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Cellular and molecular mechanisms of probiotics effects on colorectal cancer

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ABSTRACT

Colorectal cancer is the most common malignancy of the gastrointestinal tract and it seems the colonic microbiota plays a significant role in the aetiology of colorectal cancer because it can influence many aspects of intestinal tract health including its physiology, metabolism, development, and immune homeostasis. Hence, all factors modulating the gut microflora and their metabolism are very interesting in cancer prevention. Probiotic bacteria have been examined for anti-cancer effects and different mechanisms were suggested about their anti-tumour functions. This study reviewed some of the possible cellular and molecular mechanisms of probiotics such as influencing intestinal microbial composition and pathogenic bacteria, the production of biological substance like short chain fatty acids and conjugated linoleic acid, inactivation of carcinogenic compounds especially those derived from food, improvement of intestinal barrier function, modulation of immune responses, apoptosis and anti-proliferative effects and antioxidant function.

Contents

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1. Introduction

Colorectal cancer (CRC), the most common malignancy of the gastrointestinal tract, is the third most common cancer accounting for about 9.5% of all new malignant diseases and the fourth leading cause of cancer death worldwide (Siegel, Naishadham, & Jemal, 2012; Uccello et al., 2012; Wu et al., 2013). The number of new cases is rising rapidly, both due to the expansion of the elderly population as well as an increase in the prevalence of risk factors like inflammatory bowel disease (IBD) and the change in dietary habits (Konstantinov, Kuipers, & Peppelenbosch, 2013; Pericleous, Mandair, & Caplin, 2013).

The colonic microbiota is involved in the aetiology of CRC and can impress multiple processes that affect cancer risk such as controlling epithelial proliferation and differentiation, influencing the immune system and protecting against pathogens (Zhu, Gao, Wu, & Qin, 2013). Some studies have indicated that the composition of the gut microbiome is different in CRC patients from healthy controls. The human intestinal tract contains approximately 1000 species and about 10^{14} bacteria that influence all over physiology, metabolism, development, and immune homeostasis (Turner, Ritchie, Bresalier, & Chapkin, 2013; Wu et al., 2013). Some strains of bacteria have been associated with the pathogenesis of cancer, such as *Streptococcus bovis*, *Bacteroides*, *Clostridium*, and *Helicobacter pylori* and some strains including *Lactobacillus acidophilus* and *Bifidobacterium longum* inhibited carcinogen-induced colon tumour development (Zhu et al., 2013). The comparison of the composition of the human intestinal microbiota between CRC patients and healthy subjects showed significant elevation of several bacterial groups, such as *Bacteroides* and *Fusobacterium* species and significant reduction of butyrate-producing bacteria in the gut microbiota of CRC patients (Wu et al., 2013). A positive correlation was also observed between the abundance of *Bacteroides* species and CRC disease status. Chen and colleagues reported that the structures of the intestinal lumen microbiota and mucosa-adherent microbiota were different in CRC patients compared to matched microbiota in healthy individuals (Chen, Liu, Ling, Tong, & Xiang, 2012b).

However, the exact composition of intestinal microbiota and its function in the CRC progression remain unknown but it seems that an imbalance between beneficial and pathological species of bacteria may be involved in cancer. By using pyrosequencing technique, colon cancer is linked with dysbiosis mainly due to a change in dominant and subdominant species (Sobhani et al., 2011). These results have led to an interest in factors that can modulate the gut microflora and their metabolism (Rafter, 2004). Probiotic bacteria are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill et al., 2014). They usually comprise lactic acid producing bacteria (LAB) of the genera *Lactobacillus* and *Bifidobacterium* and are widely available, for instance, in yogurts and other functional foods such as cheese, fermented and unfermented milks (Burns & Rowland, 2004; Uccello et al., 2012). Despite numerous studies that have been done in this area, the exact mechanisms that probiotics can affect colorectal cancer are unknown. In the same vein, the great number of studies show that probiotics may prevent cancer initiation or its development via alteration of intestinal microbial composition, protection of host from pathogenic bacteria and fungi, the production of biological substance like short chain fatty acid and conjugated linoleic acid, inactivation of carcinogenic compounds, improvement of intestinal barrier function, modulation of immune responses, apoptosis and anti-proliferative effects and anti-oxidant function (Chen et al., 2012b; Uccello et al., 2012). Therefore, this study aimed to review the impacts of probiotics mechanisms on inhibiting colorectal cancer that were summarized in Fig. 1.

2. Probiotics, microbial composition, and CRC

The intestinal microbiota participates in a symbiotic relationship with their host and has a major role in the health of colon by preventing overgrowth of pathogens, extracting nutrients and energy from diet and contributing to normal immune function (Chen et al., 2012a; Lozupone, Stombaugh, Gordon, Jansson, & Knight, 2012). The potential pathways linking between microbiota and the host are signalling cascades, the immune