

 PAEDIATRIC UROLOGY

# The milky way to prevent neonatal bladder infection

Human milk oligosaccharides (HMO) protect neonatal bladder epithelial cells from invasion by uropathogenic *E. coli* (UPEC), according to the latest study by a team of researchers led by Lars Bode and Victor Nizet at the University of California, San Diego.

UPEC are a major cause of UTI, and recurrent UTI exposes children to the risk of severe renal damage. Breastfed neonates, however, have a degree of protection from UTI, and the researchers surmised this might be due to the presence of HMO in human milk. Human milk has a substantial, complex and variable oligosaccharide content not yet reproduced in formula milk. A number of beneficial properties have been ascribed to HMO, including prebiotic intestinal bioflora regulation, provision of nutrients for brain development, modulation of immune function and inhibition of binding to cell surfaces by pathogens. Previous findings that HMO are absorbed in the neonatal gut and subsequently found in urine led researchers to investigate the role of HMO in protection of the bladder from UPEC.

UPEC initiate infection by binding to and invading bladder epithelial cells, with disruption of intracellular signaling cascades leading to cytotoxicity. Although HMO have been shown to act as decoy receptors for a number of pathogens, they were not found to affect attachment of UPEC to human bladder cells that were grown in monolayer cell culture. They did, however, significantly reduce both internalization of the bacteria into the epithelial cells and bladder cell cytotoxicity.

Infection with UPEC affects cellular levels of proteins involved in cell adhesion, signaling cascades and apoptosis. Some of these changes—to focal adhesion molecules, desmosome components, MAPK and NF- $\kappa$ B pathway phosphoproteins—were blocked by HMO treatment. Other effects, on the E-cadherin intercellular adhesion molecule and the caspase-3 apoptotic pathway, were not influenced by HMO.

Fractionation of HMO localized the active component to the acidic portion, and a single sialylated oligosaccharide was effective in blocking NF- $\kappa$ B activation. Galactooligosaccharides, which are not found in human

milk but are added to some formula milks, reduced UPEC invasion without preventing bladder cell death or activation of MAPK and NF- $\kappa$ B pathways. These results add to the body of evidence demonstrating the beneficial effects of human milk. However, there are many situations where breastfeeding is not an available option, so it is vitally important to improve the formulations of alternatives. Understanding the properties of the components of milk should allow selection of those with specific contributions, streamlining the creation of the next generation of formula milk.



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