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Metabolic engineer synthesizes key breast milk ingredient, makes research possible

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A University of Illinois microbial engineer has synthesized a sugar in human milk that is thought to protect babies from pathogens. That's important because 2FL, the shorthand scientists use to describe this human milk oligosaccharide (HMO), has not been added to infant formula because HMOs are incredibly expensive.

"We know these oligosaccharides play a vital role in developing a breast-fed baby's gut microbiota and in strengthening their immunity. 2FL (2-fucosyllactose) is the most abundant HMO in breast milk," said Michael Miller, a U of I professor of food microbiology.

To learn more about the HMO's function, Miller would like to do research with 2FL in newborn piglets, an excellent model for the human infant.

Unfortunately, 1 milligram of 2FL costs $100, meaning a single study would require $1 million for the HMO alone, he said.

Microbiologist, meet metabolic engineer. Yong-Su Jin, a departmental colleague and professor in the U of I's Institute for Genomic Biology, believed he could synthesize this oligosaccharide found in breast milk using a strain of *E. coli* engineered for that purpose.

A new postdoctoral researcher in Jin's laboratory had done some of the legwork for such a project in Korea, and they used their combined experience and expertise to engineer an HMO that can be produced very

cheaply and quickly: 1 gram of 2FL per liter of *E. coli* broth. That means it's possible to produce 2FL in the lab, making Miller's piglet research feasible, he said.

"*E. coli* makes a starting material for 2FL as part of its normal metabolism, and that suggested to us that it was possible to use *E. coli* to produce 2FL," Jin said.

"The trick is to get the *E. coli* cells to increase their production of the starting material (GDP-fucose), which we did by overexpressing the pre-existing biosynthetic pathway. Then we had to give it the ability to transfer GDP-fucose to lactose. We solved that problem by inserting a gene from another organism," he added.

The next step was developing an *E. coli* mutant that can assimilate lactose. "Because the engineered mutant cannot use the lactose for its own growth, it instead uses lactose to make great quantities of 2FL, the HMO that many researchers want to study," he said.

Miller will soon be able to begin a study investigating the role of 2FL in infant nutrition and eventually make recommendations about whether it should be added to infant formula. "And we can use this technique to synthesize and study the hundreds of other HMOs in human milk too."

The research has other interesting possibilities unrelated to infant nutrition, he said.

Jin and Miller believe that their work has pharmaceutical applications. "Adding 2FL to the food of soldiers on deployment could keep them out of sick bay. More than half of all soldiers in the field are incapacitated at some point with diarrheal illness caused by Campylobacter jejuni," Jin said.

A second use might be reducing the number of Campylobacter infections that originate in raw or undercooked poultry. "If chickens consumed poultry feed containing 2FL, pathogens would bind to this oligosaccharide instead of the mucosal lining of the bird's intestine and be eliminated well before the chicken arrived at your supermarket," Miller added.

More information: Whole cell biosynthesis of a functional oligosaccharide, 2'-fucosyllactose, using engineered Escherichia coli" was published in *Microbial Cell Factories* and is available online at www.microbialcellfactories.com/content/11/1/48

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