Prebiotics in the Development of the Infant Immune System

Simply stated, prebiotics are non-digestible nutrients that are selectively fermented by lactic bacteria, allowing these species to proliferate and predominate in the colon, which in turn provides benefits to the host\textsuperscript{10}. Important details are needed to fully understand the implications and the impact of these compounds, including the definition of prebiotics and the roles they play in the developmental physiology of infants. It is worth noting that prebiotics are \textit{not} the same as probiotics, which are living organisms that, when consumed, survive to reach the colon to provide a benefit to the host. This brief review will focus on prebiotics.

To understand the interest in prebiotics, it is necessary to understand the importance of human microflora, the microbes that inhabit the human gastrointestinal (GI) system. These microbes play an essential role in human physiology, particularly in relationship to the development of the immune system \textsuperscript{12,18}. They ferment undigested food and debris from cells soughed off from the GI epithelium to produce nutrients and energy. In addition, these microbes have direct and indirect interactions with the lymphocytes in Peyer’s patches and intraepithelial lymphocytes, which in turn communicate with specific lymphocytes in peripheral components of the immune system, and so affect the development of immunological responsiveness\textsuperscript{18}.

The establishment of these microbial populations in the GI tract begins early in life. In fact, breast-fed infants often have different populations of microflora than formula-fed infants. Breast-fed infants tend to have more lactic bacteria, such as \textit{Bifidobacteria spp} and \textit{Lactobacteria spp}, rather than other genera, including pathogenic strains such as \textit{Escherichia}, \textit{Staphylococcus}, \textit{Streptococcus}, and \textit{Clostridia}. In contrast, formula-fed infants tend to have more adult-like populations, especially \textit{Bacteroides}, and more of the pathogen-including genera\textsuperscript{13,15}. Obviously, there has been much interest in determining what component of breast milk leads to this difference in bacterial populations.

The key components of breast milk thought to perform this function are human milk oligosaccharides. A surprisingly complex group of molecules, these oligosaccharides are principally derived from lactose, with added molecules of galactose and N-acetylglucosamine, connected by chemical bonds that are non-digestible by human enzymes\textsuperscript{5,7,8}. These are not some
small component of breast milk, but rather a major component, comprising up to 12 g/L – more than the milk’s protein content. In colostrum, this figure can be as high as 20 g/L. These non-digestible oligosaccharides arrive at the colon, where they are selectively fermented by lactic bacteria. Upon fermentation, lactic bacteria secrete various combinations of the short-chain fatty acids acetic acid, propionic acid, and butyric acid. In addition to providing an important energy source for the epithelial cells of the colon, these fatty acids reduce the colonic pH. Strains such as *Escherichia*, *Staphylococcus*, *Streptococcus*, and *Clostridia* do not grow well in acidic environments, so lactic bacteria gain a competitive advantage, allowing them to become the predominant species.

Given this impact of human milk on colonic microflora, prebiotics are plant-derived or synthetic oligosaccharides that mimic the effect of human milk oligosaccharides. They generally consist of chains of 2-8 carbohydrates that are linked by bonds that are not susceptible to human enzymes. To meet the strict definition of a prebiotic, these oligosaccharides must be proven to be selectively fermented by lactic bacteria. That is, they must be shown to be fermentable by *Bifidobacteria spp* and *Lactobacteria spp*, and not by strains such as *Escherichia*, *Staphylococcus*, *Streptococcus*, *Clostridia* or *Bacteroides*. There are currently only three oligosaccharides that meet this definition: galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), and lactulose. The most common plant-derived prebiotic is inulin, a FOS found in many common fruits and vegetables. There are manufactured versions of GOS and FOS commercially available as well as plant-derived FOS, mainly from chicory. Increasing numbers of prebiotic-containing products can be purchased at the corner grocery, such as Liv·Active Crystal Light®, Liv·Active Post® cereal, and Depmster’s® Whole Grain Prebiotic Bread.

In the above discussion, it has been suggested that both human milk oligosaccharides and prebiotics are fermented by lactic bacteria, and additionally, human milk oligosaccharides stimulate the growth of lactic bacteria. Lactic bacteria may be responsible for the type of immunological development that potentially explains breast-fed infants having less allergy and fewer infections. Thus, there has been considerable research to determine if adding prebiotics to infant formula may provide some of these same benefits to the formula-fed infant. There are
now several studies showing that prebiotics do stimulate the growth of *Bifidobacteria spp* and *Lactobacteria spp*. Some of these studies use only GOS and some use a combination of 90% GOS and 10% FOS. Furthermore, *in vitro* studies show that when lactic bacteria are grown in prebiotics instead of glucose, it not only turns on the genes for the enzymes required for the intake and metabolism of these prebiotics, but also turns on the genes for the synthesis of fimbrial proteins. Fimbrial proteins are the structures bacteria use to attach to the colon wall, to colonize and become permanent residents of the colon.

The final piece of the story is the determination of the effect of prebiotics on immunological responses. A couple of studies have now demonstrated that infants who consume prebiotic-fortified formula have fecal secretory IgA levels similar to breast-fed infants and higher than infants fed formulas without prebiotics. Interestingly, one of these studies did include a group of infants fed probiotics, and the microbes did not appear to have the same effect on stimulating secretory IgA as the prebiotics, perhaps because they did not successfully colonize. Most recently, a study was published on infants with a family history of allergy (a parent or sibling with documented allergic disease) that were randomly assigned to receive formula with or without prebiotics for the first 6 months of life. The formula was an extensively hydrolyzed whey formula fortified with 8 g/L of either prebiotics (GOS: FOS, 90:10; n = 66) or maltodextrin (n = 68). After the 6 month experimental feeding period, infants were fed commercially available formulas or food. These infants were then followed for the first two years of life, and found to have a significantly reduced incidence of symptoms of allergy, including atopic dermatitis, recurrent wheezing, and urticaria. There was also a significantly reduced incidence of overall number of infections, upper respiratory tract infections, use of antibiotics, and episodes of fever. Interestingly, the authors describe the extensively hydrolyzed whey formula as hypoallergenic. If, in fact, this hypoallergenic formula did reduce the incidence of symptoms of allergy, then the prebiotic effect would be in addition to the hypoallergenic effect.

It should also be noted that novel ingredients, such as GOS and FOS, must be given GRAS (Generally Recognized As Safe) status by the FDA to be legally added to infant formula. This is an extensive and rigorous process requiring animal, adult and infant studies, and a thorough
review of the manufacturing process and facilities. This process is generally carried out by the manufacturer of the commodity that is added to formulas.

In summary, prebiotics are nondigestible carbohydrates, selectively fermented by beneficial species of lactic bacteria, acting like human milk oligosaccharides. Evidence indicates that when included in infant formula, prebiotics increase intestinal levels of these bacteria, which in turn stimulate maturation of the infant’s immune system, leading to increased fecal IgA, and decreased symptoms of allergy and infection.

References


15. Morelli L. Postnatal development of intestinal microflora as influenced by infant nutrition. J Nutr 2008;138:1791S-1795S.


