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Review

Microbiome, inflammation and colorectal cancer

Ju Chen, Elise Pitmon, Kepeng Wang*

Department of Immunology, School of Medicine, University of Connecticut Health Center, 263 Farmington Ave., Farmington, CT, 06030, United States

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ABSTRACT

Chronic inflammation is linked to the development of multiple cancers, including those of the colon. Inflammation in the gut induces carcinogenic mutagenesis and promotes colorectal cancer initiation. Additionally, myeloid and lymphoid cells infiltrate established tumors and propagate so called "tumor-elicited inflammation", which in turn favors cancer development by supporting the survival and proliferation of cancer cells. In addition to the interaction between cancer cells and tumor infiltrating immune cells, the gut also hosts trillions of bacteria and other microbes, whose roles in colorectal inflammation and cancer have only been appreciated in the past decade or so. Commensal and pathobiotic bacteria promote colorectal cancer development by exploiting tumor surface barrier defects following cancer initiation, by invading normal colonic tissue and inducing local inflammation, and by generating genotoxicity against colonic epithelial cells to accelerate their oncogenic transformation. On the other hand, a balanced population of microbiota is important for the prevention of colorectal cancer due to their roles in providing certain bacterial metabolites and inhibiting intestinal inflammation. In this review we summarize our current knowledge regarding the link between microbiota, inflammation, and colorectal cancer, and aim to delineate the mechanisms by which gut microbiome and inflammatory cytokines regulate colorectal tumorigenesis.

Colorectal cancer (CRC) is one of the major malignancies in humans and the second and third leading cause of cancer-related deaths in males and females, respectively, in the United States [1]. Only a small fraction of human CRCs are genetically predisposed, including familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC, or Lynch syndrome), hamartomatous polyposis syndrome, and other more rare disorders [2]. Among environmental risk factors for CRC, chronic inflammation is an important contributor to this devastating disease [3]. Patients who suffer from inflammatory bowel diseases (IBD), including Crohn's disease (CD) and Ulcerative Colitis (UC), have a high risk of developing colitis-associated CRCs (CAC) with poor prognoses [3,4]. It is also important to recognize that among the 95% CRC cases where the patients had seen no IBD history, inflammation is evident in colorectal tumors and has been shown to promote cancer development [5].

1. Microbiome and colorectal cancer

The human gastrointestinal tract is a habitat for trillions of microbes. Increasing evidence suggests a pivotal role for intestinal microbiota in the development of colitis and CRC [6–10]. Patients that harbor colonic adenomas have different compositions of mucosal adhering bacteria compared to healthy controls [11–14]. Alterations in microbiota composition in patients with colorectal cancer can serve as potential non-invasive diagnostic and/or prognosis factors for the disease in humans [9,13,15–20]. Metagenome-wide association studies (MGWAS) comparing stools from healthy subjects and those from patients with advanced adenoma or carcinoma revealed microbial genes, strains, and functions enriched in CRC [21,22]. For instance, mucosal-associated *E. coli* bacteria were frequently found in tissues from patients with Crohn's disease and colorectal tumors [23]. Human colorectal tumors also harbor a significantly higher abundance of *Proteobacteria* and a lower abundance of *Bacteroidetes* [14]. A longitudinal study on a mouse model of CAC also revealed a clear shift in bacterial composition in the presence of chemically induced chronic gut inflammation [24]. These data indicate that chronic gut inflammation and CRC are linked with an altered microbial content in the gut, and result in the association of specific microbes with intestinal lesions. Whether these changes in microbial biology reflect a bystander effect of colitis or CRC, or instead, represent a causal factor for disease onset in the gut, has been vigorously studied in the past decade using mouse models of colorectal cancer. These mouse models rely on either genetic lesions that predispose mice to colonic inflammation and/or cancer, or chemicals that induce epithelial mutation and inflammation. CAC can be induced chemically in mice with a single dose of azoxymethane (AOM) carcinogen followed by repeated cycles of DSS-induced chronic colitis

* Corresponding author.
E-mail address: kewang@uchc.edu (K. Wang).

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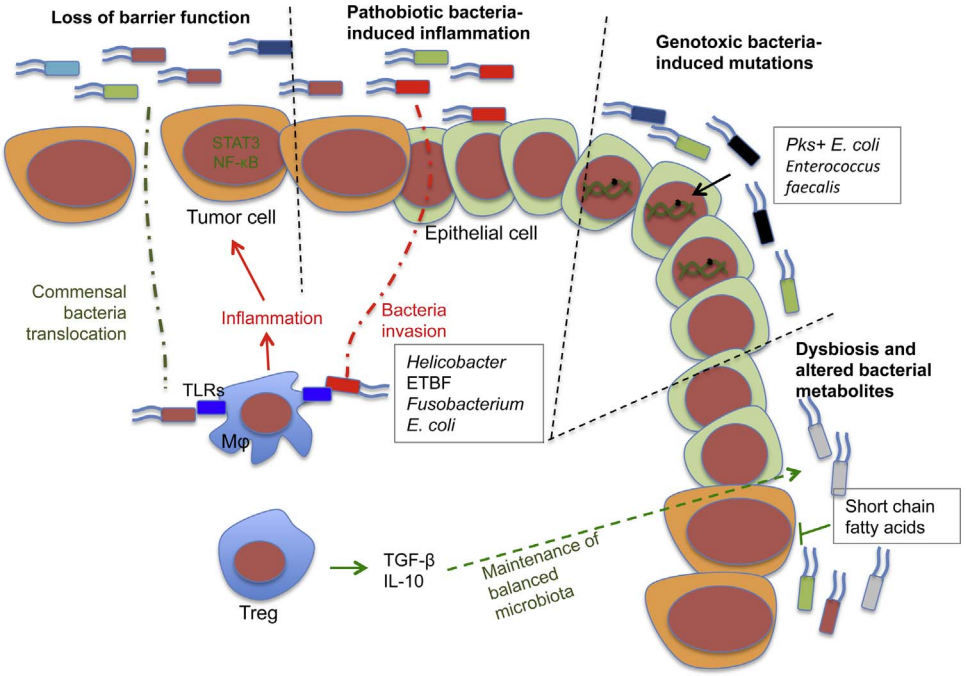

Fig. 1. Microbiota and colorectal cancer.
Gut microbiota regulate the initiation and progression of CRC. Loss of surface barrier function on colorectal tumors leads to the infiltration of commensal bacteria and their products, which in turn activate tumor-associated myeloid cells and induce tumor-promoting inflammation. Pathogenic and pathobiotic bacteria invade normal colorectal tissues and promote the onset of inflammation and tumorigenesis. Bacteria that carry genotoxic markers promote accumulation of genetic lesions in intestinal epithelial cells and initiate CRC development. Chronic inflammation in IBD and CRC alters the composition of commensal bacteria and results in dysbiosis that further propagates tissue inflammation. Commensal bacteria-derived diet metabolites regulate the process of CRC development by impacting tumor cell growth and survival, and immune cell-mediated tumor killing.

[25]. IL-10 knockout mice also develop spontaneous intestinal inflammation and colitis-associated cancer in their gut, and the latter is accelerated with AOM injection [26,27]. Mouse sporadic CRCs are frequently based on genetic ablation/mutation of genes that encode the Apc tumor suppressor or DNA mismatch repair machinery [28–30]. A comprehensive review on mouse models of cancer can be found in [31]. Using these tools, cancer biologists have uncovered important roles for chronic inflammation and gut microbiota in colorectal cancer development. We now have evidence to suggest the following four ways by which bacteria contribute to the development of CRC: 1), loss of surface barrier function on colorectal tumors leads to commensal bacteria-induced tumor-promoting inflammation; 2), pathobiotic and pathogenic bacteria promote the onset of colonic inflammation and tumorigenesis; 3), bacteria that carry genotoxic markers promote accumulation of genetic lesions in intestinal epithelial cells; and 4), alterations in bacterial composition or metabolism regulate the process of colonic tumor development (Fig. 1). In the following sections, we will introduce each of the potential mechanisms by which gut microbiota impacts CRC.

1.1. Loss of epithelial barrier function on colonic tumors results in commensal bacteria-activated inflammation

The link between chronic inflammation and cancer is clear, and about 20% of all human cancers are linked to pre-cancerous inflammation [5]. Chronic inflammation in the gut in the form of IBD also significantly increases the risk of CRC [5,32]. These evidence suggest a tumor initiating role of chronic inflammation in the gut. However, recent studies using mouse models of sporadic colorectal cancer also showed pivotal roles for inflammatory cytokines and tumor-infiltrating immune cells in CRC, after the advent of primary tumors. In humans, most, if not all, solid tumors harbor inflammatory infiltrates in the tumor stroma, regardless of pre-cancer inflammatory history. The etiology of tumor-associated inflammation in sporadic CRC has been examined and we now know that transformed colorectal epithelial cells fail to form an effective surface barrier to keep commensal bacteria and their derivative products from invading tumor stroma [33]. As a result of this barrier defect, commensal bacteria become a driving force for the induction and maintenance of tumor-promoting inflammation [33].

Using a mouse model of sporadic CRC that is based on allelic inactivation of the *Apc* tumor suppressor gene, we showed that tumor-bearing mice exhibit a marked increase in colonic barrier permeability [33]. Sporadic colorectal tumors in mice and humans produce no mucus, and exhibit disrupted production and localization of tight junction proteins [33]. As a result, commensal bacteria degradation products (such as LPS) pass through the tumor surface and engage tumor-infiltrating myeloid cells in the stroma. Sporadic invasion of commensal bacteria into tumor stoma was also seen in mouse and human tumors, and this process happens early on during colonic tumorigenesis. [33]. Invading commensal bacteria and their components engage TLRs on tumor-infiltrating myeloid cells and activate MyD88-mediated production of inflammatory cytokines, most notably IL-23 [33]. IL-23, in turn, promotes CRC development by activating the production of IL-17A, IL-6, and IL-22 [33].

Treatment of CRC-bearing mice with a cocktail of broad spectrum antibiotics results in decreased IL-23 and IL-17A expression and leads to a reduction in colorectal tumor load in wild type mice, but not in IL-23R-deficient mice [33–35]. Mice treated with antibiotics are also less susceptible to the induction of CAC by AOM/DSS protocol [36,37]. In addition to the IL-23/IL-17A pathway, commensal bacteria are also required for the upregulation of IL-17C in transformed epithelial cells through TLR/MyD88 dependent signaling [38]. IL-17C signals to colonic tumor cells in an autocrine manner and supports their survival by activating the transcription of Bcl-2 and Bcl-xL [38]. Disruption of surface barrier function by means of DSS-induced colitis leads to an increased susceptibility to CRC [39], whereas mice lacking Muc2 protein develop spontaneous colitis followed by CAC [40,41]. Mice that harbor a defective mucin glycosylation pathway also develop spontaneous colitis and colorectal tumors that are dependent on the presence of gut bacteria [42]. Intestinal epithelial-specific ablation of matriptase, a membrane-anchored serine protease that strengthens the intestinal epithelial barrier by promoting tight junction formation, causes the development of early-onset colon adenocarcinoma [43,44]. N-formylpeptide receptors are expressed on colonic epithelial cells and bind to bacterial N-formylpeptides to promote epithelial cell proliferation and renewal [45]. Mice lacking N-formylpeptide receptors show delayed DSS-induced colitis and increased colitis-associated cancer development [45]. It remains to be tested if N-formylpeptide receptors also play anti-tumor roles in mouse models of sporadic colorectal cancer. Given the fact that bacterial N-formylpeptide promotes colonic epithelial (and likely, tumor cell) proliferation, it is plausible that this