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Pre- and probiotic overview

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The dynamic relationship between gut microbiota and its human host is also known as a trophic association that might range from commensalism, where only the microbe enjoys a positive effect from the relationship, to intestinal symbiosis where both host and microbe benefit from their interaction. In the last years, we have started to understand how alterations of the gut microbiota composition leading to the disruption of host-microbial interactions are associated and/or predispose individuals to disease conditions ranging from inflammatory bowel diseases to allergy and functional gastrointestinal disorders, such as irritable bowel syndrome. While we await important insights in this field, the microbiota is already a therapeutic target. Based on the actual definitions, prebiotics are defined as substrates that are selectively utilized by host microorganisms conferring a health benefit, while probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Although their health promoting activities encompasses numerous effects, including immunostimulation, competitive exclusion of pathogens, and gut barrier enhancement, the exact mechanism of action by which these compounds exert their beneficial actions in humans is only partially known. In this review, we highlight the current insights into the clinical applications of prebiotics and probiotics in gastroenterology.

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Introduction

Humans are densely colonized by a complex and dynamic consortium of bacteria that outnumber the mammalian cells and are predicted to represent significantly genetic assortment matched to the genome of their host [1]. The gut microbiota provides many essential functions for human life during mammalian evolution, without which the human being could not have developed [2]. Remarkably, such assumption has led to the formulation of the holobiont concept, which identifies the human being as a complex organism composed by a large arsenal of prokaryotic cells that outnumbers eukaryotic cells by a factor of ten [3]. In this context, gut microbiota contributes to a great extent to host nutrition through energy harvest from the diet and vitamin biosynthesis [1,4,5•]. In addition, gut microbiota favors a wide range of host functions including, intestinal cell proliferation and differentiation, body's energy balance and pH control, development of the immune system and protection against pathogens [1,6,7]. Growing efforts have been done to characterize the components of the human microbiota using metagenomics approaches and culturomics. The gut microbiota originates during birth, and it is naturally acquired from the mother through a vertical transmission route [8]. In breast fed babies, the composition of the gut microbiota is further modulated by the action of natural prebiotic components such as milk oligosaccharides [9]. These early events in the establishment of gut microbiota are pivotal for the health of the newborn and deeply influence subsequent stages of adult life. In the last years, there has been a growing understanding on how alterations of the gut microbiota composition lead to the disruption of a microbial climax and are associated or predispose individuals to numerous disease conditions, including, inflammatory bowel diseases, irritable bowel syndrome, allergy and obesity [8,10,11]. In the human gut environment, the adaptive co-evolution of humans and bacteria may lead to the development of commensal relationships, where neither partner is disadvantaged or symbiotic relationships where unique metabolic traits or other benefits are provided. For this reason, members of the autochthonous microbiota also known as probiotic bacteria are provided as live supplements promoting some health host benefit, while food ingredients also known as prebiotics are consumed to induce the growth or activity of beneficial microorganisms.

In this review, we will discuss the current state of the art on the role of prebiotics, substances leading to host health benefits through a positive influence on gastrointestinal microbiota, and probiotics, live microorganisms that, when administered in adequate amounts, confer a health benefit on the host, in the management of gastrointestinal disorders.

Prebiotics: mechanisms of action and clinical implications

Over 20 years ago, Gibson and Roberfroid proposed for the first time the term prebiotic [12], to indicate dietary substances with the ability to modify host microbiota inducing benefit to the host. At that time, the best studied compounds in this category were fructans (fructooligosaccharides or FOS and inulin) and galactans (galactooligosaccharides or GOS), both acting thorough enrichment of native *Lactobacillus* spp. and/or *Bifidobacterium* spp. [12]. Other well characterized prebiotics are oligofructose, galactooligosaccharides, lactulose, and breast milk oligosaccharides. Most prebiotics are used as food ingredients mostly consisting of nonstarch polysaccharides and oligosaccharides [12]. Based on the definition recently proposed by the International Scientific Association for Probiotics and Prebiotics, a prebiotic is defined as 'a substrate that is selectively utilized by host microorganisms conferring a health benefit' [13••]. Because of the fact that prebiotics are not the only substances that may affect gut microenvironment, the feature of selective utilization differentiates prebiotics from other undigested dietary ingredients and compounds, such as antibiotics, minerals, and vitamins [13••]. Interestingly, recent studies using high-throughput sequencing technologies, as opposed to culture-based traditional research on gut microbial ecology, confirm the selectivity of the prebiotic fermentation [14,15]. These data showed that particularly, although not only, bifidobacteria selectively responded to the use of specific prebiotic compounds. In addition, other groups of bacteria were modulated by prebiotics, including *Faecalibacterium prausnitzii* that increased in abundance in one trial [14], *Anaerostipes* spp. and *Bilophila* spp., the first increased and the second decreased in a recent intervention study [15]. These data suggest that health benefits can derive not only from the stimulation of bifidobacteria and lactobacilli, but also from effects on other beneficial taxa including, for example, *Roseburia*, *Eubacterium* or *Faecalibacterium* spp. [13••,14,15]. The mechanism through which prebiotics confer benefits to host (Figure 1) has been suggested to be mediated by microbial metabolic products, the best studied of which are short-chain fatty acids (SCFAs) [13••,16]. SCFA, including acetate, propionate and butyrate, are well known to be linked to health outcomes. Other beneficial effects of prebiotics include the promotion of ion and trace element absorption, including calcium, iron and magnesium [16]. In addition, prebiotics enhance host immunity, increase IgA production and modulate cytokine production [16].

Several randomized controlled trials have assessed health benefits of orally administered prebiotics on healthy individuals or different target populations, in both acute and chronic diseases [13••,16]. The health endpoints of these studies (Figure 1) included functional gastrointestinal disorders (FGIDs), such as irritable bowel syndrome (IBS) and functional constipation; bowel habit and general gut health in infants; traveller's diarrhea; allergy; inflammatory bowel disease (IBD); hepatic encephalopathy; infections and vaccine response; immune function in elderly; necrotizing enterocolitis in preterm infants; urogenital health; skin health; bone health; absorption of calcium and other minerals; metabolic health (overweight and obesity; type 2 diabetes mellitus; metabolic syndrome and dyslipidemia) [13••,16]. There is high level of evidence indicating that nonabsorbable disaccharides, such as lactulose at the dose of 45–90 g/daily are beneficial in the prevention and treatment of hepatic encephalopathy [17,18]. The role of prebiotics in FGIDs, including IBS, is controversial since bacterial fermentation of carbohydrates can result in increased production of gas, thus increasing symptom experience [19,20]. Indeed, randomized controlled trials showed that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPS) reduce overall gastrointestinal symptoms, abdominal pain, bloating and passage of wind in patients with IBS [20–22]. Many FODMAPS contain fructose and, similarly to FODMAPS, prebiotics including inulin and FOS contain fructose that may produce side effects including bloating, flatulence or abdominal pain both in healthy subjects and in IBS [23,24]. GOS has been suggested to produce symptom improvement in patients with IBS, however, these data need to be confirmed [25].

Probiotics: mechanisms of action and clinical implications

The probiotic concept was proposed in 1908 by Russian Nobel laureate Elie Metchnikoff, who observed that the ingestion of fermented foods, particularly lactic acid bacteria, elicited beneficial effects on human health promoting longevity [16]. Since Metchnikoff's original findings, various studies confirmed the positive impact of probiotic strains on the health status of the host. According to FAO/WHO guidelines [26] and the most recent definition, probiotic bacteria are defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' [27••]. Their health promoting activities encompass numerous effects (Figure 1). Probiotics may prevent the overgrowth of pathogenic bacteria, increase the resistance of the gut to invasion by pathogens, improve epithelial barrier function, or ameliorate disease processes by inducing the secretion of soluble factors or the production of SCFAs [26,27••]. Although each one of the above mentioned functional claims is based on compelling basic evidence, the exact mechanism through which probiotics exert their beneficial actions in humans is only partially known, since these aspects have been evaluated mainly in preclinical studies or in small sample size trials, and the molecular mechanisms remain largely obscure [27••].