Advances in the Prevention and Treatment of Colorectal Cancer (CRC) by Lactobacillus

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Abstract. Colorectal cancer (CRC) is one of the leading death-causing cancers in the modern society that is associated with the health of human gastrointestinal tract. It is frequently diagnosed in patients with unhealthy living habits, as well as disturbed gut microbiota. Current treatment of CRC remains to be primary treatments like resection and chemotherapy. According to recent studies, administration of probiotics, especially Lactobacillus strains have been shown to have beneficial effects in treating and preventing the development of CRC. This article discussed the current mechanisms of lactobacillus treating CRC, including 1) increasing immune response, 2) promotion of the health of gut barrier, 3) anti-inflammatory effect, and 4) suppressive effects on cancer cells. As administration of lactobacillus strains is considered a promising tool of treating CRC in vitro and in vivo, more studies need to be done in clinical trials.

1. Introduction
Colorectal cancer (CRC) has become increasingly life-threatening given the fact that it is the third most deadly cancer [1]. The cause of CRC is various, including family history of CRC, heavy dose of alcohol and tobacco, etc. One of the major risk factors is the disturbance of gut microbiota. Gut microbiota, or intestinal flora, contains a huge number of bacteria and is considered crucial in communicating with human immune system and participating in a wide range variety of metabolic processes. Disruptions to gut microbiota may cause systematic downstream consequences that influence the health condition in multiple aspects. In the research of Fan X et al, it is shown that gut microbiota dysbiosis disequilibrate intestinal microbial homeostasis and facilitate the progression and development of CRC through many different pathways, such as triggering inflammatory responses, inducing DNA damage, as well as promoting cell proliferation [2]. However, probiotics, known as living microorganism, which provides extra benefits to the host other than its basic nutritional facts after digestion [3], that have potential benefits to human health, may also help maintaining the well-being of gut microbiota. Evidence have shown that probiotic bacteria may play a significant role in helping the gut microbiota regain its homeostasis by immunomodulation and anti-tumor properties as bacterial strains are responsible for detection and degradation of potential cancer-causing factors, cells, and threats to the immune system of the host [4]. Hence, probiotics are considered a promising prevention tool of CRC and possibly a treatment.

In this paper, it is discussed about the current treatment of CRC and how probiotics, especially Lactobacillus — one of the two major probiotic genus that are considered beneficial, could be a possible treatment of CRC. This paper mainly focuses on the mechanisms of prevention of CRC by Lactobacillus, including increase of immune response, promotion of health of gut barrier, anti-
inflammatory effect, and anti-cancer effects, in order to analyze how the preventive effect of Lactobacillus would re-balance the gut microbiota homeostasis and prevent the development of CRC. By comparing and contrasting the different mechanisms, we would be able to identify the advantages, as well as limitations, of each mechanism and possibly apply these advantages into the future medical development of CRC treatment.

2. Colorectal Cancer (CRC) and Lactobacillus
After CRC has become one of the leading cancers that cause death, the researches on its treatment and prevention has been deeply studied through various dimensions, including changing diet patterns, chemotherapy, etc. Most of the current treatment helps to alleviate the symptoms of CRC, but with limitations, while the use of the probiotics, especially Lactobacillus, as a promising treatment of CRC, has become more reliable.

2.1. Current treatment of CRC
CRC is the third common cancer present in both male and female. It is also the third leading cause of cancer-related death in the United States. The exact cause of CRC remains unclear while it might have a close relationship with diet patterns. In recent decades, a wide range of different diet patterns had become popular, including south beach diet, carnivores diet, and ketogenic diet. Many of them have a seem-reasonable logic for weight loss or other purposes. However, such diet-pattern change — for instance, consumption of high-fat diet — disregards its influences on the gut microbiota, as well as epigenetic and hence, may become a potential cause of CRC [5]. The high number of CRC cases globally might also be explained to some extent by a shift towards meat-based diet for recent decades [6]. While high intakes of fats and meat would induce the development of CRC and carcinogens, the consumption of other food may have an inverse effect. Evidence has shown that high intakes of vegetables and fruits, high fiber diet, folate-rich diet, high vitamins, shows an inverse relationship with the risk of developing CRC [7]. Although the actual intake may be slightly different from person to person, this result shows a possible preventive treatment based on changing dietary patterns.

While changing diet patterns may be preventive in the early stage, the main treatment skills of CRC remains to be surgery, which include laparoscopic surgery, resection, radiotherapy, as well as chemotherapies [8]. Like other therapies for cancers, surgical treatment exhibits a limited impact on the cure rates and overall survival after the surgery. The standard treatment is chemotherapy for most primary-tumor symptoms patients. The systemic chemotherapy combined with a complete resection may maximize the possibility of the recovery rate [9]. However, unfortunately, the majority cases of metastatic CRC are not curable despite current technology advances in medical treatment, making the primary goal for CRC patient to be life-extending and improving quality of life.

2.2. Probiotics-related treatments
While medical surgical techniques continue to advance, probiotics provide a reasonable potential alternative treatment for CRC patients. Bifidobacterium species and Lactobacillus species have shown anti-cancer effects in colon cancer cells by reducing tumor cell growth — anti-proliferation effect and inducing apoptosis in these cells [10]. They have also demonstrated a protective effect on the gut mucosal barrier and immunomodulatory effect [11]. Many species have multi-target beneficial effect on the gut microbiota and hence prevent lesions from developing into CRC. Although many current CRC cases are still treated by surgical procedures, since they might have a relatively quicker medical response, the developments of multiple probiotics are becoming a more reliable and effective tool of treatment in the near future. This article will mainly focus on revealing the preventive mechanisms of one of the major probiotics — Lactobacillus, on CRC.
3. Mechanisms of Preventions of Colorectal Cancer by Lactobacillus

3.1. Increasing immune responses
It was reported that the induction of Lactobacillus casei would activate the mucosal immune system, which helps to protect against pathogens and maintain mucosal homeostasis. The data have shown that the presence of Lactobacillus would induce an increase number of positive cells for CD-206 (mannose receptor), which plays a crucial role in the homeostasis system for the clearance of endogenous molecules [12]. This receptor would have a downstream effect such as facilitating the uptake of mannosylated antigens as presentation for T cells and activating the macrophages. This effect would lead to a up-regulation of the adaptive immune system of the gut, which will prevent the development of CRC.

Another Lactobacillus fermentum UCO-979C was also discovered to have beneficial effects by differentially modulating the immune response of intestinal epithelial cells triggered by TLR4 activation. It was also shown that in mice sample trials, the Lactobacillus fermentum UCP-979C could be one of the potential candidate strains of developing food that can differentially modulate immune responses against pathogens in the gastrointestinal tract. For example, Lactobacillus UCO-979C was able to enhance the number of mature B B220+CD24low cells and increases intestinal IgA content [13].

3.2. Promotion of the health of gut barrier
The gut barrier prevents the passage of harmful and toxic substances from entering the body. However, due to various dietary habits and life-style like drinking and smoking, the gut barrier could be negatively impacted to different levels. Such disruption of gut barrier may further induce gastrointestinal diseases, including CRC. Lactobacillus plantarum could provide beneficial health effects by promoting the modulation of gut microbiota that reside in the intestinal epithelium [14]. Data have shown that the lactobacillus plantarum treated group demonstrated an increase in the host defense peptides pBD2 and PG1-5, as well as a decreased concentration of epithelial inflammation-inducing cells and hence reinforcing the defense function of gut barrier. Moreover, other researches have revealed that the mixture of Lactobacillus species could heal the damage and dysbiosis caused by antibiotic intake [15]. Results have shown the four Lactobacillus species combined (JUP-Y4) help maintain the intestinal health by promote the abundance of potentially beneficial bacteria and increasing the expression of tight-junction proteins in the ileum and colon of the treated sample. As gut barrier plays a crucial role in preventing gastrointestinal diseases, the treatment of Lactobacillus provides an ideal way to increase the health of gut epithelial cells and enhance the endurance of dysbiosis-inducing substances through multiple mechanisms.

3.3. Anti-inflammatory effects
Many cases of CRC are caused by chronic inflammation in the gastrointestinal tract. It has reported that, the Lactobacillus delbrueckii showed anti-inflammatory effects by alternating the bacterial surface proteins and NF-κB activation pathway in vitro and therefore, significantly reduced the likelihood of development of colitis in the mouse intestinal tract [16]. Hence, the inhibition in inflammations would be a reliable way of preventing the CRC by eliminating its causing factors.

In addition, another strain, Lactobacillus NCK2025, showed a similar effect that reduces localized inflammation in the gastrointestinal tract and successfully treated colonic polyposis, which was known as a hereditary form of CRC and colorectal cancer [17]. Lactobacillus NCK2025 also demonstrated the anti-inflammatory effect to decrease cancer progression, as well as to alter gene expression of specific protein, SlpA, that may up-regulate the production of pro-inflammatory cytokines when it is absent [18]. By increasing the production of SlpA, the upregulation of pro-inflammatory cytokines would be suppressed and thus produce an anti-inflammatory effect on the cell surface. Such ability described a strong correlation between the treatment of Lactobacillus and anti-inflammatory effects in
the CRC samples, indicating a potential preventive way of CRC by the anti-inflammatory effects of lactobacillus.

Moreover, the combination of lactobacillus with another major probiotic genus — Bifidobacterium, showed an even stronger anti-inflammatory effect than individual strains in HT-29 cells by alternating the TLR2 expression and downstream molecular cascade effects that increase the anti-inflammatory activities in intestinal epithelial cells [19]. This application further demonstrated the feasibility of treatment and prevention of CRC by Lactobacillus as well as other probiotics.

3.4. Suppressive effect on cancer cells.

Besides the potential preventive ways that lactobacillus may act on the developing CRC, Lactobacillus strains also demonstrated a suppressive effect on cancer cells. It is shown by experiment on both murine (CT26) and human (HT29) cells that Lactobacillus casei have raised a statistically significant concentration- and time-dependent anti-proliferative effects, indicating its inhibitive effects on cancer cell developments. In mice models, an oral administration of L. casei for 13 days could significantly reduce and inhibit the growth of colon carcinoma cells. Besides, Lactobacillus casei could also induce apoptosis in carcinoma cells by up-regulating TNF-related apoptosis-inducing ligand TRAIL, as well as down-regulating Survivin [20]. Such suppressive effects on cancer cells showed us that Lactobacillus may have more profound benefits or applications than primary prevention therapies.

Lactobacillus GG (LGG) also demonstrated an anti-cancer effect by reducing tumor incidence and inducing apoptosis of cancer cells. LGG reduces the expression beta-catenin, which is a protein responsible for cell development, and anti-apoptotic proteins, and meanwhile, increases the expression of pro-apoptotic proteins like Bax, casp3, etc. These downstream effects of LGG indicate a protection effect against CRC carcinogens and a suppressive effect on the tumor cells by inducing apoptosis [21].

4. Discussion

Lactobacillus strains have different beneficial effects on preventing the development of CRC through various pathways, including increasing immune responses, promotion of gut barrier health, anti-inflammatory effects and suppressive effects on cancer cells. However, as the lactobacillus strains mentioned in the article, the experimental trials of Lactobacillus administration are only limited to applying to animal models. There are very limited studies and experiments which have shown a similar or promising effect in human trials. Future studies should focus on how the Lactobacillus strains would prevent the development of CRC in humans, as well as the responses of oral administration of Lactobacillus strains since human digestive tract may affect the effectiveness, or functions of Lactobacillus to alter the outcome of treatment.

Moreover, there should be more research to identify the clear characteristics of each probiotic strain. Based on this, it is more likely to determine the function of the combination of two or more probiotic strains. As Lactobacillus is a promising tool of treating CRC, other probiotics may serve similar functions as Lactobacillus strains, or support and facilitate the functions of Lactobacillus alone and hence produce a more desirable response in human.

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