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The Impact of Dietary Fiber on Gut Microbiota and Its Association with Colorectal Cancer Risk

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1. Abstract

The gut microbiota, a complex micro-ecosystem within the human body, plays a pivotal role in physiological processes such as food digestion, nutrient absorption, and immune regulation. It maintains a symbiotic relationship with the host, offering health benefits including cancer prevention and treatment, while also being implicated in diseases such as obesity, diabetes, atherosclerosis, inflammatory bowel disease (IBD), and cancer. Colorectal cancer (CRC), a prevalent global malignancy, ranks second in incidence and fourth in mortality in China. According to the National Cancer Center, China reported approximately 517,100 new CRC cases and 240,000 deaths in 2022 [1]. Research indicates that the composition, diversity, and abundance of gut microbiota are influenced by host lifestyle and dietary habits. CRC is closely linked to localized intestinal inflammation, a critical factor in cancer development. Dietary fiber, fermented by specific gut microbiota, produces short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate. These SCFAs exhibit anti-tumor and anti-inflammatory properties, protect the intestinal mucosa, and promote the growth of beneficial gut microbiota, thereby aiding in the prevention of chronic intestinal inflammatory diseases. Notably, the anti-cancer effects of butyrate have been validated in both cancer cell cultures and animal models.

2. Effect of Dietary Fiber on Intestinal Microbiota

Dietary fiber (DF) has multiple definitions internationally. According to the latest definition by the Codex Alimentarius Commission in June 2009, dietary fiber is defined as carbohydrates consisting of 10 or more monomeric units (the inclusion of carbohydrates with 3 to 9 monomeric units is determined by relevant regulatory authorities in each country), which cannot be hydrolyzed by enzymes in the human small intestine. It includes the following three categories: (1) naturally occurring edible carbohydrates in food; (2) carbohydrates hydrolyzed by enzymes in the human small intestine; and (3) synthetic carbohydrate polymers with potential health benefits [2]. Research has shown that dietary fiber can participate in human metabolism, preventing, treating, and alleviating various chronic diseases, including obesity, diabetes, cancer, intestinal disorders, and other non-communicable diseases such as heavy metal poisoning, cardiovascular diseases, gynecological disorders, and allergic rhinitis [2, 3].The microbiota refers to the community of microorganisms colonizing a specific location, including bacteria, fungi, archaea, viruses, and protozoa, which collectively form the complex ecosystem in the gut, known as the gut microbiota. These microorganisms create diverse microbial habitats in the small intestine, cecum, and large intestine (colon) based on pH, oxygen, and antimicrobial peptide distribution [4]. They participate in the metabolism of carbohydrates, lipids, and proteins, producing energy sources such as short-chain fatty acids (SCFAs), influencing host lipid and protein metabolism, and synthesizing vitamins crucial for host health, such as vitamin K and B vitamins. Additionally, the gut microbiota is involved in the metabolism of bile acids and polyphenols, which play significant roles in host metabolism and immune regulation. Furthermore, the gut microbiota regulates and protects the host immune system by maintaining the integrity of the intestinal mucosal barrier, promoting the development and function of immune cells, and modulating inflammatory responses [5]. Antigens derived from gut microbes can trigger various subsets of regulatory T cells, such as intraepithelial lymphocytes (IELs) residing at the basolateral surface of the intestinal epithelium, which help maintain intestinal tissue homeostasis and suppress inflammation [6]. Dietary intake significantly influences the gut environment, largely mediated by the metabolic activities of the gut microbiota on dietary compounds [7]. A fiber-rich diet or the infusion of SCFAs is closely associated with increased levels of gut hormones such as GIP and CCK. In clinical trials, patients with type 2 diabetes mellitus (T2DM) were randomly assigned to a control group receiving standard care or an experimental group on a high-fiber diet. Both groups were treated with acarbose. The results showed that dietary fiber increased the relative abundance of beneficial bacteria and butyrate fermentation, leading to better glycemic control, weight loss, and improved lipid profiles [8, 9]. The gut microbiota degrades dietary fiber to produce organic acids, gases, and a significant amount of SCFAs [10]. When dietary fiber is abundant, the gut microbiota preferentially ferments plant cell wall polysaccharides, resistant starch, mucins, and other indigestible carbohydrates, generating SCFAs in the human intestine [11]. Moreover, when the supply of fermentable fiber is reduced, some bacterial species shift to using amino acids and proteins as alternative energy sources for fermentation, a process that also contributes to the production of SCFAs and branched-chain fatty acids. The supply of dietary fiber is crucial for SCFA production, highlighting the importance of maintaining adequate dietary fiber intake to promote gut microbiota balance and diversity, which benefits overall health [12].As metabolites of the gut microbiome, SCFAs play a vital role in maintaining host health. Microbial SCFAs regulate physiological processes such as cell proliferation, differentiation, and metabolism by influencing bacterial gene expression [13]. For instance, acetate induces gene expression in Salmonella through the formation of acetyl phosphate, a response to bacterial invasion [14]. SCFAs not only serve as energy sources supporting colonocyte growth but also act as gene expression regulators and anti-inflammatory agents, modulating various cellular mechanisms and promoting gut health [15]. Additionally, SCFAs, along with the gut microbiota, influence intestinal transport functions and maintain gut homeostasis [16]. Acetate, propionate, and butyrate are the primary products of gut bacterial fermentation, and their production pathways are diverse and complex [11]. Acetate is mainly generated through acetyl-CoA

from pyruvate or via the Wood-Ljungdahl pathway (including the eastern and western routes) [17]. The primary pathway for propionate production is the succinate pathway, which converts hexoses and pentoses into succinate and then into propionate. Other pathways include the acrylate pathway and the propanediol pathway, which utilize lactate and deoxyhexoses (such as fucose and rhamnose), respectively, to produce propionate [18]. Butyrate is generated through the glycolysis of acetate, lactate, amino acids, and carbohydrates via the butyryl-CoA:CoA transferase or phosphotransferase and butyrate kinase pathways. It can also be formed by the condensation of two acetyl-CoA molecules into acetyl-CoA, which is then converted into butyrate. Additionally, proteins can produce butyrate through the lysine pathway [19]. These pathways demonstrate the ability of gut bacteria to generate SCFAs through multiple metabolic routes, adapting to different nutritional environments to maintain host health.

3. Dietary Fiber and Colon Cancer Risk

The development of colorectal cancer is influenced by a combination of dietary, non-dietary, and genetic factors. Dietary factors, in particular, play a significant role in its etiology. Studies have identified red meat, processed meat, excessive alcohol consumption, body fat, and abdominal fat as risk factors for colorectal cancer, while dietary fiber, garlic, milk, and calcium contribute to its prevention. Additionally, non-starchy vegetables, fruits, folate, vitamin D, and selenium may have protective effects, whereas iron, cheese, animal fats, and sugar may increase the risk of the disease [20].Histone deacetylases (HDACs) are enzymes that remove acetyl groups from histones, leading to tighter DNA wrapping. Among short-chain fatty acids (SCFAs), butyrate is the most effective inhibitor of HDAC activity, both in vitro and in vivo. By inhibiting transcription factors Sp1/Sp3, butyrate recruits HDACs to promoter regions, resulting in histone hyperacetylation. Many of butyrate's anticancer properties, including the suppression of cell proliferation, induction of cell differentiation or apoptosis, and regulation of gene expression, are mediated through HDAC inhibition. Butyrate also exerts anti-inflammatory effects by modulating HDACs, downregulating the NF-κB signaling pathway, and activating PPAR-γ, a nuclear hormone receptor with anti-inflammatory properties. This regulation impacts genes related to inflammation and immunity, such as the inhibition of pro-inflammatory cytokines (e.g., IFN-γ, TNF-α, IL-1β, IL-6, and IL-8) and the upregulation of IL-10 and TGF-β[21-25]. Butyrate plays a critical role in M2 macrophages, which are involved in inflammation resolution, wound healing, and tissue repair through the production of arginase 1 (Arg1). It alleviates symptoms of DSS-induced colitis in mice by reducing disease activity index (DAI) and serum levels of pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β). Butyrate also promotes Arg1 protein expression in colon tissue, facilitating M2 macrophage polarization through the inhibition of HDAC1 gene expression and increased acetylation of histone H3 at lysine 9, enhancing STAT6 phosphorylation. These findings underscore the importance of butyrate in regulating intestinal inflammation and promoting tissue repair. Additionally, butyrate maintains epithelial barrier function by inhibiting pro-inflammatory mediator secretion in macrophages and promotes the expression of amphiregulin (AREG), a key factor in cell proliferation and tissue repair, mediated by GPR43 and Blimp-1 proteins in dendritic cells (DCs) [26-28]. Cytokine release and leukocyte recruitment are critical components of the inflammatory response, and SCFAs, particularly butyrate, play a vital role in regulating these processes. Butyrate inhibits the activation and expansion of antigen-specific cytotoxic CD8+ T cells by affecting antigen-presenting DCs and promotes the degradation of the cell metabolism regulator c-Myc, reducing Th17 cell differentiation and alleviating colitis [29,30]. It also enhances IL-10 production by regulatory T cells (Tregs), preventing excessive T-cell responses and maintaining intestinal homeostasis [31]. Butyrate-stimulated TGF-β production promotes epithelial recovery and improves inflammatory processes, while its activation of the aryl hydrocarbon receptor (AhR) enhances epithelial barrier function and regulates immune cells. AhR knockout mice are susceptible to DSS-induced colitis, and IBD patients exhibit downregulated AhR activation [32, 33]. Leukocyte recruitment is a critical aspect of the inflammatory response, and SCFAs, particularly butyrate, regulate this process by inhibiting chemokine production, reducing leukocyte surface adhesion molecule expression, promoting macrophage polarization, and regulating cell adhesion molecules and chemokines. Dietary fiber, as a source of SCFAs, influences host physiology by producing metabolites that reduce inflammatory responses in colon cells. Thus, SCFAs and their dietary sources are essential for regulating inflammatory responses and maintaining intestinal health.

4. Dietary Fiber and Gut Health

Dietary fiber is fermented by gut microbiota into SCFAs, which play a crucial role in preventing colon cancer. However, dietary fiber itself also has independent effects on colon health. Prebiotic polysaccharides improve intestinal nutrition by increasing biomass and stool weight, regulating bowel movement frequency, reducing constipation, and enhancing the health of the intestinal mucosa [34,35]. Both dietary fiber and SCFAs stimulate the production and secretion of mucus, while dietary fiber mechanically increases mucus production in the intestinal epithelium [36]. Dietary fiber binds to secondary bile acids (BAs) in the intestinal lumen, preventing the accumulation of toxic BAs, or influences host physiology by promoting the breakdown of BAs, thereby triggering the G protein-coupled receptor 5 (TGR5) and promoting the production of glucagon-like peptide-1 (GLP-1). According to the results of two published human studies, changes in dietary fiber and fat content significantly affect gut microbiota within 2-3 days [37, 38]. After switching African Americans to a high-fiber, low-fat diet for two weeks, colonic mucosal inflammation was significantly reduced, and secondary bile acid synthesis was inhibited. Increasing the intake of high-fiber diets or fiber supplements may lower blood pressure, improve blood sugar, aid in weight loss, and reduce the risk of colorectal cancer [39].Despite the positive effects of dietary fiber in maintaining the intestinal microenvironment and preventing or alleviating colon-related inflammation and cancer, there are practical limitations. Due to differences in dietary habits among populations in different regions, the impact of dietary fiber on colon cancer varies individually. For example, one study found that high intake of fruits and berries was associated with a reduced risk of colon cancer in women, but no significant association was observed with the intake of high-fiber grain products. This may be because the participants' dietary habits had already reached a potential threshold level for preventing colorectal cancer [40]. Additionally, differences in gut microbiota related to dietary habits also influence the effects of dietary fiber on colon cancer. One study found that by comparing the gut bacteria of rural (Burkina Faso) and urban (Italy) children, changes in gut microbiota were related to lifestyle (dietary habits). The gut bacteria of urban children were more suited to metabolizing meat proteins, fats, and sugary foods, while the gut bacteria of rural children were better adapted to digesting fibers and carbohydrates from fermented vegetables [41]. Butyrate regulates the proliferation, apoptosis, and angiogenesis of colon cancer cells through multiple signaling pathways, while dietary fiber not only exerts anti-cancer effects by fermenting into SCFAs but also has significant impacts on gut health. However, individual dietary habits and differences in gut microbiota may limit the effectiveness of dietary fiber. Therefore, in the practice of preventing colon cancer, it is necessary to comprehensively consider the type, intake, and individual differences of dietary fiber.

5. Summary and Outlook

Changes in the intestinal environment are largely linked to the metabolic activity of the intestinal flora in response to dietary compounds, and the intake of dietary fiber can increase the relative abundance of beneficial intestinal bacteria, particularly those capable of producing butyrate. Butyrate can respond to intestinal inflammation and reduce the inflammatory response through complex regulatory mechanisms that modulate cytokines and leukocyte recruitment, playing an important role in the prevention and treatment of colon cancer. However, the molecular mechanisms of butyrate's effects on cancer cells are not entirely clear, which may be related to the limitations of the raw material used to produce butyrate—dietary fiber. Further research is needed to substantiate these findings.

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