Inflammation-Modulating Effect of Butyrate in the Prevention of Colon Cancer by Dietary Fiber

Abstract

The intestinal microbiota plays key roles in human health, and adverse dysbiosis shifts of the microbiota have been associated with chronic diseases, including large bowel cancer. High-fiber diets may reduce the risk for large bowel cancer in association with gut microbiota modulation and butyrate production. Butyrate can inhibit histone deacetylases and associated signaling pathways in cultured cancer cells, promoting cancer cell apoptosis. However, butyrate has prevented colon cancer through the regulation of immune homeostasis rather than histone deacetylases inhibition. It could be important to further examine the pathways of how butyrate encourages immune system changes. We posited that butyrate-activated T-regulatory cells block proinflammatory T cells and thus reduce proinflammatory cytokine production; these cytokines increase cell proliferation and cell survival, the 2 most important cancer cell characteristics. Butyrate can exert anticancer effects through inhibition of multiple signaling pathways. It is possible that a low concentration of butyrate could modulate the immune system before other pathways to exert an anticancer effect. Increasing the concentration of butyrate in the intestines may produce a synergistic inhibitory signaling pathway response and an anti-inflammatory effect.

Introduction

The total mass of bacteria that have been recently reported to inhabit the human body has been calculated to be approximately 0.2 kg. The cohort of bacteria in the intestines provides beneficial actions that span millennia in evolutionary time by producing nutrients, preventing pathogenic microbe invasion, invoking immune responses, and preventing carcinogenesis. The intestinal microbiota is now known to play an important role in the prevention of colon cancer. An important evolutionary mechanism is to process dietary fiber that increases intestinal butyrate concentration, which plays multiple roles in colon health, including cancer prevention effect (Figure 1). Dietary fiber includes plant cellulose, lignin, and pectin, which are resistant to digestion in the small intestine and which then can undergo bacterial fermentation in the large bowel.

Epidemiologic studies have provided evidence that high-fiber diets are associated with a low incidence of cancer, in contrast to consumption of red meat, which has been reported to increase the risk of cancer. It has also been demonstrated that the key for high-fiber diets to exert anticancer effect is the production of butyrate through the action of the gut microbiota. In the absence of fermentation processes provided by the intestinal cohort of bacteria, a high-fiber diet has no anticarcinogenic effects. The anticancer effect of butyrate has been demonstrated by both in vitro and in vivo studies.

Many explanations have been proposed for the anticancer effect of butyrate, including its roles on immunity, signaling pathways, gene expression, and epigenetic modulations. Most studies investigating the mechanisms of anticancer effect of butyrate have been performed in vitro in cultured cancer cell lines. A recent report not only showed the important role of butyrate in the anticancer effect of dietary fiber in vivo but also elucidated the possible mechanism of action of butyrate. The study demonstrated that
Figure 1 Roles of Butyrate in Colon Health. Butyrate, Produced From Dietary Fiber Through Microbiota-Mediated Fermentation, has Multiple Benefits to Colon, Such as Providing Energy to Colonocytes, Reducing Intestinal Permeability Through Tight Junction, Reducing Mucosal Inflammation, Increasing Apoptosis, Decreasing Proliferation of Cancerous Cells, and Increasing Commensal Microbiota

Inflammation and Colon Cancer

It is now recognized that various types of inflammation can increase cancer incidence, such as colitis, obesity, infection, and autoimmune diseases.\(^{11,12}\) Chronic inflammation has been well demonstrated to be causal in large bowel cancer. Colonocytes are the most rapidly dividing cells in the human body, with colon cell turnover of approximately 3 to 10 billion colonocytes per day.\(^{13}\) Only a few stem cells in the bottom of the aberrant crypt foci can differentiate into a large number of mature colonocytes, at an approximate rate of 1 cell position moving upward per hour, whereas an aberrant crypt foci is renewed in 2 to 8 days.\(^{14}\) Therefore, cell death and survival of colonocytes must be specifically and actively regulated to prevent accumulation of genetic and epigenetic changes. In inflammation, the balance of cell death and proliferation is dysregulated; immune cells produce proinflammatory cytokines, which increase cell proliferation and decrease cell apoptosis of colonocytes, leading to increased cancer risk. The proinflammatory cytokines interleukin-6 (IL-6), IL-17, and IL-23 have been well demonstrated to be involved in the pathogenesis of colon cancer.\(^{15-17}\)

These cytokines can activate multiple signaling pathways to increase cancer incidence. As early as 2004, researchers have found that the multiple functional nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) plays a key role in inflammation-associated colon cancer; studies have also shown that NF-κB is essential in inflammation-associated hepatoma.\(^{11,18}\) Recently multiple signaling pathways have been revealed to be involved in inflammation-associated cancer.\(^{12,19}\)

IL-6 is well known to activate signal transducer and activator of transcription 3 (STAT3) signaling pathway to increase carcinogenesis.\(^{15}\) Activation of STAT3 results in increased cell proliferation and decreased cell apoptosis, which are the most important carcinogenesis characteristics. Moreover, the IL-6/STAT3 pathway can also result in decreased immune responses through inhibition of dendritic cells.\(^{20}\) Several IL-6/STAT3 pathway inhibitors have been approved by US Food and Drug Administration.\(^{15}\) These inhibitors have been tested for use in combination with immune checkpoint inhibitors.\(^{15}\)

IL-17 can promote carcinogenesis through activation of NF-κB and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways after binding to its receptor IL-17 receptor located within colonocytes.\(^{16}\) IL-17 can also increase the production of IL-6 production from cancer cells.\(^{16}\) Thus, anti–IL-17 therapy has been proposed to overcome drug resistance to targeted therapy against vascular endothelial growth factor (VEGF) in colon cancer.\(^{16}\) NF-κB is well known to play a key role in the transformation of inflammation into cancer.\(^{21}\) NF-κB consists of a group of transcription factors (RelA, RelB, c-Rel, NF-κB1/p50, and NF-κB2/p52), which form homo- or heterodimers. NF-κB is activated when its inhibitor, such as IκBα, is degraded under stimulation of various factors, including IL-17.\(^{21}\) The downstream proteins of NF-κB include cytokines, IL-1, IL-8, IL-6, monocyte chemotactic protein (MCP)-1, tumor necrosis factor (TNF)-α; antiapoptotic factors cIAPs, c-FLIP, A20, and Bcl-XL; angiogenesis regulator VEGF and matrix metalloproteinase (MMP)-2 and MMP-9, which promote cancer initiation in nontransformed cells and cancer progression in cancer cells.\(^{21}\)

IL-23 has also been demonstrated to play a key role in colitis-associated colon cancer.\(^{17}\) IL-23 promotes T-cell–mediated colitis through IL-17 and IL-6.\(^{22}\) IL-17 and IL-6 activate multiple signaling pathways for carcinogenesis. One study showed that IL-23 and IL-17 have synergistic effects in promoting inflammation and cancer development.\(^{23}\)

Overall, these proinflammatory cytokines interact with each other to promote multiple signaling pathways to increase cancer risk. Activation of these signaling pathways has been demonstrated to increase cell survival and increase cell proliferation. Because colonocytes are quick-turnover cells, increased survival could lead to quick abnormal accumulation of cell mass and gene mutations.

Inflammation-Modulating Effect of Butyrate

Many studies have been performed to elucidate the molecular mechanisms for the anticancer effect of butyrate. The most appreciated mechanism is that butyrate inhibits histone deacetylases (HDAC) and thus results in inactivation of many oncogenic signaling pathways. However, the finding is only largely supported
by in vitro studies; in vivo studies with butyrate did not show changes in intracellular pathways mediated by HDAC but was reported to affect G protein–coupled receptor 109α (GPR109α). Bishehsari et al.10 used a mouse polyposis model (TS4/4PC mutations) to demonstrate that mice with polyposis possessed decreased butyrate-producing bacteria. Animals whose food was supplemented with dietary fiber increased butyrate-producing bacteria and butyrate, with a concomitant reduction in the number of polyps. Importantly, GPR109α levels in cecum tissues were increased by butyrate while HDAC indicator H3K9ac levels were not.10 GPR109α activation in macrophages and dendritic cells causes these cells to differentiate into Tregs and IL-10–producing T cells.24

Tregs play key roles in the regulation of proinflammatory cells (Figure 2). It has been found that in tumor tissues, Tregs are increased as a counteractive measure to cancer development.25 Experiments with GPR109α-knockout mice showed increased colon inflammation and colon cancer.26 In the study of Bishehsari et al., Tregs were increased, indicating the role that these immune cells play in inhibiting inflammation at the early stages of carcinogenesis.

Perspectives

Because of the central role of butyrate in the prevention of colon cancer, it may be studied extensively to further elucidate the mechanisms by which butyrate is a colon cancer–preventive agent. The effects of butyrate on GPR109α expression may be studied in various types of cells individually. Therefore, the roles of different cells such as macrophages, dendritic cells, and Tregs in butyrate-associated colon cancer prevention are characterized.

The bacterial genera from the intestinal microbiota that produce butyrate could be well identified so that suitable bacterial strains could be selected for use and administration as probiotics. At present several bacteria have been shown to produce butyrate.3 These bacteria are decreased in colon cancer patients. Therefore, it is possible that supplementation with these bacteria may be helpful in the prevention and treatment of colon cancer through increased intestinal butyrate levels.

Probiotics could be produced that facilitate the increase of butyrate concentrations in the intestine. Because dietary fiber is an important source of butyrate, various fibers that produce the highest levels of butyrate could be studied.

Conclusion

Butyrate has been well demonstrated to be effective in the prevention of colon cancer. The present in vivo study by Bishehsari et al.10 has revealed that the associated mechanism is the modulation of immune responses. Butyrate readily acts on cell surface receptors such as GPR109α and thus increases Treg expression, resulting in decreased inflammation. Unlike in cultured cancer cells, butyrate does not cause alterations of HDAC and downstream signaling pathways; in this regard, higher concentrations may be required. Possibilities exist to manipulate the intestinal microbiota and to therefore select dietary fiber to increase production of butyrate in the large bowel for the prevention of colon cancer.

Disclosure

The authors have stated that they have no conflict of interest.

References

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