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REVIEW

Emerging roles of lactic acid bacteria in protection against colorectal cancer

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Abstract

Colorectal cancer (CRC) is the third leading cause of cancer deaths worldwide and the fourth most common cancer diagnosed among men and women in the United States. Considering the risk factors of CRC, dietary therapy has become one of the most effective approaches in reducing CRC morbidity and mortality. The use of probiotics is increasing in popularity for both the prevention and treatment of a variety of diseases. As the most common types of microbes used as probiotics, lactic acid bacteria (LAB) are comprised of an ecologically diverse group of microorganisms united by formation of lactic acid as the primary metabolite of sugar metabolism. LAB have been successfully used in managing diarrhea, food allergies, and inflammatory bowel disease. LAB also demonstrated a host of properties in preventing colorectal cancer development by inhibiting initiation or progression through multiple pathways. In this review, we discuss recent insights into cellular and molecular mechanisms of LAB in CRC prevention including apoptosis, antioxidant DNA damages, immune responses, and epigenetics. The emerging experimental findings from clinical trials as well as the proposed mechanisms of gut microbiota in carcinogenesis will also be briefly discussed.

Key words: Gut bacteria; Gastrointestinal; Carcinogenesis; Probiotics; Microbiota

Core tip: The gastrointestinal tract inhabits trillions of bacteria that interact with the host at multiple levels to maintain its normal functions. Disruptions in this complex cross-talk ecosystem result in physiological changes associated with colorectal tumorigenesis, including cell proliferation, immune responses and apoptosis. This review summarizes the role of lactic acid bacteria as anti-tumorigenic probiotics and suggests the possibility of altering gut microbiota to prevent or halt development of colorectal cancer.

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INTRODUCTION

Colorectal cancer (CRC) is one of the major health challenges, representing the second cause of cancer deaths and the fourth most common cancer diagnosed among

Table 1 List of lactic acid bacterial strains and their functions

Prevention	LAB strains	Functions
Apoptosis	*Lactobacillus acidophilus*	Anti-cancer cell growth and differentiation
		Direct induction of Beclin-1 and GRP78
	L. reuteri	Proliferation (Cox-2, cyclin D1) and cell survival (Bcl-2, Bcl-xL)
		Enhances MAPK activities including c-Jun N-terminal kinase and p38 MAPK
	L. acidophilus and *L. rhamnosus*	Induce Beclin-1 and GRP78, as well as indirectly through the induction of Bcl-2 and Bak
	L. acidophilus and *L. casei*	5-fluorouracil apoptosis induction
Antioxidant	*Bifidobacterium longum* and *L. acidophilus*	Antioxidative activity, inhibiting linoleic acid peroxidation
DNA damage	*Streptococcus thermophilus*	Releasing ROS protective factors
Immune response improvement	*L. acidophilus*	Stimulates DCs to produce inflammatory cytokines IL-12 and regulatory IL-10
	LTA-deficient *L. acidophilus*	Induces IL-10 in DCs, down-regulates IL-12 levels
		Increases densities of effector $Foxp3^{+}ROR\gamma t^{-}$ Tregs
	L. acidophilus, L. casei and *B. longum*	Enhance the total numbers of T cells, NK cells, MHC class II+ cells, and CD4-CD8+ T cells
	L. casei Shirota (LcS)	Induces cytokines, such as IFN-γ, interleukin-β (IL-1β) and TNF-α
	B. adolescentis	Increases the production of TNF-α
Epigenetics	LTA-deficient *L. acidophilus*	Enhances the expression of tumor suppressor genes
New anticancer function	*Pediococcus pentosaceus* FP3	Adhere to colon cancer cells and trigger bioproduction of SCFA
	L. salivarius FP25	
	L. salivarius FP35	
	Enterococcus faecium FP51	

LAB: Lactic acid bacteria; LTA: Lipoteichoic acid; SCFA: Short-chain fatty acid; DC: Dendritic cell; NK: Natural killer; IL: Interleukin; TNF: Tumor necrosis factor.

men and women in the United States[1,2]. Like other types of cancers, the resistance to programmed cell death and uncontrolled proliferation of the cells are main features of CRC influencing therapeutic efficacy. Although consequential progress in the treatment of cancers has been made during the last few decades, there are still many persistent issues chief among them the resistance to chemotherapy which requires better clinical resolution[3]. Recently, it has become increasingly evident that the large and complex bacterial population hosted by the large intestine and known as "gut microbiota" plays an critical role in colorectal carcinogenesis[4,5]. One group of them is probiotics which are "live microorganisms which, when administered in adequate amounts, confer a health benefit to the host" (WHO[6]). In fact, it is not the general probiotic bacteria that have this biotherapeutic action but those who have a particular anticancer activity well beyond the activity of the usual probiotic bacteria[7]. The most common group of this class of probiotics is lactic acid bacteria (LAB). Accumulating recent evidence shows that LAB inhibit initiation or progression of carcinogenesis through various pathways, thus paving the way for potential therapeutic methods for colorectal cancer (Table 1). In this review, we will discuss emerging findings from both experimental and clinical studies describing the latest developments of LAB's role in CRC prevention and their potential mechanisms of action.

AN OVERVIEW OF LAB IN DISEASES

As the most common types of microbes used as probiotics, LAB are comprised of an ecologically diverse group of microorganisms united by formation of lactic acid as the primary metabolite of sugar metabolism, including *Lactobacillus*, *Streptococcus*, *Enterococcus*, *Lactococcus*, *Bifidobacterium* and *Leuconostoc*[8]. Their beneficial effects were initially revealed by E. Metchnikoff (1845-1919), a Russian scientist who proposed that extended longevity of the people of Balkan could be attributed to their practice of ingesting fermented milk products[9]. Recent studies showed that LAB could be successfully used to manage diarrhea[10,11], food allergies[12], and inflammatory bowel disease (IBD)[13-15]. The potential role of LAB has been extensively reviewed elsewhere[8,16], and their beneficial effects include reinforcement of the natural defense mechanisms and protection against gastrointestinal disorders[17]. Several publications have indicated that LAB play an important role in prevention of CRC[16,18]. Although there is no general consensus on the role of LAB in CRC treatment, it is generally agreed that specific LAB strains can beneficially activate anticancer mechanisms, thereby regulating the host's immune response[3,18].

APOPTOSIS INDUCTION BY LAB

Apoptosis is a form of genetically programmed cell death, playing a key role in the regulation of cell numbers (Figure 1)[19,20]. An important pathogenetic event in many types of cancers is the reduced ability to trigger apoptosis associated with alteration of control processes of cell proliferation[21]. The regulation of cell survival and death at molecular level on the apoptotic process can have a huge chemopreventive and therapeutic potential[22]. Several studies showed that LAB can play a role in the regulation of cell apoptosis *via* intrinsic and extrinsic pathways which are potentially critical mechanisms in the prevention of CRC. Chen *et al*[23] analyzed the effect of oral administration of *Lactobacillus acidophilus* (*L. acidophilus*) on colorectal cancer in mice. Their results indicated that *L. acidophilus* reduced the severity of colorectal car-

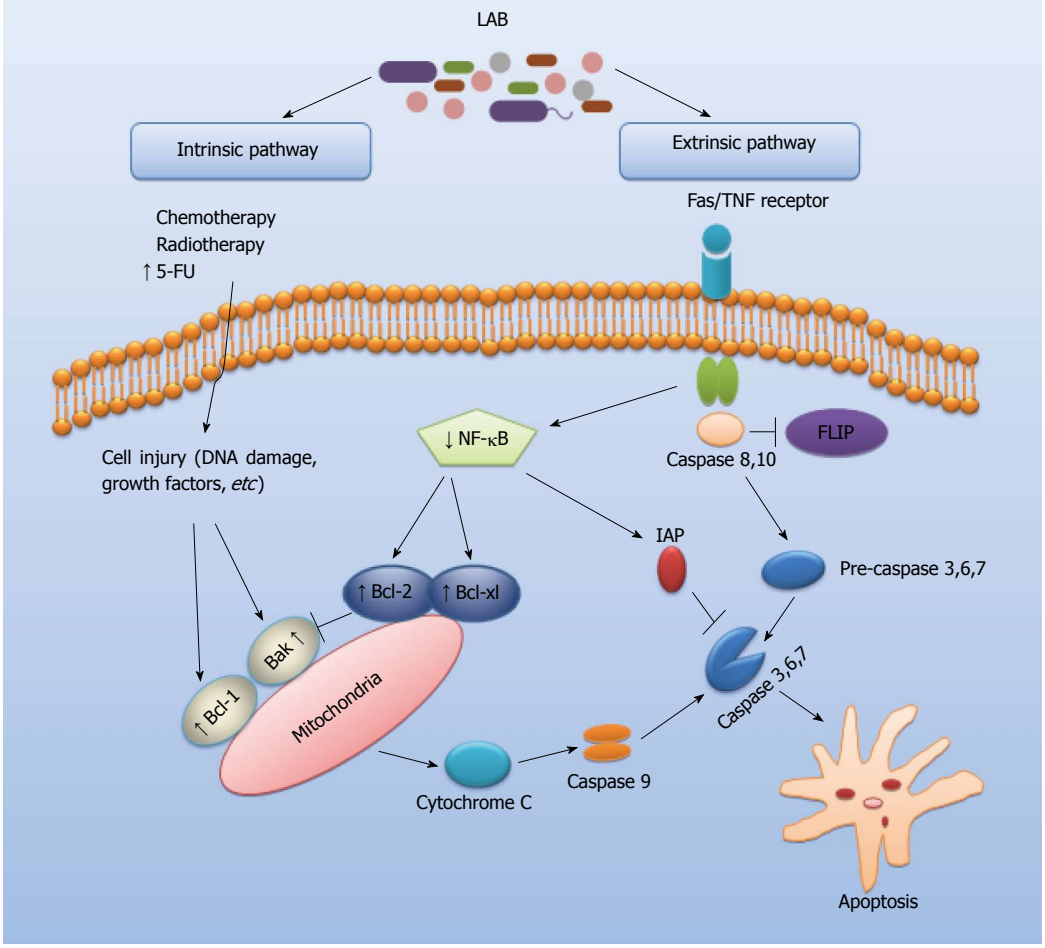

Figure 1 Potential mechanisms of action of lactic acid bacteria *via* extrinsic and intrinsic pathways of apoptosis[19,20]. The apoptosis signaling pathways can be activated by lactic acid bacteria (LAB) through the extrinsic and intrinsic pathways. The extrinsic pathway engages Fas/tumor necrosis factor receptors or other factors to induce caspase related pathway. The intrinsic pathway requires mitochondrial localization and activation of Bax and Bak that can be prevented by anti-apoptotic Bcl-2 family proteins or pharmacologic inhibitors. LAB enhanced the apoptosis induction capacity of 5-fluorouracil (5-FU) and induced the activation of autophagic cell death promoted directly by the induction of Beclin-1 and GRP78, as well as indirectly through the induction of Bcl-2 and Bak. LAB may act to prevent cancer *via* downregulating nuclear factor-kappaB (NF-κB)-dependent gene products which regulate cell proliferation (Cox-2, cyclin D1) and survival (Bcl-2, Bcl-xL).

cinogenesis and enhanced apoptosis in treated mice. It has been shown that *Lactobacillus reuteri* (*L. reuteri*) may prevent colorectal cancer *via* downregulating nuclear factor-kappaB (NF-κB)-dependent gene products which regulate cell proliferation (Cox-2, cyclin D1) and survival (Bcl-2, Bcl-xL)[24]. Furthermore, *L. reuteri* suppressed tumor necrosis factors (TNF)-induced NF-κB activation including NF-κB-dependent reporter gene expression in a dose- and time-dependent manner to slow down cancer cell growth. Such activities of *L. reuteri* might be involved in the extrinsic pathway of apoptosis by which LAB act to protect against CRC (Figure 1). Other studies reported that exopolysaccharides of *L. acidophilus* and *L. rhamnosus* were antitumourigenic against HT-29 colon cancer cells and that this activity was due to the activation of autophagic cell death promoted directly by the induction of Beclin-1 and GRP78, as well as indirectly through the induction of Bcl-2 and Bak[25]. Moreover, the combination of *L. acidophilus* and *L. casei* enhanced the apoptosis-induction capacity of 5-fluorouracil in colorectal carcinoma cell line LS513, suggesting that these probiotics may be used as adjuvants in anticancer chemotherapy[26]. Therefore, an improved understanding of probiotics-mediated effects on apoptosis signaling pathways is critical for development of future LAB-based CRC treatments.

ANTIOXIDANT ACTIVITIES OF LAB

The metabolic antioxidant activities of LAB may be assigned to reactive oxygen species (ROS) scavenging, enzyme inhibition, and reduction activity or inhibition of ascorbate autoxidation in the intestine by neutralizing free radicals[27]. It is assumed that ROS play a key role in IBD and CRC. Several *in vitro* studies showed that LAB strains possess antioxidant properties and inactivate ROS *via* enzymatic mechanisms such as coupled NADH oxidase/peroxidase system and catalase[28-32]. Lin *et al*[33] showed that a strain of *Bifidobacterium longum* (*B. longum*) and *L. acidophilus* display antioxidative activity, inhibiting linoleic acid peroxidation by 28%-48% which is dominant in lipid peroxidation process. The heat-killed cells of *L. acidophilus* 606 and the soluble polysaccharide components of

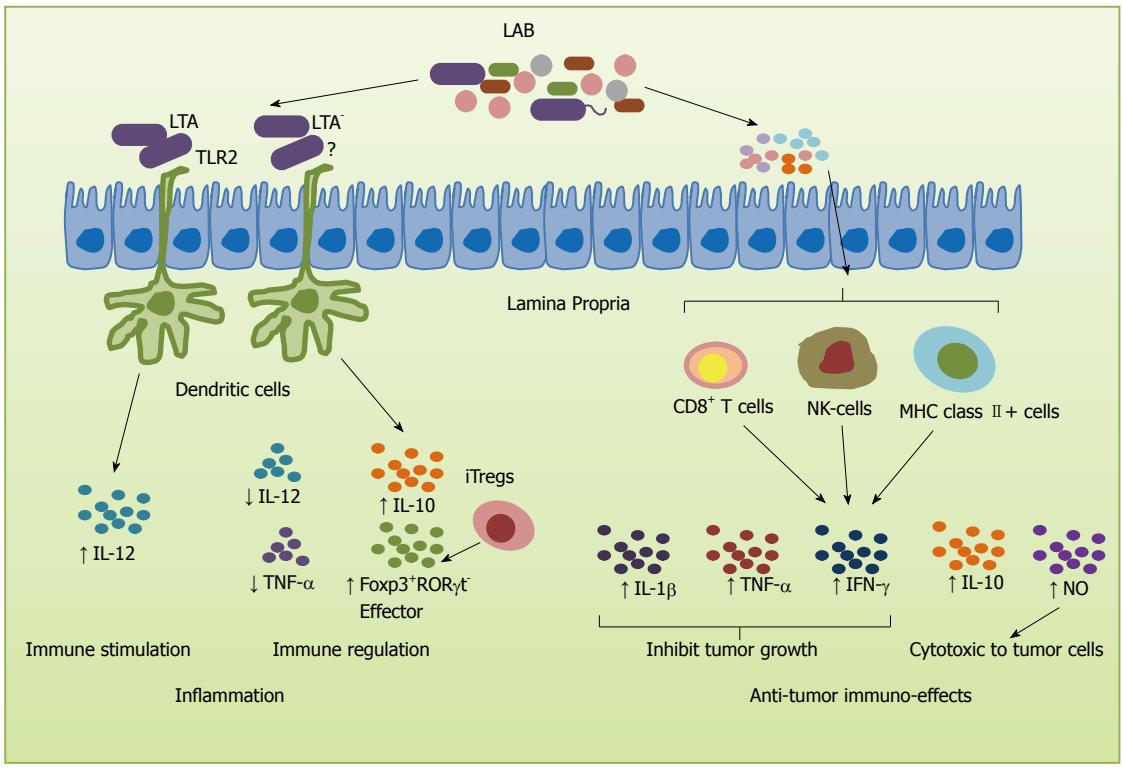

Figure 2 Immune responses induced by lactic acid bacteria. Lactic acid bacteria (LAB) can provoke immune responses *via* two main pathways: inflammation and anticancer immune response. The inflammation pathways involve lipoteichoic acid (LTA) which can stimulate T cells to release interleukin (IL)-10, IL-12 and increase effectors Foxp3⁺RORγt⁻ Tregs. In the anticancer immune response pathway, LAB stimulate the immune cells, such as T cells, dendritic cell (DC), natural killer (NK) and MHC class Ⅱ cells to induce IL-10, tumor necrosis factor (TNF)-α, interferon (IFN)-γ and IL-1β to inhibit tumor growth.

this strain exhibit potent antioxidative activity[34]. Several recent studies revealed prevention of oxidative DNA damage in human derived colon (HT29) cells by LAB[35]. These results indicate that the majority of strains including *Streptococcus thermophilus* have a protective effect against oxidative damage by releasing ROS protective factors into the medium. Furthermore, the obligatory homofermentative *lactobacilli* display high antioxidant activity whereas this property is highly strain-dependent among facultative and obligate heterofermentative *lactobacilli*[36,37]. Taken together, these studies implicate LAB as key molecules in antioxidant activity which may prevent CRC.

IMMUNE RESPONSE IMPROVEMENT BY LAB

The immune system plays a critical role in control of tumor promotion and progression[38]. The interaction of several elements of the immune system, such as antigen-presenting cells (APCs), different subsets of T cells, B cells, natural killer (NK) cells, and dendritic cells (DCs), is usually activated by damage, invasion or mutation[39]. Recent studies implicate LAB in immune responses critical for colorectal cancer prevention and therapeutics[40].

LTA related protection against pro-inflammation during tumor development

During tumor development, the first line of immune defense is formed by innate immune cells that confer protection against acute inflammation[41]. de Visser *et al*[42] showed that intestinal inflammation parallels the development of CRC. Probiotics play an important role in this process, with several studies showing their role in increasing the production of IL-10, an anti-inflammatory cytokine[43-45]. In fact, recent studies showed that *L. acidophilus* stimulated innate cells to produce inflammatory and regulatory cytokines by interacting surface layer proteins with other cell surface components such as lipoteichoic acid (LTA) which is a zwitterionic glycolipid found in the cell wall of several Gram-positive bacterial strains[46-50]. LTA can stimulate DCs through Toll-like receptor 2, resulting in cytokine release[51,52]. Some specific Lactobacillus species can stimulate DCs to produce IL-12 and regulatory, inflammatory cytokine IL-10[46,47]. However, disruption of LTA synthesis resulted in a *L. acidophilus* derivative that acts on intestinal immune cells to augment production of IL-10 in DCs, down-regulate IL-12 levels, and significantly mitigate dextran sulfate sodium- and CD4+CD45RB^{high} T cell-mediated colitis in mice[53]. These alterations of cell surface components of *L. acidophilus* provide a potential strategy for the treatment of inflammatory intestinal disorders and cancer therapy. Reinforcing the role of LTA, studies using LTA-deficient *L. acidophilus* (NCK2025) strain led to normalization of innate and adaptive pathogenic immune responses and caused regression of established colonic polyps. Not only IL-12 and TNF-α were down-regulated by NCK2025,

but also IL-10 in DCs was significantly enhanced and CD4+ T-cells were activated. The mice acquired significant protection from colitis with increased densities of effector $Foxp3^{+}ROR\gamma t^{-}$ Tregs in response to oral administration of *L. acidophilus* NCK2025[54] (Figure 2).

Anti-tumor immune effects induced by LAB

Under pathological states, such as colon cancer, probiotics may inhibit disease *via* modulation of the mucosal and systemic immune response and by reduction of the inflammatory response to host microbiota[41]. Another possible anti-tumor mechanism is the activation of immunity by immune cells to fight with the tumor cells, delay the onset of tumor or increase the survival rate. Galdeano *et al*[55] analyzed the profile of cytokines induced by some LAB strains and observed that the most remarkable effect for all the probiotic strains tested is the increase in TNF-α, interferon-γ (IFN-γ) and the regulatory cytokine IL-10. LAB such as *L. acidophilus*, *Lactobacillus casei* (*L. casei*) and *B. longum* have been shown to possess immunomodulatory and antitumor effects by suppressing the proliferation of tumor cells and prolonging survival[56]. The increase in survival was correlated with an increase in cellular immunity as reflected by the enhancement in the total numbers of T cells, NK cells and MHC class Ⅱ+ cells, and CD4-CD8+ T cells in flow cytometry analysis. Several strains of LAB have been shown to exert powerful anti-tumor effects. For example, *L. casei* Shirota (LcS) has been shown to exert strong anti-metastatic effects on transplantable tumor cells and to suppress chemically-induced carcinogenesis[57]. Intrapleural administration of LcS into tumor-bearing mice induced production of several cytokines, such as IFN-γ, interleukin-β (IL-1 β) and TNF-α, inhibiting tumor growth and increasing survival[58,59]. Furthermore, oral feeding of LcS significantly enhanced NK cell cytotoxicity which delayed tumor onset or suppressed tumor incidence[60]. Likewise, a butanol extract of another LAB strain, *B. adolescentis*, significantly increased the production of TNF-α and NO, which regulate immune modulation and are cytotoxic to tumor cells[61] (Figure 2). Taken together, these studies provide convincing evidence demonstrating the important role of LAB and their byproducts in the protection against carcinogenesis processes.

EPIGENETIC TARGETING PRODUCED BY LAB

The term "epigenetics" is used to describe those mechanisms which are able to modify the expression levels of selected genes without necessarily altering their DNA sequences, including DNA methylation, histone tail modifications, chromatin remodeling, as well as mechanisms mediated by non-coding RNA molecules. Epigenetic modifications are often induced by environmental factors[62]. It is now clear that epigenetic phenomena occur together with gene mutation and contribute to the progression of normal colonic mucosa to CRC[63]. Recently, in the field of cancer biology, increasing attention has been given to the role of epigenetic alterations in the etiology of cancer. A particularly active area of research involves histone deacetylase inhibitors (HDACi), a well known class of epigenetic drugs, used not only for cancer therapy but for cancer chemoprevention through strong anti-proliferative effects on tumor cells[64-66]. Probiotic metabolites such as butyrate, a short-chain fatty acid (SCFA), are therefore an important class of therapeutic compounds. Waldecker *et al*[67] reported that butyrate was one of the most potent HDACi in human colon cancer cell lines, suggesting an integral role of butyrate as an anti-inflammatory derivative of microbial fermentation in the colon. In studies using fecal fermentation, supernatants were found to be rich in butyrate and exhibited strong HDAC inhibitory properties in several colon cancer cell lines[68]. The ability of butyrate to de-repress epigenetically silenced genes in cancer cells, such as cell cycle inhibitor p21 and the pro-apoptotic protein Bcl-2 homologous antagonist/killer, and to activate these genes in normal cells, has important implications for cancer prevention and therapy[69]. It has been hypothesized that increased colonic concentration of butyrate can be an important mediator against CRC[70,71]. Recently, Lightfoot *et al*[72,73] tested possible epigenetic modifications induced by LTA-deficient *L. acidophilus* and found that oral NCK 2025 enhances the expression of tumor suppressor genes. This indicates that differential epigenetic regulation of CRC-related genes by NCK2025 represents a potential therapy against CRC.

NEW LAB ANTICANCER DISCOVERIES

In addition to the anticancer properties of LAB discussed above, recent findings showed that LAB also exerts antiproliferation activities of colon cancer cells *via* synergistic actions between adherence to cancer cells and SCFA bioproduction. To this end, Thirabunyanon *et al*[74] investigated probiotic action of LAB in the prevention and biotherapy of colon cancer. Four probiotic bacteria *Pediococcus pentosaceus* FP3, *Lactobacillus salivarius* (*L. salivarius*) FP25, *L. salivarius* FP35, and *Enterococcus faecium* FP51 showed antiproliferation properties at the rates of 17%-35%. The proposed mechanism of the proliferative inhibition was assigned to the synergic induction by directly adhering to colon cancer cells and triggering bioproduction of SCFA, mainly butyric and propionic acids. Using cell-free supernatants from LAB *L. casei*- and *L. rhamnosus*-treated cells, Escamilla *et al*[75] showed a decrease in colon cancer cell invasion *in vitro* by inducing matrix metalloproteinase-9 activity and zona occludens-1. These properties of *L. casei* and *L. rhamnosus* GG may prove useful in designing strategies for CRC prevention or treatment.

CLINICAL TRIALS, EMERGING FINDINGS

Clinical trials examining the effect of LAB or probiotics on cancer are presently ongoing. The SYNCAN project

funded by the European Union involving a 12-wk randomized, double blind trial of a food supplement containing *Lactobacillus* GG, *Bifidobacterium* Bb-12 in adenoma patients aims at testing colon cancer risk biomarkers[76]. It is hoped that the results of this study will provide much-needed information on the cancer protective effects of these bacterial strains. In randomized clinical trials, probiotics have been shown to decrease postoperative infectious complications in patients with CRC[77]. Similarly, functional outcome and health-related quality of life were significantly improved in patients who underwent surgical resection of CRC following *L. acidophilus* and *Bacillus natto* treatment[78]. Although there are no clinical studies in which LAB or probiotics are shown to reduce recurrence of CRC, *L. casei* has been shown to decrease significantly the recurrence of other cancers such as superficial bladder cancer[79]. Thus, based on current evidence, the effects of LAB in CRC are encouraging, although clinical as well as mechanistic studies are needed to identify the bacterial products and their interaction with the host in prevention or treatment of CRC. It is worth mentioning that some progress has been made in identification of "bacterial biomarkers" for cancer detection. In this regard, Brim *et al*[80] analyzed the *SLC5A8* gene, which encodes a transporter of butyrate, in 50 colon adenomas from patients and found that 82% of these patients displayed a high level of methylation, pointing to its potential use as a marker for early detection.

CONCLUSION

It is clear that LAB are of paramount importance in the prevention of CRC. Insights into the cellular and molecular mechanisms which include apoptosis, antioxidant, immune responses, and epigenetics opened the door for the development of novel therapeutic approaches. Although a wide range of studies have shown remarkable potential of LAB strains in interfering with colorectal carcinogenesis, conclusive clinical evidence supporting the role of probiotics in CRC treatment is still lacking. More epigenetic studies on LAB are required to demonstrate their effects in cancer prevention. Although several mechanisms of actions of LAB in carcinogenesis have been described in *in vitro* and animal model studies, we are still far from pinpointing the exact cellular signaling responsible for their effects. Nevertheless, the demonstrated functions of LAB in repairing defective apoptotic processes or controlling cell proliferation in cancer have made them an attractive tool for helping treat CRC. For example, based on the mechanism of apoptosis, one could modify LAB such as *L. reuteri*, *L. acidophilus* and *L. rhamnosus* to increase their anticancer effects *in vivo*. Likewise, the use of individual LAB like *L. acidophilus* or combination of different LAB strains to strengthen the ability of the immune system against cancer development can prove useful in prevention and treatment. However, it is clear that further investigations are strongly required to uncover the usefulness of probiotics in CRC treatment in clinical settings.

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