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Benefits of short-chain fatty acids and their receptors in inflammation and carcinogenesis

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ABSTRACT

Epidemiological studies have linked increased incidence of inflammatory diseases and intestinal cancers in the developed parts of the world to the consumption of diets poor in dietary fibers and rich in refined carbohydrates. Gut bacteria residing in the intestinal lumen exclusively metabolize dietary fibers. Butyrate, propionate and acetate, which are collectively called short-chain fatty acids (SCFAs), are generated by fermentation of dietary fibers by gut microbiota. Evidences indicate that SCFAs are key players in regulating beneficial effect of dietary fibers and gut microbiota on our health. SCFAs interact with metabolite-sensing G protein-coupled receptors GPR41, GPR43 and GPR109A expressed in gut epithelium and immune cells. These interactions induce mechanisms that play a key role in maintaining homeostasis in gut and other organs. This review summarizes the protective roles of GPR41, GPR43 and GPR109A in dietary fibers-, gut microbiota- and SCFAs-mediated suppression of inflammation and carcinogenesis in gut and other organs.

Contents

1. Introduction

Diet has a profound and long-lasting effect on our health. The effect of specific dietary components such as dietary fibers goes beyond their nutritional value and positively influences multiple aspects of human health. Industrial development in the modern era has been associated with a change in lifestyle leading to the consumption of refined foods and decreased intake of whole grains, fruits and vegetables, which are major sources of dietary fibers. The change in lifestyle in recent years has coincided with an increase in inflammatory diseases such as ulcerative colitis, Crohn's disease (together called as inflammatory bowel diseases or IBDs), allergies, intestinal cancers and others (Schatzkin et al., 2007; Hou et al., 2011; Hansen et al., 2012; Thorburn et al., 2014). Ever since these observations have been made, the role of dietary fibers and the underlying mechanisms in the prevention of inflammatory diseases and cancers have been extensively investigated. Bacteria residing in the gut metabolize dietary fibers into SCFAs (Hamer et al., 2008). SCFAs are generated at ~100 mM concentration in the colonic

Abbreviations: GPR41, G protein-coupled receptor 41; GPR43, G protein-coupled receptor 43; GPR109A, G protein-coupled receptor 109A; HDAC, Histone deacetylases; DSS, dextran sulfate sodium; AOM, azoxymethane; APC, adenomatous polyposis; DC, dendritic cell; Treg, T regulatory; LPS, lipopolysaccharide; GF, germ free; SLC5A8, solute carrier family 5 member 8; MCT1, monocarboxylate transporter-1; SCFAs, short-chain fatty acids.

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lumen at an approximate ratio of 60:20:20 for acetate, propionate and butyrate, respectively (Ganapathy et al., 2013). Significance of SCFAs in the promotion of health is strengthened by two lines of epidemiological findings: (1) reduction in specific constituents of gut microbiota that play a key role in the fermentation of dietary fibers into butyrate in feces of individuals with colorectal cancer and ulcerative colitis (Frank et al., 2007; Wang et al., 2012); (2) lower intake of dietary fibers is associated with enhanced risk for the development of ulcerative colitis, Crohn disease and colorectal cancers (Schatzkin et al., 2007; Hou et al., 2011; Hansen et al., 2012). Concentrations of SCFAs are highest in colonic lumen and almost negligible in peripheral blood (Bergman, 1990) suggesting that they act locally on epithelium and immune cells present in the colon to induce health-promoting effects. The objective of this review is to provide current evidences, which demonstrate that GPR41, GPR43 and GPR109A act as molecular links between gut microbiota, dietary fibers, SCFAs and the promotion of health.

2. Dietary fibers

Dietary fibers are carbohydrates that are indigestible in the small intestines of mammals due to a lack of enzymes. Dietary fibers are a complex mixture of branched and unbranched polysaccharides composed of short to long chains of monosaccharides. Different dietary fibers differ in their ability to undergo fermentation in colonic lumen (Eswaran et al., 2013). Soluble dietary fibers such as oligofructose, inulin, psyllium and cornstarch have higher fermentability, and thus generate higher amounts of SCFAs. In contrast, insoluble dietary fibers such as cellulose and hemicellulose have low fermentability and, therefore, contribute minimally to SCFA production in the colon. In general, dietary fibers with smaller and unbranched chains tend to be more soluble. Dietary fibers with long-chain carbohydrates have either high solubility (e.g. inulin), intermediate solubility (e.g. psyllium) or no solubility (cellulose). Due to their high fermentability, soluble dietary fibers act as an energy source for a selected group of gut bacteria, possess the ability to promote growth of beneficial microorganisms in the intestine and thus are used as "prebiotics" (Gibson et al., 2010).

3. Gut microbiota

Human intestinal lumen is inhabited by trillions of microorganisms collectively termed as gut microbiota (O'Hara & Shanahan, 2006; Tsai & Coyle, 2009). Metabolic activity of the gut microbiota is qualitatively and quantitatively similar to an organ. In addition, various molecular, cellular and metabolic components of gut microbiota constantly interact with our organs and impact our health. Therefore, gut microbiota has also been called as the forgotten organ (O'Hara & Shanahan, 2006). Gut microbiota consists of ~100–1000 different bacterial species. Collective genome of gut microbiota contain ~150 times more genes than the number of genes in our body and therefore have also been referred to as our second genome (Grice & Segre, 2012). Colonization of the gut begins immediately after birth and is a continuously ongoing process throughout the life of an individual. Members belonging to phyla *Bacteroidetes* and *Firmicutes* dominate the composition of gut microbiota, whereas members from *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, *Cyanobacteria* and *Verrucomicrobia* are minor constituents of gut microbiota (Eckburg et al., 2005; Sekirov et al., 2010). The relationship between the host and most of the gut microbiota has evolved as mutualistic or symbiotic (Backhed et al., 2005; Mazmanian et al., 2008). Multiple health benefits of symbiotic bacteria or symbionts on human health have been recognized and well appreciated. Positive effects of gut microbiota on human health include providing vitamins and energy source to the host, helping in the development of intestinal tissue and immune system, limiting inflammatory responses at local and distal organs, decreasing carcinogenesis and inhibiting colonization of gut with pathogenic microorganisms (Rakoff-Nahoum et al., 2004; Lee & Mazmanian, 2010; Ley, 2010; Vijay-Kumar et al., 2010; Nicholson et al., 2012). Notwithstanding, with the evolution of symbiotic bacteria in the gut, certain bacterial inhabitants of gut, which are called pathobionts, exert disease-promoting effects on hosts, such as inducing inflammation, carcinogenesis and obesity (Garrett et al., 2010; Chow et al., 2011; Elinav et al., 2011; Palmer, 2011). Thus, gut microbiota possess properties that both positively and negatively affect the health of the host.

Owing to a complex and intricate relationship, a dynamic equilibrium exists between host and gut microbiota, which plays a critical role in maintaining intestinal homeostasis. Within gut microbiota, several distinct bacterial communities live at a certain ratio under steady state condition (Faith et al., 2013). A change in environmental factors, lifestyle, disease and infections lead to alterations in the composition of bacterial communities, and this process is termed as dysbiosis (Carding et al., 2015). Dysbiosis is present in many inflammatory diseases such as IBD, metabolic syndrome and colorectal cancers. Epidemiological studies have shown a decrease in butyrate-producing gut bacteria, such as those belonging to genus *Roseburia* and family Lachnospiraceae, in the feces of individuals with colon cancer compared to healthy donors. Similarly, feces from individuals with ulcerative colitis, a risk factor for the development of colorectal cancers, also contain significantly reduced numbers of butyrate-producing gut bacteria belonging to the family Lachnospiraceae (Frank et al., 2007; Wang et al., 2012). There is evidence suggesting that dysbiosis may be involved in the development of certain diseases. Transfer of gut microbiota from diseased animals into germ-free or susceptible mice causes pathologies in recipients similar to those present in donors (Garrett et al., 2007; Turnbaugh et al., 2008; Vijay-Kumar et al., 2010; Kostic et al., 2013; Shanahan & Quigley, 2014). Similarly, correction of dysbiosis is associated with alleviation of the diseases (Everard et al., 2013). Collectively, these findings suggest that manipulation of gut microbiota may serve as an attractive target for designing therapeutic modalities for the prevention and or treatment of certain diseases.

4. Short-chain fatty acids (SCFAs)

Among SCFAs, butyrate has been extensively investigated for its role in suppression of colonic inflammation and carcinogenesis (Hamer et al., 2008). Fermentation of dietary fibers into butyrate is a stepwise process, which is facilitated by distinct constituents of gut microbiota. In colon, majority of butyrate-producing bacteria are anaerobes and belong to *Clostridium* clusters IV and XIVa (Nagano et al., 2012). Studies performed in vitro using butyrate-producing colonic bacteria such as *Roseburia intestinalis* DSM14610 and *Anaerostipes caccae* DSM14662 (both are members of *Clostridium* cluster XIVa) show that they are poor fermenters of dietary fibers (Falony et al., 2006). Butyrate production was at a minimum in these cultures even in the presence of dietary fibers. On the other hand, *Bifidobacterium* ferments dietary fibers vigorously to produce acetate, fructose and lactate, but no butyrate. In mixed cultures, where both *Bifidobacterium* and *R. intestinalis* or *A. caccae* are present, the addition of dietary fibers lead to butyrate production (Belenguer et al., 2006). Mechanistic studies show that when acetate and fructose, which are released following fermentation of dietary fibers by *Bifidobacterium* are added to the cultures of *R. intestinalis* or *A. caccae*, respectively, butyrate production is observed (Falony et al., 2006). Thus, metabolites generated by *Bifidobacterium* are used by *R. intestinalis* or *A. caccae* for their growth and this process is called cross-feeding. The magnitude at which this cross-feeding exist in vivo remains poorly defined. In several human and animal studies, dietary fibers regularly increase the number of *Bifidobacterium* in the gut (Gibson et al., 2010). Efforts have been made to analyze the effect of dietary fibers on the numbers of butyrate-producing gut bacteria. The protein product of Butyryl-CoA:acetate CoA transferase (*BcoA*) gene catalyzes the critical final step in butyrate production among gut microbiota. A recent human study found that dietary fibers enhanced