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REVIEW ARTICLE

Gut microbiota, inflammation and colorectal cancer

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Abstract Although genes contribute to colorectal cancer, the gut microbiota are an important player. Accumulating evidence suggests that chronic infection and the ensuing inflammation contributes to tumor initiation and tumor progression. A variety of bacterial species and tumor-promoting virulence mechanisms have been investigated. Significant advances have been made in understanding the composition and functional capabilities of the gut microbiota and its roles in cancer. In the current review, we discuss the novel roles of microbiota in the progression of colon cancer. Although microbiota technically include organisms other than bacteria e.g., viruses and fungi, this review will primarily focus on bacteria. We summarize epidemiological studies of human microbiome and colon cancer. We discuss the progress in the scientific understanding of the interplay between the gut microbiota, barrier function, and host responses in experimental models. Further, we discuss the potential application in prevention, diagnosis, and therapy of colon cancer by targeting microbiota. We discuss the challenges lie ahead and the future direction in studying gut microbiome in colon cancer to close the gap between the basic sciences and clinical application.

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Introduction

Colorectal cancer is the 3rd most common cancer in both males and females in the US and the 2nd leading cause of cancer deaths with the estimated new cases of nearly 133,000 and deaths of 50,000 in 2015.[1] Worldwide, 1,360,000 new cases and 694,000 deaths per year are estimated.[2] Cancer incidence in the large intestine is also known to be approximately 12-fold higher than that of the small intestine, which has been attributed to several magnitude greater bacterial density in the large intestine ($\sim 10^{12}$ cells per ml) compared with that in the small intestine ($\sim 10^{2}$ cells per ml).[3] With advance in metagenomic technology, growing evidence now suggests that dysbiosis, i.e., imbalance in of normal intestinal microbiota, can promote chronic inflammatory conditions and the production of carcinogenic metabolites, leading to neoplasia.[4,5]

Gut microbiota represents a complex ecosystem that develops in close parallel with hosts and depends on the physiological environment of hosts. Humans have coevolved with their microbes over thousands of years. The gut bacterial population stabilizes during the first years of life and then remains stable throughout our life in terms of the major populations. Human gut microbiota are dominated by four main phyla: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. The corporate number of microbial species in human gut is estimated to be 1000—1150, with each individual harboring at least 160 (Qin, Li et al 2010). The number of genes of gut microbiota exceeds the number of genes in the human genome by 150 times. A large portion (38%) of the total gene pool is commonly shared from individual to individual. The "core human microbiome" refers to the central part of microbial gene pool existing in all or most of humans. The "variable human microbiome" is the microbial genes in a specific cohort of people, which is determined by a combination of host factors (Turnbaugh, Ley et al 2007). In the modern society, the host-microbial relationship is now being dramatically affected by shifts in the collective human microbiome resulting from changes in the environment and societal norms (Sun and Chang 2014).

In this review, we will discuss the roles of gut microbiota in colorectal cancer, summarizing both epidemiologic observations and the data from experimental animals. Although microbiota technically include organisms other than bacteria e.g., viruses and fungi, this review will primarily focus on bacteria, of which significant recent progresses have been made in understanding their role in human health. Specifically, understanding of the interplay between the gut microbiota, barrier function, and inflammatory responses will uncover new therapeutic targets in colorectal cancer. We will discuss the potential application in prevention, diagnosis, and therapy of colorectal cancer by targeting gut microbiota. Moreover, we will also discuss challenges lie ahead and the future direction in studying gut microbiome in cancer to close the gap between the basic sciences and clinical application.

Epidemiological studies of microbiome and colorectal cancer

At least two approaches have been employed to study colorectal cancer-associated microbiome. One is the targeted, more hypothesis-testing studies to examine whether exposure to specific bacteria species of interest increases the risk of colorectal cancer. The second type is studies aiming to identify differences in overall microbial composition by disease status. The latter has gained more popularity recently with advances in genomic technology for high throughput sequencing and discussed here first.

Microbiome core structure, diversity, richness and colorectal cancer

Most common materials used in these types of investigation are fecal or mucosal biopsy/resection samples and have been analyzed primarily by pyrosequencing. But it is now clear that bacterial populations in feces and mucosa are distinct.[6,7] As summarized in Table 1, the majority of these studies have demonstrated beta diversity by principal coordinate or component analysis illustrating structural difference of gut microbiome, where samples belonging to different disease status (cancer, adenoma, or controls/normal adjacent tissue) cluster in different two dimensional spaces,[7—12] indicating the presence dysbiosis. Analysis of community diversity/richness indies based on 16SRNA gene sequencing has shown significantly reduced microbial diversity in feces of colorectal cancer patients than in controls[13] and in cancer tissue compared with mucosa at least 10 cm apart from cancer.[14] On the contrary a richness index was higher in rectal mucosa of colorectal cancer patients than in that of control subjects[7] or in cancer tissues than paired normal tissue.[11] Others did not find differences in these alpha diversity indices.[9,10,15,16] With or without using additional quantitative PCR (qPCR), these studies have also found that specific bacterial groups were more common or less common in colorectal cancer cases than control specimens.[7—16] Because each study has used different taxonomic levels/classifications for the comparison, there have little consistency in changes associated with colorectal cancer. However, there were multiple studies reporting overrepresentation of *Fusobacterium* and Porphyromonasand and underrepresentation of *Faecalibacterium* (Table 1). Yet, it should be noted that some of these studies were based on very small numbers of samples and control subjects were often not comparable with cases in terms of basic demographic factors (such as age). In summary, while these studies underscore marked differences in gut microbial membership between colorectal cancer patients and healthy controls, it is difficult to generalize characteristics of cancer associated gut microbiome.

Individual bacterial species and colorectal cancer risk

Streptococcus bovis

Streptococcus bovis (SB) is a gram-positive bacterium and lower-grade opportunistic pathogen that can cause systemic infections (endocarditis or bacteremia) in humans. It is a group D streptococcus with the specific ability to grow in 40 percent bile.[17] Intestinal mucosal lesions have been deemed to serve as a portal for these bacteria to the systemic circulation. Based on biochemical traits, DNA homology and divergence in 16S rRNA sequences, SB can be