Mucus Degradation and Gut Microbes: Maintaining Gut Barrier Function in the Preterm Infant

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The gut epithelium acts as a barrier

The neonatal gut is rapidly colonized after birth by bacteria it encounters from its environment.[1] One of the major purposes of the gut epithelium is to prevent the translocation of these bacteria to the body and bloodstream. Complex cell-to-cell interactions and interlocking proteins that hold the epithelium together (tight junction proteins) help regulate this epithelium.[2] While gut epithelial cells themselves play a role as a physical barrier, they also secrete antimicrobial factors and mucin which help keep bacteria in the gut away from the epithelium itself. Antimicrobial proteins, like defensins and antibodies are secreted to enhance the barrier effect. Mucus also plays a critical role in helping to keep bacteria at a friendly distance and allow for diffusion of nutrients from the lumen to epithelial cells.[3]

The breakdown of intestinal barrier function is a major way by which pathogens invade the gut tissue, and long-term breakdown of gut barrier function (e.g. a "leaky gut") plays a role in many diseases such as infectious enteritis, inflammatory bowel disease, Crohn's disease, and neonatal bowel diseases including necrotizing enterocolitis (NEC).[3] While the etiology of NEC remains unclear, immature gut host defenses and intestinal dysbiosis are thought to play a critical role.[4] In the preterm infant, intestinal development continues to take place postnatally, and optimizing intestinal barrier function may be key in preventing diseases such as NEC.

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The gastrointestinal tract is the main system involved in the uptake of nutrients and water, and simultaneously serves as an essential barrier against harmful substances and pathogens from the environment. As part of this defense system, the large intestine is comprised of an inner mucus layer that separates the commensal bacteria from the host epithelium, and an outer, looser mucus layer that serves as the natural habitat for the commensal bacteria.[3] Components such as immune cells, the intestinal microbiota, and anti-microbial peptides all interact across this mucus barrier—safely away from the gut epithelium.

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Mucus as a key part of the gut barrier

Mucus itself is made up of glycoproteins (mucins), which are proteins modified by the addition of O-glycan groups made up of complex sugars.[5] Normally, a healthy gut epithelium excretes a thick mucus barrier between 150-300 microns thick in the large intestine. Therefore, because mucin is a protein, a lack of sufficient protein in the diet can reduce the secretion of mucins and the thickness of the mucus barrier. Especially in infants whose diets contain insufficient protein, such as preterm infants, this could contribute to the prevalence and severity of infection.[6]

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Bacteria in the gut often break down mucus when dietary fibers are inaccessible.[5] This breakdown releases sugars from the complex mucus glycoprotein, which attract potential pathogens. The consumption of these released sugars has been shown to play a role in both *C. difficile* and *Salmonella* infections, and the diffusion of these sugars creates a gradient that bacteria can follow toward the gut epithelium to cause infection.[7] However, only some species of bacteria can actually break down mucus. Among others, *Bacteroides* and *Akkermansia* are the primary mucus degraders in the human gut, along with some species of *Bifidobacterium*, such as *B. bifidum*.[8] These bacteria secrete enzymes that break apart the mucin glycan from the mucin protein and then consume the degraded sugars released from the protein, which thins the mucus barrier in the process. Among healthy adults, this represents a small burden on available energy, but in infants — and especially hospitalized infants — this could be a major contributor to energy deficits and blunt the efficacy of nutritional interventions.

Protecting the mucin barrier

In contrast, key infant-associated gut microbes like *Bifidobacterium longum* subsp. *infantis (B. infantis)* do not break down mucus. Recent clinical studies have shown that colonization by *B. infantis* EVC001 helps to reduce the abundance of mucus degrading taxa like *Bacteroides* and, in

concert with an exclusive human milk diet, help protect the mucus barrier in the gut.[9] These recent clinical studies show that colonization of the infant gut by *B. infantis EVC001* helps reduce the abundance of taxa which thrive on the breakdown of mucin glycans and produce compounds like lipopolysaccharide (LPS, or endotoxin) which trigger inflammation in the gut. *B. infantis* is highly efficient in metabolizing oligosaccharides found in human milk (HMO). This is advantageous in multiple regards, including increasing the production of acetate and lactate, which effectively lowers the intestinal pH and inhibits the growth of pathogenic bacteria.[10] These biochemical changes elicited by *B. infantis* are thought to be mechanisms by which *B. infantis* colonization reduces the abundance of mucus degrading bacteria and promotes a protective environment in the infant intestine.

There is a unique but limited opportunity immediately following birth during which the infant gut microbiome is established. In the absence of protective infant-adapted bacteria, such as *B. infantis*, there is optimal opportunity for mucin-degrading pathogenic bacteria to colonize the infant gut. Common medical interventions, such as C-section delivery and antibiotic administration may inhibit the transfer of *B. infantis* from mother to infant, which has led to the absence of this bacterium in the majority of infants born in developed counties today. To ensure colonization with this beneficial bacterium, and to inhibit growth of mucus-degrading pathogens, early supplementation with an activated form of *B. infantis*, such as the clinically studied strain *B. infantis* EVC001, is a safe and effective method of creating a protective intestinal environment in newborns.

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