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Review

Microbiome and colorectal cancer: Unraveling host-microbiota interactions in colitis-associated colorectal cancer development

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ABSTRACT

Dysbiosis of gut microbiota occurs in many human chronic immune-mediated diseases, such as inflammatory bowel disease (IBD) and colitis-associated colorectal cancer (CAC). Reciprocally, uncontrolled immune responses, that may or may not be induced by dysbiosis, are central to the development of IBD and CAC. There has been a surge of interest in investigating the relationship between microbiota, inflammation and CAC. In this review, we discuss recent findings related to gut microbiota and chronic immune-mediated diseases, such as IBD and CAC. Moreover, the molecular mechanisms underlying the roles of chronic inflammation in CAC are examined. Finally, we discuss the development of novel microbiota-based therapeutics for IBD and colorectal cancer.

1. Introduction

Colorectal cancer (CRC) is the 3rd most commonly diagnosed cancer in the world [1] and is responsible for over 59,560 deaths approximately in the North America in 2016, according to American and Canadian cancer society [2,3]. Recent incidence and mortality rates have been decreasing gradually in some developed countries [4], and this is possibly due to implementation of preventive strategies such as early diagnosis and removal of colonic polyps through screening tests. However, CRC rates are still expected to increase to more than 2.2 million new cases and 1.1 million deaths by 2030 worldwide [4], suggesting that CRC remains a major global health burden. In the United States, it is estimated that the medical costs associated with CRC will be approximately $18 billion by 2020 [5].

Nowadays, it is widely accepted that inflammation or inflammatory bowel disease (IBD) is highly associated with CRC, namely colitis-associated CRC (CAC) [6]. IBD involves two major clinically defined subtypes: ulcerative colitis (UC) and Crohn's disease (CD), each increases the cumulative risk of CAC by up to 20% and 8% after 30 years of disease occurrence, respectively [9–11]. This increased incidence rate of CRC in IBD patients depends on disease severity, duration, treatment and management. IBD has long been considered to have a genetic component, but likely also involves immune responses to environmental agents [7]. The nature of these environmental agents is unclear [8,9], although recent reports support the notion that specific microbes or dysbiosis of intestinal microbiota drives IBD in genetically susceptible individuals [10]. These reports support the view that IBD results from altered interactions between intestinal microbes and the mucosal immune system [9,11].

Inflammation, gut microbiota, specific genetic mutations, and other environmental triggers, have all been regarded as etiological factors of CRC (Fig. 1). However, the molecular mechanisms by which microbiota mediates chronic inflammation followed by CRC development are not fully understood. This review will discuss recent advances in this field of research, particularly emphasizing studies that examine the roles of gut microbiota in IBD and CAC.

2. Composition and functional activities of gut commensal bacteria

The gut microbiota is composed of a complex community of over 100 trillion microbial cells, composed predominantly of species from *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Verrucomicrobia* and *Actinobacteria* [12,13]. As will be discussed below, the gut microbiota carries out a range of functions that benefit the host, from pathogen protection, immune modulation, and nutrient supply, to host metabolism [14]. Due to the diversity of the gut microbiota, it is empirically difficult to define the healthy or diseased-related gut microbiota composition, but increasing evidence suggests that alterations in the gut microbiota composition may contribute to the healthy or pathological gut environment [15].

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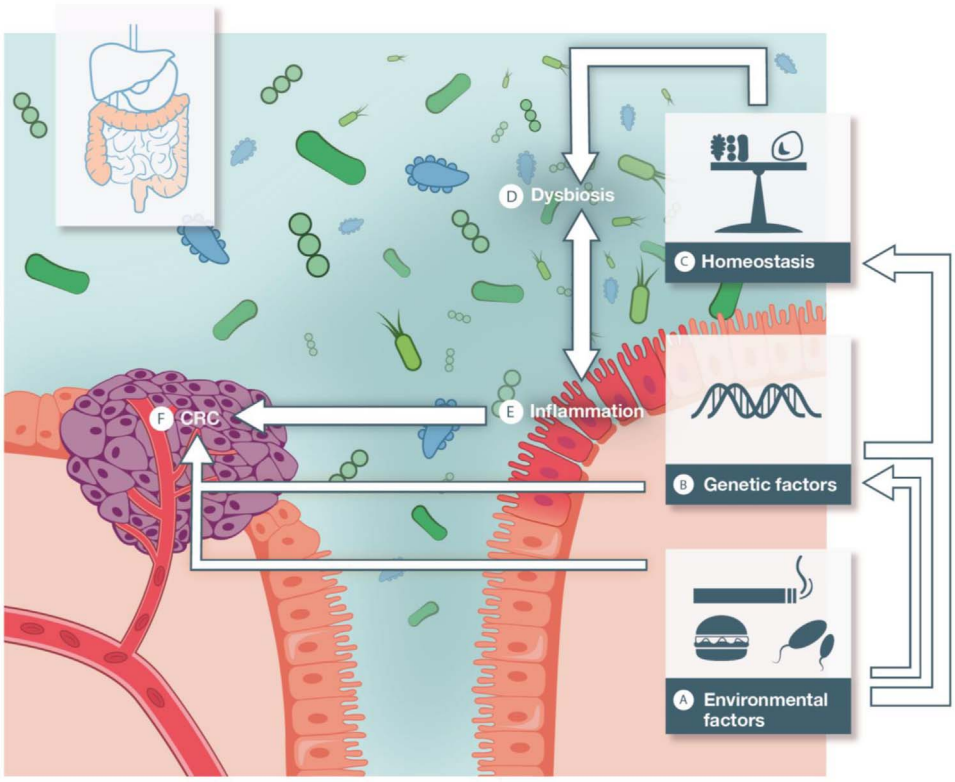

Fig. 1. Etiological factors that contribute to CRC development and progression. Environmental factors, genetic background and dynamic balance between host immune system and microbiota (gut homeostasis) are all associated with CRC development and progression. In addition to direct induction by environmental factors (A) or genetic factors (B), CRC is also believed to involve the confluence of environmental factors (A) and genetic factors (B) to tip the homeostasis (C), triggering dysbiosis (D) and chronic inflammation (E), and eventually result in a higher risk for developing CRC (F).

2.1. Pathogen protection and immune modulation

It is well-known that gut microbiota plays a crucial role in the resistance against invading pathogens through multiple mechanisms. In the healthy gut, microbiota can prevent enteric pathogen colonization via colonization niches to form a 'physical barrier', or through nutrient competition. Bacteriocin or short chain fatty acids (SCFAs) produced by several members of commensal bacteria, directly inhibit the growth of pathogens [16]. Moreover, in response to pathogen-associated molecular patterns (PAMPs), microorganism-associated molecular patterns (MAMPs), or metabolites produced by pathogenic or commensal bacteria, the host immune system drives stimulatory or regulatory effector responses, such as the secretion of antimicrobial peptides (AMP), lysozymes, IgA, and the differentiation of T regulatory (Treg) cells, to maintain gut homeostasis [17,18]. The activation of pattern recognition receptors, such as NOD-like receptors (NLR), induces the expression of several types of AMPs and lysozymes to enhance infection control and modulate microbiota [19]. The differentiation of B cells to IgA-producing plasma cells is activated by various signals from commensal microbiota through dendritic cells, T follicular helper cells, and intestinal epithelial cells (IECs), leading to IgA mediated opsonization and neutralization of toxins and bacteria [20–22]. Similarly, Treg cell differentiation in the gut is not only induced by conditioning factors produced by IECs [23] and immune cells [24], but also activated by a variety of signals from commensal microbiota, such as polysaccharide A and microbial metabolites [25,26].

2.2. Microbial contribution to nutrient balance and host metabolism

The gut microbiota acquires nutrients from various resources, such as undigested or partially digested dietary components (e.g., proteins, lipids and carbohydrates) and host components, such as mucus. Several metabolites produced by the microbiota upon acquisition of these nutrients also benefit host health and metabolism [27]. Non-digestible carbohydrates within the intestine are fermented by commensal bacteria and transformed into SCFAs, such as butyrate, propionate and acetate, serving as an important energy resource for the host with a prominent impact on anti-inflammatory responses and cell proliferation [28–30]. In addition to carbohydrates, proteins and amino acids from both exogenous and endogenous sources can be fermented by the gut microbiota to generate a number of metabolites, including branched-chain amino acids [31], as well as potentially deleterious products in the gut, including ammonia, amines, phenols and indoles, which are absorbed and detoxified by the intestine and the liver [32]. Vitamins, not synthesized by human cells directly, are acquired from food or metabolites generated by microbiota. For example, commensal bacteria in the gut produce vitamin K and most B vitamins, some of which are acquired by and benefit the host directly [14,33].

3. Host-microbiota interactions that cause inflammation and CRC

Homeostasis between the host immune system and the gut microbiota is essential for maintaining gut health, but this dynamic equilibrium is particularly susceptible under certain circumstances, and can lead to the development of inflammation and CAC. Multiple underlying mechanisms by which gut homeostasis is undermined have been proposed, including pathogenic bacterial infection, dysbiosis, and a defective host immune system (Fig. 2), which can increase the exposure of bacterial antigens or toxins to epithelial and immune cells. Subsequently, the host increases immune responses against commensal bacteria and/or pathogens, resulting in inflammation and tumor initiation [34].