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Galacto-oligosaccharides and colorectal cancer: Feeding our intestinal probiome

Jose M. Bruno-Barcena [a], *M. Andrea Azcarate-Peril* [b,c,*]

[a] *Department of Plant and Microbial Biology, North Carolina State University, Raleigh, North Carolina, USA*
[b] *Department of Cell Biology and Physiology, University of North Carolina School of Medicine, Chapel Hill, USA*
[c] *Microbiome Core Facility, University of North Carolina School of Medicine, Chapel Hill, USA*

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ABSTRACT

Prebiotics are ingredients selectively fermented by the intestinal microbiota that promote changes in its structure and/or metabolism, conferring health benefits to the host. Studies show that β (1-4) galacto-oligosaccharides [β (1-4) GOS], lactulose and fructo-oligosaccharides increase intestinal concentration of lactate and short chain fatty acids, and stool frequency and weight, and they decrease fecal concentration of secondary bile acids, fecal pH, and nitroreductase and β-glucuronidase activities suggesting a clear role in colorectal cancer (CRC) prevention. This review summarizes research on prebiotics bioassimilation, specifically β (1-4) GOS, and their potential role in CRC. We also evaluate research that shows that the impact of prebiotics on host physiology can be direct or through modulation of the gut intestinal microbiome, specifically the probiome (autochtonous beneficial bacteria). We present studies on a potential role in CRC *progression* to finally describe the current state of β (1-4) GOS generation for industrial production.

Contents

* *Corresponding author.* Department of Cell Biology and Physiology, 332 Isaac Taylor Hall – Campus Box 7545, School of Medicine, University of North Carolina, Chapel Hill, NC 27599-7545, USA. Tel.: +1 919 966 9838; fax: +1 919 966 6927.
E-mail address: azcarate@med.unc.edu (M.A. Azcarate-Peril).

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1. Prebiotics: Definition and scope of review

Prebiotics are "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improve host health" (Gibson & Roberfroid, 1995). The gut bacteria play an active role in the digestion of carbohydrates, a fermentative process that yields short-chain fatty acids (SFCA) like acetic, propionic and butyric acids, and various gases like hydrogen, methane and CO_2. The concept of prebiotics is relatively recent; however, the differences between non-digestible and digestible carbohydrates, and the methods to quantify them were established early in the last century. Digestible carbohydrates were considered those available for digestion and absorption in the small intestine that rapidly increased blood glucose levels (McCance & Lawrence, 1929) (had a high glycemic index) whereas non-digestible carbohydrates were not digested and hence had a low glycemic index. The methods for determination of digestible carbohydrates target the reducing sugars, including sucrose and starch as a measure of the available carbohydrates in food products. The non-digestible carbohydrates are reported as the amount of insoluble residue, corrected for protein and ash (reviewed by McCleary, 2003).

Prebiotics are short-chain oligosaccharides resistant to digestion in the upper gastrointestinal tract; thus, they can reach the colon undigested, to selectively stimulate the growth of the beneficial members of the intestinal microbiota or probiome (Azcarate-Peril et al., 2008) that carry functional β-galactosidases and/or β-glucosidases. The most recent definition of prebiotics states that "a dietary prebiotic is an ingredient selectively fermented that results in specific changes in the composition and/or activity of the gastrointestinal (GI) microbiota thus conferring benefit(s) upon host health" (Gibson, Scott, Rastall, Tuohy, & Hotchkiss, 2010). Three commercially available dietary ingredients: galacto-oligosaccharides (GOS), lactulose, and fructo-oligosaccharides (FOS) are used as food additives in Japan and Europe. In the United States, the Food and Drug Administration (FDA) has not stated health claims for probiotics or prebiotics but requires a notification of safety when applying for commercialization of a new dietary ingredient. Additionally, the FDA Centers for Biologic Evaluation and Research and Drug Evaluation and Research (CBER and CDER, respectively) published a draft document regarding the need to file an Investigational New Drug application when doing human research (U.S. Food and Drug Administration, 2006) in which is mentioned that, according to the National Center for Complementary and Alternative Medicine (NCCAM), prebiotics are included in the domain called "biologically based practices", which "includes, but is not limited to, probiotics, botanicals, animal-derived extracts, vitamins, minerals, fatty acids, amino acids, proteins, whole diets, and functional foods". Prebiotics commercialized in the US that have submitted notification to be considered as new dietary ingredients (NDI), and are GRAS (generally regarded as safe) for use in foods and term infant formulas, include Vivinal GOS® (Friesland Foods Domo®) and Oligomate 55N/55NP (Yakult Pharm. Ind. Co.). Vivinal GOS® is generated using the β-galactosidase from *Bacillus circulans* while Oligomate, which has been traditionally used as a food ingredient in Japan, is generated using whole cells of *Sporobolomyces singularis* overexpressing its own β-hexosyl transferase. Fig. 1 shows the proportion of components in commercial and a non-commercial, enriched GOS formulation recently developed (Dagher, Azcarate-Peril, & Bruno-Barcena, 2013). The commercial β (1–4) galacto-oligosaccharide [β (1–4) GOS] formulations contain approximately 50% β-(1–4) GOS, and residual glucose, lactose and galactose. The host and the microbial physiological responses to prebiotics, which are poorly digested by endogenous enzymes and fermented by the intestinal microbiota containing functional β-galactosidases and/or β-glucosidases, are referred to as "prebiotic effects" and have been extensively documented in humans and animals (Howard, Gordon, Pace, Garleb, & Kerley, 1995; Lomax & Calder, 2009; Moro et al., 2002).

1.1. *Galacto-oligosaccharides (GOS)*

GOS are the most inexpensive alternative often added to infant formulas to mimic the beneficial effects of the oligosaccharides present in human breast milk and are one of the most extensively evaluated prebiotics. They are considered prebiotics as originally defined by Gibson & Roberfroid (1995): they are not absorbed in the upper part of the gastrointestinal tract, they are specific substrates for one or a group of beneficial bacteria of the probiome (resulting in the modulation of the intestinal microbiota in favor of a healthier composition), and have beneficial systemic effects on the host. Technically, GOS can have α- or β-configurations by the nature of the glycosidic bonds between the sugar molecules (Table 1). The majority of published scientific articles use the term GOS when referring to β (1–4) GOS, while the abbreviation TOS has been alternatively employed (Djouzi & Andrieux, 1997). β (1–4) GOS are generally produced by enzymatic transglycosylation using β-galactosidases or β-glucosidases and have a generic formula of β (1–4) [D-galactose]n-D-glucose where n ranges between 3 and 10 sugar moieties (Nilsson, 1988). Due to their glycosidic bond, they are not metabolized in the small intestine reaching the colon intact, where they serve as substrate for specific members of the microbiota capable of hydrolyzing the galactose–glucose bonds (Ohtsuka et al., 1991). These carbohydrates and the carbohydrate fragments formed from the hydrolysis of the complex polymeric substances are further transformed by the butyrate-producers in the colon (see a more detailed description of the effect of GOS on the intestinal microbiota later). Products of GOS metabolism include SCFAs, lactate, acetate, and gases in proportions depending upon the α- or β-configuration of the sugars (Djouzi & Andrieux, 1997). *Bifidobacterium* species are the most studied members of the probiome able to metabolize GOS, FOS, and human milk oligosaccharides (HMOs). Consequently, an increased abundance of bifidobacteria is the most reported effect of GOS and this is termed "bifidogenic effect" (Davis, Martinez, Walter, Goin, & Hutkins, 2011; Sangwan, Tomar, Singh, Singh, & Ali, 2011).

1.1.1. *GOS and CRC prevention*

There is a strong genetic component in the development of colorectal adenomas or cancers, which in conjunction with environmental factors including diet and lifestyle have a major impact on risk (reviewed in Azcarate-Peril, Sikes, &