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A milk oligosaccharide, 2'-fucosyllactose, may ameliorate necrotizing enterocolitis in preterm pigs

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Necrotizing enterocolitis (NEC), a severe intestinal disease occurring in 5-10% of hospitalized preterm infants, is associated with exaggerated tissue responses to the gut microbiota. Mother's milk decreases the risk of NEC, potentially due to bioactive compounds that modulate gut colonization and tissue responses. Human milk oligosaccharides (HMOS) are largely indigestible to infants but are found at concentrations up to 12 g/L in human breast milk, while only trace amounts are present in cow's milk. Important biological functions other than nutritional have been documented for several HMOs such as prebiotic, anti-inflammatory or anti-microbial actions. 2'-fucosyllactose (2'-FL), that accounts for 75% of the human milk HMOS, has been shown to have prebiotic effects on bifidobacteria while it potentially inhibit epithelial adhesion of pathogens due to structural homology with intestinal bacterial receptors. We hypothesized that a 2'-FL supplemented infant formula would modify the gut microbiota, decrease epithelial adhesion of pathogens and thereby reduce the risk of NEC. To test the hypothesis, we used a sensitive model with cesarean delivered preterm pigs that at a high proportion spontaneously develop NEC after 5 days of formula-feeding.

Twentyone newborn preterm pigs were fitted with umbilical catheters and orogastric tubes. Parenteral nutrition and minimal boluses of formula (3 mL/kg/3h) was given for 48 h followed by full enteral feeding (15 mL/kg/3h) with control formula (FORM, n=11) or 2'-FL fortified formula (2FL, 5 g/L, n=10). To standardize initial gut colonization, maternal fecal bacteria (2.5×10^4 cfu) were given as an oral inoculum with the first minimal formula bolus. On day 5, all pigs were euthanized for tissue collection and NEC evaluation.

Five 2'-FL-pigs (50%) and nine controls (82%) developed NEC (P=0.18) with a tendency to increased intestinal NEC-lesions in controls compared to 2'-FL-pigs (small intestine: 1.8±0.3 vs. 1.4±0.2, P=0.36; colon: 2.7±0.6 vs. 1.5±0.5, P=0.14). A 40% reduction of anaerobic bacteria was observed in cecum contents of 2'-FL pigs compared to controls ($1.6\times10^{10}\pm9.8\times10^9$ vs. $2.7\times10^{10}\pm2.6\times10^{10}$ cfu/mL) but the decrease was not significant (P=0.24). Bacterial density along the intestinal mucosa, as detected by fluorescence in situ hybridization of general bacteria, was similar between groups (P=0.68). Similarly, there were no significant effects of the 2'-FL on intestinal structure and function, as assessed by intestinal wet weight, proportion of mucosa, villus

height, in vivo lactose uptake capacity and brush border enzyme activities (sucrase, maltase, lactase, peptididases).

Adding 5 g/L 2’FL to infant formula, tended to decrease incidence and severity of NEC in preterm pigs. Since bacterial colonization and intestinal structural and functional parameters were not significantly affected, further investigations are needed to test if the given dose of 2’FL potentially modified tissue responses to colonizing bacteria and enteral feeding. It should further be investigated if other doses of 2’-FL may more efficiently alter bacterial colonization or mucosal responses to diets and bacteria and thereby increase NEC resistance in preterm neonates.

Conflicts of interest: David S. Newburg is affiliated with Glycosyn, the commercial partner donating 2’-FL for the studies.