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Prospects for colorectal cancer prevention targeting intestinal microbiome

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It has been reported that a so-called clean colon procedure, in which all precancerous lesions, colorectal tubular adenomas / colorectal tubulovillous adenomas, are endoscopically resection treatment is extremely useful for preventing colorectal carcinogenesis and death from colorectal cancer [1-4]. The effectiveness of chemopreventive measures to take the antidiabetic drugs metformin and low-dose aspirin has also been reported [5-7]. Recently, there have been reports suggesting the involvement of intestinal microorganisms such as *Fusobacterium nucleatum* (*F. nucleatum*) in colorectal carcinogenesis [8-13], and there is a possibility that a strategy targeting intestinal microorganisms will be taken as future methods for preventing colorectal carcinogenesis. This review describes the prospects for new strategies on colorectal carcinogenesis prevention targeting intestinal microbiome such as *F. nucleatum*.

Currently, there are no clinical research reports on intestinal microbes and prevention of colorectal carcinogenesis in human, but there are reports in animal models. When the antibacterial drug metronidazole was administered to the *F. nucleatum*-infected group and the non-infected group in mouse colorectal cancer model, the tumor size was smaller in the *F. nucleatum*-infected group and the tumor size did not change in the non-infected group. In addition, *F. nucleatum* in colorectal cancer tissue was significantly decreased in the metronidazole-administered group, and the uptake of BrdU, which is one of the cell proliferation markers, into cell was decreased in the metronidazole-administered group, and the cell proliferation was also suppressed [14]. These results suggest that *F. nucleatum* eradication may suppress the growth of colorectal cancer, and it is interesting to see if the same results can be obtained in human.

The next part is a commentary on the preventive effects of probiotics and prebiotics for colorectal carcinogenesis. Probiotics and prebiotics have been collectively called or functional lactic acid bacteria foods or functional foods in recent years. Prebiotics is a concept proposed by Gibson et al. [15,16]. which is an indigestible food ingredient that beneficially affects specific microbes living in the large intestine and improves the intestinal gut flora to a healthy state, and oligosaccharide is a typical example [17]. Furthermore, Functional foods which combine probiotics and prebiotics are called symbiotics.

The following papers are representative reports on preventive mechanisms of colorectal carcinogenesis in probiotics and prebiotics.

The first report is that probiotics bind to the causative agent of carcinogenesis and suppress gene mutations. This is the function of probiotics itself, as below; *Streptococcus cremoris* Z-25, *Lactobacillus acidophilus* IFO 13951 and *Bifidobacterium bifidum* IF014252 bind to Trip-P1 (3-amino-1,4-dymethyl-5H-pyrido[4,3-b]-indole), GR-1 (2-Amino-6-mechyldipyrido-[12-a:3',2'-d]-imidazole), Phe-P-1 (2-amino-5-phyenylpyridine), IQ (2-amino-3-metylimidazo[4,5-f]-quinoline), MeIQ (2-amino-3,4-dimethylimidazo[4,5-f]-quinoline), MeIQx (2-amino-3,8-dimethylimidazo[4],5-f]-quinoxaline) and other heterocyclic amines (HCA). HCA is a carcinogen that is mainly found in charred meat and fish. In addition, probiotics have also been reported to have the effect of inhibiting the carcinogenic precursors into carcinogens [18]. However, the details of binding mechanism to HCA and the details of conversion mechanism carcinogenic precursors into carcinogens have not yet been clarified.

The second reports are the antitumor effect of the intestinal pH lowering effect of the production of short-chain fatty acids. Gut flora, including probiotics, and prebiotics lower the pH in the intestine by producing short-chain fatty acids such as butyric acid, propionic acid, and acetic acid. By reducing the number of intestinal microbes that become pathogens by lowering the intestinal pH, inflammation is suppressed and the homeostasis of the intestinal environment is maintained [19,20]. However, the intestinal environment such as the ascending colon and the transverse colon is under strong acidity, and colorectal cancer is observed even under strong acidity. Therefore, this theory is not convincing.

The third reports are on the suppression of inflammation and carcinogenesis by activating the host immunity of probiotics. This is a report that probiotics indirectly exert antitumor effects by maturing dendritic cells and activating natural killer cells (NK cells) [21]. For example, butyric acid not only lowers the pH of the intestinal lumen, but also nourishes the mucosal tissue of the large intestine and promotes histone acetylation by inhibiting the deacetylation of histone as a DNA-binding protein, at the molecular level. This promotes the expression of Foxp3, promotes the differentiation of regulatory T cells (T reg) from naïve T cells and suppresses inflammation, and induces apoptosis to suppress carcinogenesis [22]. Propionic acid and acetic acid have also been reported to induce apoptosis *in vitro* [23]. On the other hand, it has also been reported that Treg is also involved in carcinogenesis [24-28]. It has been reported that the apoptosis or tumorigenicity-promoting effect of Treg is determined by the amount of butyric acid produced [29,30], but the detail has not been clarified.

The fourth is our reports. Our reports analyze the mechanism of antitumor action of short-chain fatty acids produced by probiotics and prebiotics. We confirmed by analysis of the intestinal microbiome that

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feeding healthy volunteers with probiotics (*Bifidobacterium longum*: BB536) and prebiotics (Oligosaccharides) increased the production of short-chain fatty acids such as butyric acid, which has antitumor effects. Therefore, we added butyric acid, isobutyric acid, and acetic acid adjusted to 11 levels of concentration to human colorectal cancer cells (DLD-1 cells, WirDr cells) and cultured them to examine the proliferative ability of colorectal cancer cells. The results showed that the cell proliferation ability of colon cancer cells was significantly suppressed by the addition of the above-mentioned short-chain fatty acids and butyric acid had the strongest cell proliferation-suppressing ability among the short-chain fatty acids [31]. Then, we investigated the mechanism of antitumor action of short-chain fatty acids in cultured cells by DNA microarray analysis. In the analysis of the mechanism by DNA microarray, the expression of genes involved in the cell proliferation systems such as cell rotations and DNA replications were strongly suppressed [32]. It was new findings that short-chain fatty acids did not affect the expression of cancer-related genes which were previously considered essential for carcinogenesis and strongly suppressed the expression of genes involved in the cell proliferation. Our reports are drawing attention as a new mechanism on colorectal carcinogenesis suppression of probiotics and prebiotics.

Currently, there are still little evidence for the suppressive effects of probiotics and prebiotics on colorectal cancer, and they have not been used in clinical practice is the detail on suppressive mechanisms of probiotics is elucidated in the future, it should more likely to be used in clinical treatments. We look forward to the further developments of research in this field.

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