Review Paper

SAGE Open Medicine

SAGE Open Medicine
Volume 7: 1–5

DOI: 10.1177/2050312119825784
journals.sagepub.com/home/smo
SAGE

Bifidobacterium animalis subspecies *lactis* engineered to produce mycosporin-like amino acids in colorectal cancer prevention

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Abstract

Colorectal cancer is the third most common cancer and the third leading cause of cancer-related death. The pathogensesis of colorectal cancer involves a multi-step and multi-factorial process. Disruption of the gut microbiota has been associated with gastrointestinal diseases such as colorectal cancer. The genus *Bifidobacterium* is considered an important component of the commensal microbiota and plays important roles in several homeostatic functions: immune, neurohormonal, and metabolic. *Bifidobacterium animalis* subsp. *lactis* is a well-documented probiotic within the species *Bifidobacterium*. Mycosporin-like amino acids are low molecular weight amino acids demonstrated to exert prebiotic effects and to modulate host immunity by regulating the proliferation and differentiation of intestinal epithelial cells, macrophages and lymphocytes, as well as cytokine production. Their modulation of the metabolism of the immune system and transcription factors could exert a beneficial effect on colorectal cancer. *B. animalis* does not produce mycosporin-like amino acids. If one could create a *B. animalis*–producing mycosporin-like amino acids via genetic open reading frame engineering it should exert more potent immuno-stimulatory properties and, thereby, become a potent strain-specific microbial based therapy in colorectal cancer prevention.

Keywords

Mycosporin-like amino acids, *Bifidobacterium*, genetic engineering, colorectal cancer

Date received: 13 July 2018; accepted: 31 December 2018

Introduction

Colorectal cancer (CRC) is the third most common cancer and the third leading cause of cancer-related death. Approximately 140,250 new cases of large-bowel cancer are diagnosed each year and account for approximately 8% of all cancer deaths.[1] It should also be stressed that the prevalence of CRC is rapidly increasing in the developing world. The colonic bacterial community impacts on various host functions which include the digestion and absorption of nutritients, modulation of host metabolism, interactions with the immune system, neuroendocrine activity and motility as well as gut barrier and epithelial integrity; processes that, if disrupted, could contribute to carcinogenesis in CRC. Of these, the development of inflammation and alterations in the colonic microbiota are the two factors most closely associated with progression to CRC.[2–4]

Literature review

Bifidobacteria *and gut microbiota*

The gut microbiota contains a diverse community of commensal, symbiotic and potentially harmful micro-organisms.[5,6] The gut microbiota exerts anti-inflammatory, antioxidant, anti-oncogenic effects and contributes to the immunological, hormonal and metabolic homeostasis of the host.[7,8] The genus *Bifidobacterium* belongs to the phylum actinobacteria and comprises Gram-positive, non-motile, often branched anaerobic bacteria.[9] *Bifidobacteria* are one of the major species in the human colon microbiota, and members of this species are frequently used as probiotics.[10] *Bifidobacterium* species have immune modulatory, metabolic and anti-inflammatoryeffects.[9,11–13] *Bifidobacterium* species have the highest level of intrinsic hydrogen peroxide resistance causing antioxidant

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activity.[14] Several studies have shown that *Bifidobacteria* differ from other bacteria in their role in oligosaccharide metabolism and the capacity to perform fermentation.[9,15] *Bifidobacteria* use the fructose-6-phosphate phosphoketolase pathway to ferment carbohydrates; through this pathway, indigestible fructans are converted into short-chain fatty acids (SCFAs), such as butyrate, propionate and acetate which have beneficial effect on intestinal immunity and metabolism.[16] *Bifidobacteria* are the main sources of butyric acid production, and they are used as probiotic ingredients in many foods.[17,18] *Bifidobacterium animalis* subsp. *lactis* is a catalase-negative, rod-shaped bacterium which was first isolated in 1983. At the time of isolation, *B. animalis* subsp. *lactis* was considered as belonging to the species of *Bifidobacterium bifidum*.[19]

Mycosporin-like amino acids and gut microbiota

Mycosporin-like amino acids (MAAs) are low molecular weight (<400 Da) amino acids. MAAs act as absorbers of ultraviolet (UV) light and as photo protectants.[20–22] MAAs also play a role in protecting against sunlight damage by acting as antioxidant molecules scavenging toxic oxygen radicals.[22] MAAs are unique components of red seaweeds, and seaweed products are used as nutrional supplements in the management of bowel diseases.[23–26] MAAs have been described to affect the intestinal mucosa, enhancing villus height and surface area, as well as the intestinal microbiota, increasing the abundance of *Bifidobacterium* and, importantly, reducing the prevalence of *Clostridium* species in animal models.[27] MAAs have been shown to regulate intestinal epithelial cell differentiation and cytokine (interleukin (IL)-1β and IL-6) production.[28] Cell differentiation and modulation of cytokine production have a beneficial effect on intestinal epithelial cells.[29–33] In in vivo experiments, the anti-inflammatory effects of MAAs were demonstrated. They can also reinforce intestinal barrier function.[34,35] In addition, MAAs exhibit potent antioxidant activity by mopping up reactive oxygen species (ROS).[36] The MAAs Myc-Gly and Myc-Tau inhibit the adverse effects of ROS in biological systems via lipid peroxidation, inactivation of mitochondrial electron transport and hemolysis of erythrocytes.[37] Tryptophan is an essential amino acid for the synthesis of the neurotransmitter serotonin (5-hydroxytryptamine (5-HT)). Impaired tryptophan metabolism has been implicated in the pathophysiology of conditions such as acquired immunodeficiency syndrome–related dementia, Huntington's disease and Alzheimer's disease.[38] Furthermore, impaired tryptophan metabolism could contribute to the development or exacerbation of inflammatory bowel disease.[39] MAAs induce the activity of the tryptophan by degrading enzyme indoleamine 2,3-dioxygenase. Indoleamine 2,3-dioxygenase is the rate-limiting enzyme in the breakdown of the essential amino acid tryptophan into kynurenine, which represents an anti-proliferative strategy by reducing the growth of invading pathogens and malignant cells.[40] It seems that modulation of tryptophan metabolism via MAAs has a beneficial effect on gut microbiota.

Discussion

Bifidobacteria *and colon cancer*

Epithelial inflammation constitutes an important initiating factor in the development of colitis-associated CRC. Inflammation may arise after mucosal invasion by intestinal bacteria.[41] Later, inflammation can induce persistent immune dysregulation and then neoplastic changes of the mucosa. Chung et al. demonstrated that *Bacteroides fragilis* triggers a pro-carcinogenic, multi-step inflammatory cascade that requires IL-17R and involves nuclear factor (NF)-κB signaling in colonic epithelial cells in the context of intestinal dysbiosis.[42] When pathogenic bacteria invade the protective mucus layer of the colon, the equilibrium is disturbed and DNA damage begins with tumor formation along with chronic inflammation.[43]

Abnormal patterns of DNA methylation in the intestinal tract can lead to the formation of aberrant crypt foci which are thought to later progress into adenoma and cancer and damage the intact barrier and intestinal epithelium.[43] Aberrant DNA methylation and dysregulation of intestinal cell proliferation may precede the activation of oncogenesis, through ROS and p53, which are needed for neoplastic progression.[44] DNA methylation is associated with CpG island (CGI)-associated promoters in both intestinal epithelial stem cells and differentiated cells. Global hypomethylation leads to increased gene expression, heterozygosity and global loss of chromosomal stability.[44,45] In addition, hypermethylation[46] leads to inactivation of important tumor-suppressor genes.

These epigenetic changes play an important role in the formation of colorectal adenomas and carcinomas. Ghadimi et al.[47] reported that *Bifidobacterium* restores epigenetically mediated changes in the human intestinal mucosal immune system via reducing histone acetylation and enhancing DNA hypermethylation. Disrupted methylation patterns can occur during inflammation in colonic disorders. They also showed that *Bifidobacterium* diminishes the expression of IL-17 and IL-23, which play an important role in inflammatory bowel disease. Schroeder et al.[48] showed that *Bifidobacterium* strains promote mucus layer integrity and reverse abnormalities in the altered colonic microbiota. Colonic permeability is decreased, and the growth rate of the inner mucus layer increased in an intact colonic microbiota.

Bifidobacteria are the main source of butyrate production, and butyrate has potent anti-inflammatory and anti-tumor effects. A higher abundance of butyrate-producing bacteria was found in stools of native Africans with low CRC risk as compared to Afro-Americans with a higher risk.[49] Clarke et al.[50] reported that butyrate inhibits

proliferation and induces differentiation and apoptosis of CRC cells. Increased levels of butyrate reduce the incidence of carcinogen-induced colon tumors. Free fatty acid receptor 2 (Ffar2) is a receptor for SCFAs (acetate, propionate and butyrate), and Sivaprakasam et al. showed that Ffar2 is downregulated in human colon cancers. They also reported that the administrationof *bifidobacterium* alleviated intestinal inflammation and carcinogenesis in Ffar2−/−mice.[51] Butyrate may play a role in mediating key processes in oncogenesis including genomic instability, inflammation and cell energy metabolism.

Krüppel-like factors (Klfs) are zinc-containing transcription factors that modulate proliferation, differentiation, growth and apoptosis. A total of 17 Klfs have been identified, and their biological structure and contribution to human diseases have been described by Bialkowska et al.[52] Klf5 is highly expressed in crypt epithelial cells of the intestine and plays a critical role in regulating the proliferation of both normal intestinal epithelial cells and CRC cells.[52] Klf4 is an inhibitor of cell growth and exerts contrasting effects on Klf5.[53] Klf4 and Klf5 bind to similar DNA sequences. Klf5 inhibits the activating effect of Klf4 on the Klf4 promoter, and Klf4 abrogates the inhibitory effect of Klf5 on the same promoter.[54] Engevik et al.[55] reported that *Bifidobacterium*-associated mice have a 20-fold increase in the goblet cell differentiation marker Klf4 at the level of mRNA compared with germ-free controls. *Bifidobacterium* may play a role in mediating key processes in the modulation of Klf4 and Klf5 expression.

It seems that *Bifidobacterium* strains have protective and preventive effects on colonic microbiota composition and may have an impact on the epigenetic regulation of CRC

MAAs and colon cancer

Harmful irradiation directly damages biomolecules, including lipids, proteins and DNA and induces oxidative stress through mutagenic free radicals. MAAs act as UV absorbers. In this way, MAAs play an additional role in the antioxidant system. In addition, MAAs modulate intestinal epithelial cell differentiation and cytokine production.[26] NF-κB is aberrantly activated in tumor cells, contributing to their advantage in survival and proliferation. The modulation of NF-κB signaling in response to stress can also be a strategy for cytoprotection, as several survival pathways can be activated.[32] It seems that modulation of NF-κB and tryptophan metabolism via MAAs has a beneficial effect on the immune system. Besides these properties, MAAs also inhibit thiobarbituric acid reactive oxygen species (TBAR),[36] which are elevated in colon cancer.[56]

Recommendation

Combination of Bifidobacteria *and MAAs*

There are two biosynthetic pathways of MAAs. The first pathway[57] is the shikimate pathway, also known as the synthesis pathway from aromatic amino acids. The second pathway is the pentose phosphate pathway.[58] In both pathways, 4-deoxygadusol is the common precursor. Transaldolase is an enzyme in the non-oxidative phase of the pentose phosphate pathway; *Bifidobacterium* strains contain transaldolase. Cyanobacteria are a phylum of bacteria that obtain their energy through photosynthesis and are the only photosynthetic prokaryotes able to produce oxygen. MAAs are an essantial class of secondary metabolites of Cyanobacteria known for their protection against UV radiation and other stress factors.

A biosynthetic gene cluster for MAAs has been demonstarted in Cyanobacteria.[59] *Anabaena variabilis* PCC 7937 (Cyanobacterium) is able to synthesize MAAs.[59] *A. variabilis* PCC 7937 is not a component of commensal gut microbiota. It is a component of aquatic and terrestrial ecosystems. Genome studies identified a combination of genes, YP_324358 (predicted DHQ synthase) and YP_324357 (O-methyl transferase), which were present only in *A. variabilis* PCC 7937 and missing in other Cyanobacteria. *Anabaena* sp. PCC 7120 has been induced to produce MAAs using ORF after genomic transfer (*YP_324358* and *YP_324357* genes) from *A. variabilis* PCC 7937.[60] It seems that Cyanobacterium is the source of MAAs, and we hypothesize that the genes of Cyanobacterium involved in MAAs biosynthesis could be transferred to the strain *B. animalis* subsp. *lactis* BB-12.[61,62] Genetically modified *Bifidobacteria* can modulate the immune system to further reduce chronic inflammation and increase colonic mucosal stability. A greater degree of suppression of inflammation and increased mucosal stability might arrest colorectal tumorigenesis at different stages including tumor initiation, promotion, progression and metastasis.[63] In addition, experimental data reveal the important role of NF-κB in colon tumor cells, as well as in the surrounding cancerous and reactive microenvironment.[64,65] It can be predicted that this combination may be more effective in preventing CRC through the NF-κB pathway. In addition, elevated levels of TBARs are associated with colon cancer initiation and progression,[58] and this combination can prevent cancer formation by lowering TBAR levels.

Conclusion

Significant progress has been made in recent years in recognizing the importance of the gut microbiota to CRC. Key findings include the discovery of oncogenetic mechanisms that link the gut microbiome to CRC, including reduced SCFA production, chronic inflammation, alterated transcription factors and the immune response. Creating MAA-producing *Bifidobacteria* species via genetic engineering could result in a bacterium that is more potent in the prevention of CRC. MAAs produced via genetic engineering might be used not only as a probiotic but also as a pharmacological agent in CRC.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval was not sought for this study because this is a proposal study.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Informed consent was not sought for this study because this is a proposal study.

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