamma\delta$ T cells) produce IL10 and TGF- β which has antitumor activity, on the other hand it can also produce IL17 which promote cancer activity, suggesting the two-opposite role of (IEL) in colorectal cancer. Invariant natural killer T (iNKT) cells can recognize endogenous lipids presented by CD1d molecules on tumor cells and subsequently eliminate

Introduction

Colorectal cancer (CRC) is one of the most common public health burden. It is the third leading cause of cancer worldwide after lung and prostate, with nearly 600,000 death each year [1].

Most of colorectal cancers originate from epithelial cells of the colorectal mucosa, being identified by the formation of glandular structures and histologically classified as adenocarcinomas. The carcinogenesis process of CRC includes four main phases; initiation, promotion, progression and metastasis [2,3].

tumor cells directly through iNKT cell-mediated lysis. In the absence of CD1d expression on tumor cells, iNKT cells mediate tumor cell lysis indirectly through activation of NK cells and CD8+ tumor specific T- cells.

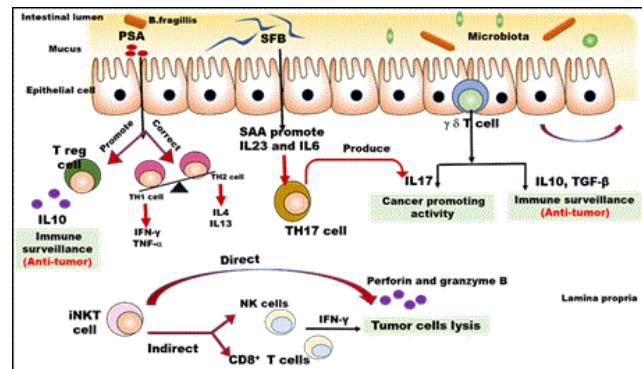


Figure 1 Cross talk between gut microbiota and Lamina propria T cells.

Gut microbiota and TH1-TH2 axis

TH1 CD4⁺ T lymphocytes produce cytokines IL-2, interferon (IFN)-gamma and tumor necrosis factor (TNF)-beta which in turn activate macrophages and responsible for cell mediated immune response. On the other hand, humoral immunity and antibody production are strongly associated with TH2 CD4⁺ T lymphocytes producing cytokines including IL-4, IL-6 and IL-10 [6]. Immune deviation towards TH1 anti-inflammatory responses results in tumor rejection as TH1 pathways are responsible for cytotoxic T-cell lymphocytes (CTL), natural killer (NK) cells, macrophages and monocytes, all of which can attack cancer cells and generally defend against tumors [6,7]. Conversely deviation towards TH2 type inflammation response promote tumor growth [8,9]. Almost all malignancies are associated with suppression of the cell mediated immunity. Several studies have reported that shift in immune function has been demonstrated in patients with colorectal cancer [10-12]. The numbers of TH1 CD4⁺ cells were decreased in patients with colorectal tumors, with low production of cytokines from TH1 lymphocytes whilst there was elevation in the levels of cytokines produced by TH2 lymphocytes [13,14]. The further the disease process has progressed the more significant these imbalances become with high levels of the humoral immunity associated cytokines having a prognostic influence in terms of disease-free survival and tumor recurrence post-surgery [15].

Interactions between lamina propria CD4⁺ T cells and the gut microbiota, often with epithelial cells or dendritic cells functioning as the intermediaries, are critical for shaping the adaptive immune response in the intestine. As bacterial colonization of the intestine is considered to be one of the most important factor for mammalian immune system function. It has been found that *B. fragilis* was the first identified bacterial species which are sufficient enough to correct the Th1 and Th2 cell imbalances observed in non-gut

lymphoid tissues in germ free mice. *B. fragilis* is a Gram-negative anaerobic symbiont which colonize 30-70% of human lower intestinal tract as primarily reservoir [16,17]. Colonization of GF mice with *B. fragilis* induced overall CD4⁺ T cell expansion and increased numbers of Th1 cells to levels similar to those of conventionally raised mice. Mechanistically, *B. fragilis* is mainly exert their function through production of polysaccharide A (PSA) [17,18]. Among carbohydrates, PSA is known to be potent T cell-dependent rather than a T cell-independent antigen. Also, it is the most effective T-cell dependent antigen that can strongly regulate host immune system [17].

It has been found that PSA produced by *B. fragilis* in germ free mice, can induce Th1 expansion and cytokine production. Th1 development is mainly depend on IL12 which are produced by activated dendritic cells. PSA is the most effective polysaccharide known to signal dendritic cells to induce IL-12 production [19].

Gut microbiota and Th17

Several recent studies tried to focus on how the commensal bacteria affects the development of Th17 cells and their in promoting CRC. Th17 cells have been implicated in the pathogenesis of several human autoimmune diseases and inflammatory disease models via proinflammatory cytokines production [20-23]. On the other hand, Th17 cells play an important role in host defense against extracellular bacteria and parasites [24]. Several animal studies have found that Th17 cells which are mainly localized in the lamina propria of the small intestine and the colon and play a critical role in defense against *Shigella flexneri* and *Citrobacter rodentium* [25,26].

Although, it was found that segmented filamentous bacteria (SFB) factors lead to increase number of Th17 cells, many questions still remain about how SFB drive gut Th17 cell development. Which provide a suggested link between gut microbiota and Th17 cells. SFB adhesion to the epithelium induces Th17 development via production of serum amyloid A (SAA) which in turn induced dendritic cells to produce IL-6 and IL-23, the key cytokines for Th17 development which are contributed to progression of intestinal inflammation [24] as shown in **Figure 1**.

IL-17, pleiotropic proinflammatory cytokine which are highly produced in the tumor microenvironment, plays important roles in both angiogenesis and tumor immunity. Accumulative evidences have suggested that IL17 expression is elevated in many human tumors such as breast, ovarian, hepatocellular and CRC [27]. Consistently with a positive role of IL-17 in promoting tumor development, tumor tissues have a higher frequency of IL-17+ cells T cells compared with untransformed bowel tissues [28]. The protumor role of IL-17 which is mediated by inflammation-associated signaling pathways, provides additional support for the already well-established link between inflammation and tumorigenesis [29]. It has been proposed that enterotoxin producing *Bacteroides fragilis* (ETBF) human, colonic commensal bacterium, are able to promote colonic tumorigenesis in APC mutant mice through

activation of Stat3 pathway and Th17-cell polarization and the block of IL23 R and IL17 could reduce the tumor formation [30]. It has been reported that worsen of intestinal epithelial barrier result in microbial pathogen invasion and microbial products release are driving IL-23/IL-17 axis activation and promoting tumor growth and progression in CPC-APC mice [31].

Gut microbiota and regulatory T-cells

Although, Treg cells are one of the key players for maintaining intestinal homeostasis, immune surveillance and immune therapy of cancer due to suppressing anti-tumor immune responses, several studies using *Apc Min/+* mice revealed a protective role of IL-10-producing Treg cells in bacterial-induced chronic inflammation and cancer [32] and even hereditary colon cancer, suggesting that Treg cells might play a protective role in cancer by suppressing inflammation [33].

The gut contains a high frequency of Treg cells which comprise two main subtypes, naturally occurring Tregs that develop in the thymus before trafficking to other sites in the body and inducible Tregs that develop in the periphery [34-40]. *Foxp3+* intestinal Tregs are mainly localized in the lamina propria of the small intestine and colon [41] and according to these findings, it was implied that accumulation of Tregs in the colon and SI is differentially regulated and the colonic Treg differentiation is more heavily influenced by the microbiota [41]. Several results among mouse models of colitis have shown that disruption of regulatory T-cell networks can initiate chronic intestinal inflammation in the presence of a triggering intestinal microbiota [42].

It was important to demonstrate how single organism and defined bacterial communities can instruct Treg responses. Recent works provide our knowledge with the answers to these questions, as they show that *B. fragilis* and its immunomodulatory molecule, PSA, are capable of driving Treg differentiation [43]. PSA derived from the human commensal *Bacteroides fragilis* is a symbiosis factor that stimulates immunologic development within mammalian hosts. One of the most important function of PSA is enhancement of suppressive function of circulating *Foxp3(+)* Tregs [44,45].

Intraepithelial Lymphocytes (IELs)

IELs are specialized T cells that are consisting of two major groups depending on expression of T-cell receptor- $\gamma\delta$ (TCR $\gamma\delta$) or TCR $\alpha\beta$, also can be divided into two populations, including natural and induced IELs. In human, IELs, are mainly found in direct contact with the enterocytes, to exert their critical role in the maintenance of intestinal homeostasis [46]. Because of the specific location of IELs in intestinal mucosa, they are involved in resisting to the invasion of foreign pathogens and preserving immune regulation. It has been found that TCR $\gamma\delta+$ IELs perform their defense mechanism against intestinal pathogens via secretion of IFN- γ and TNF, and importantly to drive proinflammatory effects [47,48]. TCR $\gamma\delta+$ T cells could increase the production of TGF- β and IL-10 to perform their

suppressive function in intestinal inflammation and so immune regulation of intestinal mucosa [49,50].

In the first study on effect of regulatory role of gamma-delta T cells in immunopathogenesis of colorectal cancer, they found that the imbalance e in V δ 1 and V δ 2 T cells creates an immunosuppressant microenvironment in rectal cancer tissues, which may enable tumors to limit antitumor immunity and evade immune surveillance in rectal cancer patients [51].

Recently, a protumour role for IL-17-producing $\gamma\delta$ T cells was reported for the first time in human cancer. Specifically, V δ 1+T cells were the major source of IL-17 involved in chronic inflammation in colorectal cancer. Moreover, IL-17-producing $\gamma\delta$ T cells secreted IL-8, tumour necrosis factor (TNF) and granulocyte-macrophage

Colony-stimulating factor (GM-CSF), which recruited immunosuppressive MDSCs into the malignant microenvironment, further driving protumour inflammation.

Importantly, the extent of IL-17-producing $\gamma\delta$ T cell infiltration positively correlated with the clinical stage of the disease, highlighting the potential cancer-promoting role of IL-17-producing $\gamma\delta$ T cells in human colorectal cancer [52].

Gut microbiota and CD1d⁺, NKT cells

Unlike T-cells, NKT cells are initially recognized to co-express T cell and natural killer cell (NK cell) markers (hence, the name NKT cells) and later defined by their ability to recognize self and non-self-lipid antigens presented by the atypical MHC class I molecule CD1d, which is required for NKT cell positive selection in the thymus [53]. Classification of NKT cells into invariant (i) or type I NKT cells and non-invariant or type II NKT cell is mainly depend on the expression of T- cell receptor (TCR).

Importantly, it has been found that intestinal microbiota exerts their regulatory effect through CD1d-iNKT cell. Thus, in addition to microbiota-dependent control of intestinal iNKT cells, CD1d and NKT cells regulate intestinal microbial colonization and the composition of the microbiota [54]. Moreover, CD1d deficiency is associated with intestinal dysbiosis in accordance with the regulation of the intestinal microbiota by CD1d and NKT cells. Similarly, CD1d-deficient mice are susceptible to wide variety of mucosal pathogens [55]. Collectively, mucosal iNKT cells and the intestinal microbiota cross-regulate each other in a bidirectional manner.

In cancer, although few number of clinical trials in have been performed in human to investigate its role in cancer, there was a strong evidence for the role of type I NKT cells are predominantly protective, helping to orchestrate CD8+ T cells and NK cells to inhibit tumor growth through their production of interferon- γ , and through their activation of dendritic cells to make IL-12 and other cytokines [56]. Conversely, we have seen that type II NKT cells are the primary type of NKT cells responsible for suppression of tumor immunity, through their ability to make IL-13 and induce production of TGF- β by myeloid cells [57]. Indeed, it is becoming increasingly recognized that one of the important sources of the TGF- β that

suppresses tumor immunity may be the immune system itself, not just the tumor, and this may be largely through this mechanism of type II NKT cell induction or other mechanisms that trigger TGF- β production by myeloid cells. IL-13 from NKT cells can also recruit M2 tumor-associated macrophages that can suppress tumor immunity [58,59].

A recent study was done on a mouse colitis-associated colorectal cancer model reported that a significant decrease in iNKT cells were associated with increased in numbers of tumors and resulted in more severe colitis in an AOM /DSS colorectal cancer model. Furthermore, activation of iNKT cells by GC resulted in a decrease in the incidence of tumors in this model, probably due to the inhibition of IL-13-producing NK1.1 $^+$ T cells. These findings provide support for the hypothesis that iNKT cells are implied in protection against tumors in colitis-associated cancer [60].

Upon activation with a-GC, iNKT cells display powerful anti-tumor cytotoxic activity [61], rapidly release cytokines (such as GM-CSF, TNF- α , IFN- γ , IL-4, IL-10 and IL-13 [62,63] and promote maturation of dendritic cells into APC that are capable of activating conventional T cells [64].

Further work is required to determine the regulation of mucosal NKT cells frequency, and function of human colorectal cancer.

Conclusion

There is a growing awareness of the importance of gut microbiota in mediating colorectal cancer as it's the third leading cause of cancer all over the world. However, it remains questionable how the cross talk between gut microbiota and laminal CD4 T-cells and intraepithelial lymphocytes could influence on their involvement in colorectal malignancy. Herein this review we have provided a different suggested role in the colorectal carcinogenesis. Commensal gut microbiota could have antitumor activity via gamma IFN and TNF producing CD4 $^+$ TH1 cells and IL10 secreted by FoxP3 $^+$ regulatory T cells. Invariant natural killer T (iNKT) cells, which are naturally found in intestine, can recognize endogenous lipids presented by CD1d molecules on tumor cells and subsequently eliminate tumor cells directly through iNKT cell-mediated lysis. In the absence of CD1d expression on tumor cells, iNKT cells mediate tumor cell lysis indirectly through activation of NK cells and CD8+ tumor specific T- cells. $\gamma\delta$ T cells are intraepithelial lymphocytes have produce IL10 and TGF- β which has antitumor activity. On the other hand, some segmented filamentous bacteria (SFB) drive Th17 development which has cancer promoting activity via production of IL17. Further prospects for better managements of colorectal cancer aim to metagenomics and metatranscriptomic surveys of the microbiota which in turn will provide our knowledge with information about the membership and function of the microbial world within the gut.

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