Mutation in zinc transport protein may inhibit successful breast-feeding

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Shannon Kelleher, Penn State associate professor of cellular and molecular physiology and colleagues found that mice lacking the zinc transporter ZnT2 had reduced mammary gland development and severe defects in function during lactation. Credit: Patrick Mansell, Penn State

Zinc plays an important role in a woman's ability to successfully breast-feed her child, according to health researchers.

It has long been known that zinc, an essential trace element, is passed to infants through mother's breast milk. The levels of zinc in mother's milk and the effects of zinc deficiency in infants have been previously studied, but the role of zinc in breast development and function in lactating mothers is a relatively new area of research.

The protein ZnT2 transports zinc in specific tissues in the body, including the mammary glands. Shannon L. Kelleher and colleagues have previously found that some women have mutations in ZnT2, and that when the protein does not function correctly, breast milk will have very low amounts of zinc, which can cause severe zinc deficiency in exclusively breast-fed infants. Their recent research on mice suggests that ZnT2 mutations may also cause other deficiencies in breast milk and may create difficulty for breast-feeding in general.

"This finding changes the paradigm," said Kelleher, associate professor of cellular and molecular physiology, Penn State College of Medicine. "It is no longer only about transporting zinc into milk, but now it's also about milk composition and milk production."

The researchers studied the function of ZnT2 by observing the development of mammary glands in mice—both with and without functioning ZnT2—reporting their results in the current issue of the *Journal of Biological Chemistry*. The group of mice lacking ZnT2 showed reduced mammary gland development and severe defects in function during lactation.

ZnT2 transports zinc by importing it into vesicles—small organelles within the cell—that then secrete zinc into the breast milk. Zinc is also necessary to trigger the growth of mammary glands, mammary epithelial

cells and secretion pathways. Kelleher and colleagues found that without functional ZnT2, zinc accumulates in the cytoplasm, becoming toxic to the cell.

"It is believed that 'breast is best,' but breast-feeding is hard to do," said Kelleher, pointing out that breast-feeding isn't instinctive, but is a learned behavior. "We believe that there is biology behind some breast-feeding issues. If we can identify women who will have trouble with breast-feeding while they're still pregnant (by identifying mutations in their ZnT2 proteins), then maybe we can help them better prepare before the baby comes."

If zinc is not transported by ZnT2, its absence impacts milk composition and volume. The researchers found that along with insufficient zinc levels in breast milk, mice without ZnT2 had significantly reduced beta-casein, fat and lactose in their milk. All are important for sustaining infant health. These mice were also unable to produce an adequate volume of milk for their offspring.

"We really need to better understand the biological factors of lactation," said Kelleher. "Seventy-five percent of mothers intend to breast-feed when they leave the hospital. Six months later, only 14 percent are still exclusively breast-feeding."

In the future, Kelleher hopes to sequence the gene that codes for ZnT2 in women to figure out how lactation is affected and how to help pregnant and lactating women who have ZnT2 mutations.

Kelleher is also associate professor of pharmacology and surgery, College of Medicine, and nutritional sciences, College of Health and Human Development. Sooyeon Lee, graduate student, nutritional sciences and cellular and molecular physiology; Samina Alam, research associate, cellular and molecular physiology and surgery, both at Penn

State; Stephen R. Hennigar, former graduate student, nutritional sciences, and currently a postdoctoral scientist, U.S. Army Research Institute of Environmental Medicine; and Keigo Nishida, research scientist, RIKEN Center for Integrative Medical Sciences, and assistant professor, pharmaceutical sciences, Suzuka University of Medical Science, all worked on this research as well.

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