

Published in final edited form as:

*Curr Opin Biotechnol.* 2009 April ; 20(2): 135–141. doi:10.1016/j.copbio.2009.01.002.

## Mechanisms of Probiosis and Prebiosis: Considerations for Enhanced Functional Foods

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### Abstract

The technologies of metagenomics and metabolomics are broadening our knowledge of the roles the human gut microbiota play in health and disease. For many years now, probiotics and prebiotics have been included in foods for their health benefits, however we have only recently begun to understand their modes of action. This review highlights recent advances in deciphering the mechanisms of probiosis and prebiosis, and describes how this knowledge could be transferred to select for enhancing functional foods targeting different populations. A special focus will be given to the addition of prebiotics and probiotics in functional foods for infants and seniors.

### Keywords

probiotics; prebiotic; functional food; infant; seniors

### Introduction

Our knowledge regarding the microbial community that inhabits the human body is expanding at a rapid pace. New worldwide initiatives like sequencing of the human microbiome [1] along with rapid advances in metabolomics to detect and quantify the products of microbial metabolism [2] are contributing to a better comprehension of the role of symbionts in health and disease. For instance, activities of the gut microbiota are now known to play a central role in host energy requirements [3].

For well over a century, certain microorganisms have been regarded as probiotics, defined recently as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” [4]. Probiotics are largely administered through functional foods such as dairy products. Lactobacilli and bifidobacteria are currently the most marketed probiotic bacteria worldwide. Prebiotics, or “non-digestible food ingredients that beneficially affect the

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host by selectively stimulating the growth and/or activity of one or a limited number of bacteria that can improve the host health”[5], are an alternative (or adjunct) approach to probiotics and target indigenous beneficial bacteria already established in the gut.

As foods are supplemented with probiotics and new functional ingredients, it is important to understand the beneficial properties of these products and how they aim to improve human health. Here, we explain mechanisms of probiosis and prebiosis and describe how this knowledge can help to design food with improved functionality to target certain populations. Both probiotics and prebiotics have to be consumed regularly to expect to measure the health benefits reported on the related human studies.

## I. Mechanisms of Probiosis

The probiotic arsenal includes multiple mechanisms for preventing infection and enhancing the immune system and providing increased nutritional value to food (Figure 1). Each mechanism of action is strain-dependent, making it important to select and scientifically compare individual probiotics for their intended purpose(s).

### Probiotic protection against pathogens

Probiotics can enhance the host defense system against pathogens. The mucosal epithelial cell barrier is the first line of defense against pathogen attack that may be enhanced by the promotion of mucin production or reduction of gut permeability. Promoting mucin production and reducing intestinal permeability may prevent penetration of pathogenic organisms and toxic substances. Factors from probiotic microorganisms can increase mucin production in cell culture [6], prevent enteropathogen-induced epithelial cell injury [7], and reduce intestinal permeability in mice [8]. Certain proteins are important for probiotic adhesion to host cell surfaces and can obstruct pathogen adhesion to the same surface. For example, surface-layer (S-layer) proteins present on the surfaces of *L. crispatus* and *L. helveticus* were able to prevent adhesion of the foodborne pathogen, *Escherichia coli* O157:H7 to HeLa, HEp-2 and T84 cells [9,10].

Another line of probiotic defense against infection is the production of an array of antimicrobial compounds capable of inhibiting the growth of many foodborne pathogens. In general, lactic acid bacteria produce organic acids, predominantly lactate and acetate, which create an acidic environment that is inhibitory to pathogens. Probiotics can also synthesize proteins or peptides capable of inhibiting specific pathogenic strains. Many lactic acid bacteria produce well characterized inhibitory peptides which include, but are not limited to: lantibiotics (class I), peptide bacteriocins (class II), and bacteriolysins (class III) [11], however antimicrobial compounds produced by *Bifidobacterium spp.* are not especially well understood [12]. The probiotic, *L. reuteri*, produces an antimicrobial agent, reuterin. Reuterin has broad-spectrum activity against a variety of pathogens including bacteria, fungi, protozoa and viruses, and can be differentially expressed by various *L. reuteri* strains [13]. These antimicrobial compounds have potential applications as food preservatives or prophylactic agents against enteric infections.

### Immunomodulation by probiotics

Different strains of probiotics can either stimulate or suppress aspects of the immune response [14]. Probiotics can stimulate immunity by increasing mucosal antibody production, boosting pro-inflammatory cytokine expression and enhancing host defensin production. Suppressive effects are manifested by decreasing cytokine expression, systemic inflammation, cellular proliferation and increasing apoptosis. Surface proteins have been implicated as key factors involved in immunomodulation. For example, aggregation-competent (but not aggregation-

deficient) *L. crispatus* modulates the expression of innate immune receptors Toll-like receptor-2 and Toll-like receptor-4 on the surfaces of epithelial cells in the colonic mucosa of mice [15]. Also, mutant strains of *L. casei* deficient in cell wall-associated polysaccharides are unable to exert immunosuppressive effects on macrophage cytokine production as seen by the wild-type strains [16]. Probiotic bacteria are also known to secrete factors responsible for modulating immune responses. For instance, secreted factors from *L. reuteri* decrease nuclear factor- $\kappa$ B dependent gene expression, resulting in diminished cell proliferation and enhanced mitogen-activated protein kinase activities important for inducing apoptosis [17]. As fermented milk drinks are popular sources of probiotics, it is important to note that *L. helveticus* is capable of producing factors during milk fermentation responsible for increasing calcineurin expression, resulting in an augmented population of mast and goblet cells in the mouse GI tract [18].

### Delivery formulations and probiotics: special considerations

Probiotic concentrations and mechanisms can be affected in many ways from food processing to ingestion. Foods are altered by the production process, food matrix effects, digestion, and metabolism [19]. These factors ultimately affect the final form of food that reaches the target site. Microencapsulation can increase the survival and stability of bioactive ingredients through food processing, storage and GI transit [20,21]. However, only a limited number of studies have documented effects of probiotics in different food matrices and the possible synergies or inhibitions that could occur in the presence of other nutrients. Survival and activity of probiotics can be enhanced by encapsulation in the presence of prebiotics utilized by probiotics [5]. While food processing is a concern, cell survival through the GI tract is an important probiotic consideration. Recent genomic studies have highlighted the intrinsic ability of certain probiotics to resist bile and acid shock during GI transit [22,23]. The functionality of probiotics may be affected by food matrices and delivery strategies.

## II. Mechanisms of Prebiosis

The effects of prebiotics have been primarily directed toward the colon, but an increased amount of evidence demonstrates that prebiotics exert their effect beyond the GI tract [24]. Prebiotics selectively stimulate beneficial microbes within the gut microbiota. These compounds may directly stimulate immunity, protect against pathogens, and facilitate host metabolism and mineral absorption [24]. The different mechanisms of prebiotic action are summarized in Figure 2.

### Selective stimulation of beneficial bacteria

In the GI tract, prebiotics selectively stimulate indigenous beneficial bacteria such as bifidobacteria and lactobacilli. Current studies aim to understand the selective fermentation of prebiotics, such as fructooligosaccharides (FOS) and galactooligosaccharides (GOS). Investigation of the genes responsible for fermentation of prebiotics in lactobacilli and bifidobacteria has highlighted the role of specific enzymes and oligosaccharide transporters for degradation of prebiotics [25-28]. However, recent studies show that other gut commensals, such as *Faecalibacterium prausnitzii*, also have the ability to degrade these compounds, producing butyrate as an end-product of fermentation [29]. Products of prebiotic fermentation by lactobacilli and bifidobacteria, such as lactic and acetic acid, can be subsequently degraded by other bacteria such as *Anaerostipes caccae* or *Roseburia intestinalis* [30-32]. These close relationships between microbes explain the increase in short-chain fatty acids (SCFA), including butyrate, often seen in the presence of prebiotics, despite the fact that lactic acid bacteria fail to produce butyrate.

## Changes in SCFA affect immunomodulation and host metabolism

By changing the composition and functionality of the microbiota, prebiotics play a role not only by facilitating competitive exclusion of potential pathogens, but also in modulating the immune system and enhancing host defense [33]. SCFAs are able to improve mucosal morphology by increasing mucin production and decreasing translocation by binding to SCFA receptors on immune cells within the gut lymphoid-associated tissue (GALT) [33]. One SCFA especially, butyrate, has attracted ample attention as a product of prebiotic fermentation that inhibits the growth of colonic cancer cells *in vitro* [34]. SCFAs may be important in host metabolism as these compounds provide energy to the host. Butyrate is a primary energy source for colonocytes. SCFAs can bind to specific receptors, such as G-protein coupled receptor 41 (Gpr41). This receptor is a strong regulator of host energy balance whose effects are dependent upon the gut microbiota. [35]. Hepatic lipogenesis was reduced in Gpr41-deficient mice, consistent with reduced intestinal absorption and delivery of SCFAs. In rats, FOS increased intestinal hormone glucagon-like peptide-1 (GLP-1) levels in the portal vein, and proglucagon mRNA in the proximal colon leading to an increased satiety, as well as glucose tolerance and insulin sensitivity [36]. These different mechanisms illustrate the complexity of regulation of the immune system and host metabolism by prebiotics.

### Anti-adhesive prebiotics

An extension to the prebiotic concept is the use of oligosaccharides that selectively prevent adhesion of certain bacterial species by mimicking binding sites. Recent studies suggest that prebiotics can act as a decoy for pathogen-binding cellular receptors in the gut [37]. GOS reduced the adherence of enteropathogenic *E. coli* in HeP and CaCo-2 cells [38]. While this field of research is intriguing, no human trials have examined prebiotics in prophylactic studies and it warrants further investigation.

### Mineral absorption

Addition of prebiotics in food may offer other benefits by improving host absorption of minerals (like calcium or magnesium). Recent advances in this field show that inulin type-fructans enhanced calcium absorption primarily via the colonic mucosa in humans [39]. Crude fractions of chicory (a source of inulin) have shown improved bone parameters relative to native or reformulated inulin in rats, suggesting possible synergies between inulin-type fructans and other nutrients [40].

## III. Probiotics and prebiotics in foods tailored for specific populations

Food products have been developed for specific age groups such as infants or the elderly [41]. These populations are of particular interest due to the early immune development in infants and a marked decline in immune function (immunosenescence) in the elderly. Functional foods containing probiotics or prebiotics are quickly gaining attention in the U.S. We have used the U.S. market as an example for illustrating some tailored probiotic and prebiotic products for certain populations (Table 1).

### Probiotics and prebiotics in infants

Human trials have been performed in order to assess the effects of probiotics in a variety of disorders including infantile colic, infectious or antibiotic associated diarrhea, and atopic dermatitis [42-45]. Prebiotics are also relevant in infant nutrition, as formula-fed infants usually have lower numbers of bifidobacteria compared to the breast-fed infants [46] and many infant studies have shown prebiotic effects [46]. Prebiotics can simulate the bifidogenic effects of breast milk oligosaccharides and have been shown to exert long-term effects (up to 2 years) for protecting against infection and lowering the incidence of allergy [46,47]. GOS is one

prebiotic compound widely studied in infant feeding. In an effort to investigate the broad effects upon the host, a combination of two probiotics and two different GOS compounds have been tested using integrative metabolic profiling and modeling of multiple compartments in germ-free mice [2]. Unique changes in the host metabolism were triggered by combinations of prebiotics (two different GOS) and probiotics (*L. paracasei* or *L. rhamnosus*). These effects are intriguing, but more studies are needed to explore metabolic profiling following administration of prebiotics only.

### Probiotics and prebiotics in the elderly

The composition of the elderly intestinal microbiota differs from that of younger adults with higher numbers of detrimental bacteria at the expense of more beneficial groups [48]. This population is also prone to immunosenescence and an elevated risk of colon cancer. Both probiotics and prebiotics (GOS and FOS) have been tested successfully in the elderly, showing improved intestinal microbial composition and immune function [41,49-51]. The prebiotic inulin leads to elevated butyrate production and experimental evidence shows that this prebiotic can modulate colon cancer risk in human colonic epithelial cells, animals and in human intervention trials [34].

### Conclusions

As we begin to understand gut microbiome–host metabolic interactions and how they affect human health, probiotic and prebiotic supplementation are important strategies to modulate the gut microbiota and its metabolic output [52]. Probiotics and prebiotics may have systemic effects on the host immune system and metabolism, as revealed by integrative systemic metabolic and microbiome profiling. Recent studies have demonstrated the potentially extensive impact of prebiotics on the composition of the gut microbiota, stimulating directly or indirectly putative beneficial gut commensals other than lactic acid bacteria. Consequently, these findings open other exciting areas of research for the discovery of new probiotic strains and synbiotic combinations. Well-designed clinical studies in humans are still needed to further investigate the optimal dose, duration and specific effects of each probiotic strain and/or prebiotic when embedded in food matrices, for different populations such as infants and elderly that have a different gut microbial composition and immune status. By elucidating the mechanisms of probiosis and prebiosis, scientists can design enhanced functional foods tailored to improve host health.

### Acknowledgments

J.V. currently receives support from the National Institutes of Health (NIH) (NIDDK R01 DK065075; NCCAM R01 AT004326; NCCAM R21 AT003482), the Office of Naval Research, the Defense Advanced Research Projects Agency (DARPA), and Public Health Service Grant DK56338, which funds the Texas Medical Center Digestive Diseases Center.

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- of special interest
- of outstanding interest

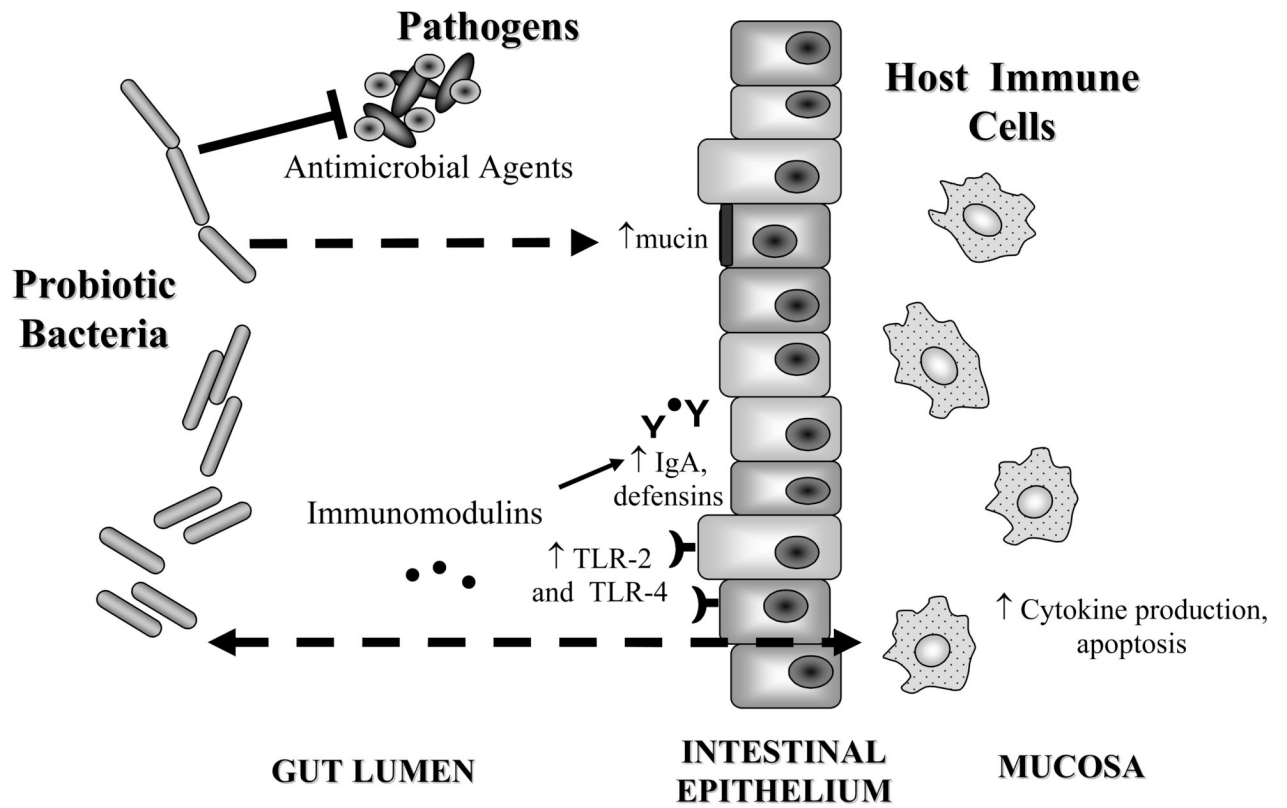
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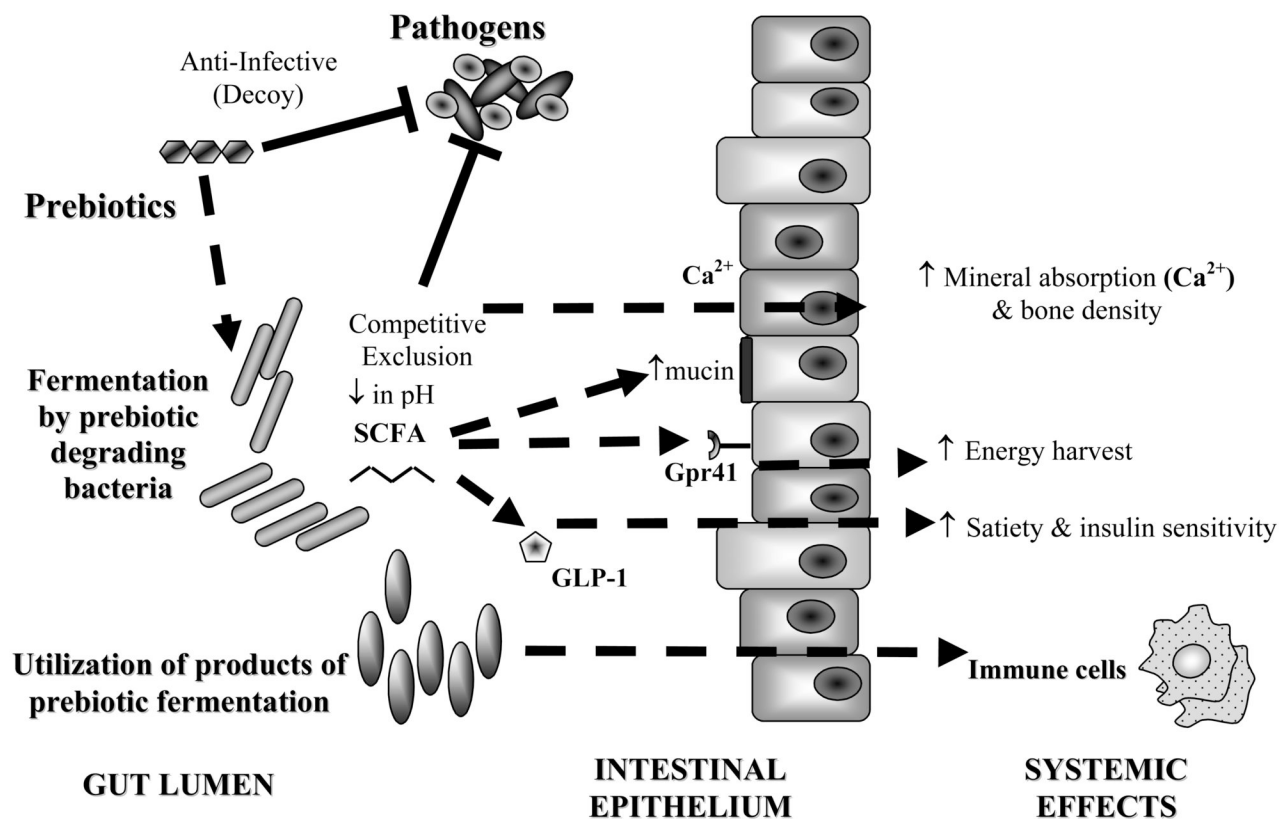
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**Figure 1. Depiction of the beneficial roles of probiotics in the mammalian gastrointestinal tract**  
 IgA: Immunoglobulin A; TLR: Toll-like receptor



**Figure 2. Depiction of the beneficial roles of prebiotics in the mammalian gastrointestinal tract and their systemic effects**

$\text{Ca}^{2+}$ : Calcium; GLP-1: Glucagon-Like Peptide-1; Gpr41: G-protein coupled receptor 41; SCFA: short-chain fatty acid.

**Table 1**  
**List of selected food products marketed in the USA containing probiotics and prebiotics**

Product	Functional Additive (Quantity per Serving when indicated)	Health Claim
<i>Infants and Children:</i>		
GOOD START® NATURAL CULTURES™ Infant Formula	<i>B. lactis</i>	Increases levels of key antibodies, and promote natural protective barrier in the digestive tract
Early Advance™ Infant Formula	Galacto-oligosaccharides	Help stimulate growth of healthy bacteria, which support developing immune system
BiogaiaAB Reuteri Drops	<i>L. reuteri</i> Protectis DSM 17938 (100 million)	Reduces infantile colic
DanActive™ Dairy Drink	<i>L. casei</i> DN-114001 Immunitas™	Strengthens body's defenses
Danimals® Yogurt	<i>L. rhamnosus</i> GG™	Positive effects on gastrointestinal and immune function, and oral health
Stonyfield Farm® Yo-Baby Yogurts	<i>L. bulgaricus</i> , <i>S. thermophilus</i> , <i>L. acidophilus</i> , <i>bifidobacteria</i> , <i>L. casei</i> , and <i>L. rhamnosus</i>	Helps aid in digestion and supports immune system
BiogaiaAB Probiotic Straw and LifeTop Cap	<i>L. reuteri</i> DSM 17938 (100 million)	Maintain overall gut health
<i>Adults and Elderly:</i>		
Activia® Yogurt	<i>B. animalis</i> DN-173 010 Regularis™	Regulates the digestive system by helping reduce long intestinal transit time
BiogaiaAB Probiotic LifeTop Cap	<i>L. reuteri</i> DSM 17938	Maintain overall gut health
BiogaiaAB Prodentis Chewing Gum and Lozenges	<i>L. reuteri</i> DSM 17938 and <i>L. reuteri</i> Prodentis ATCC PTA 5289	Reduces gingivitis
DanActive™ Dairy Drink	<i>L. casei</i> DN-114001	Helps strengthen body's defenses
LiveActive™ Cheese	<i>B. lactis</i> and <i>L. rhamnosus</i>	Replenish live cultures in digestive system, promoting digestive health
LiveActive™ Cottage Cheese	Inulin (3 g)	Serves as food source for probiotic bacteria
Silk plus for Bone Health Soy Milk	Fructan (1 g)	Helps promotes bone health
LiveActive™ cereals	Inulin (3 g)	Helps promote digestive health
Stonyfield Farm® Yogurts and Smoothies	<i>L. bulgaricus</i> , <i>S. thermophilus</i> , <i>L. acidophilus</i> , <i>bifidobacteria</i> , <i>L. casei</i> , and <i>L. rhamnosus</i>	Helps aid in digestion and supports immune system
Yo-Plus™ Yogurt	<i>B. lactis</i> Bb-12™ and Inulin	Help maintain healthy balance of friendly bacteria in digestive system