How mammals fuel milk production may have implications for cancer

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A new study in the December issue of the journal *Cell Metabolism*, published by Cell Press, offers insight into the manner in which the mammary glands of mammals meet the incredible metabolic demands of milk production. As the normal pathways of breast development undoubtedly affect breast cancer, the findings may have therapeutic implications, the researchers said.

The researchers found that one of three "isoforms" of the gene known as Akt is specifically required for lactating mice to synthesize sufficient quantities of milk to support their offspring. While the loss of so-called Akt1 does not lead to structural abnormalities, they found, mothers deficient for the gene exhibit a disruption of the coordinated metabolic changes that normally occur at the onset of lactation.

"The developmental program that prepares the mammary gland for lactation is among the most critical and highly conserved in mammals, as provision of nutritional support is essential for the survival of offspring," said Lewis Chodosh, lead author of the study at the University of Pennsylvania School of Medicine. "Given its remarkable importance, it has been a relatively understudied field."

"Our studies demonstrate that Akt1 is required for orchestrating many of the dramatic developmental changes in metabolism that occur in the mammary gland at the transition from pregnancy to lactation."

Although breast cells do not proliferate during lactation after the initial

24 hours, the metabolic demands and synthetic capacity of the lactating mammary gland exceed that of any other tissue, the researchers explained.

“The breast is one of the few scenarios in which metabolism isn’t tied to the proliferation or growth of cells,” Chodosh said. “The breast is an unusual organ that’s essentially a synthetic factory for milk. There’s nothing else like it.”

During a typical 21-day course of lactation, a mouse will produce its entire body weight in lipid as well as three times its total body weight in milk, which consists of lipid, protein, and lactose. To accomplish this, two distinct developmental programs must be executed: first, cells must proliferate and differentiate to form the structures that will ultimately serve as the site of milk synthesis, the researchers said. Second, mammary epithelial cells must coordinately activate multiple biosynthetic pathways—as well as deactivate pathways that break lipids down—in order to have the metabolic capacity to synthesize large quantities of milk.

Earlier studies by the researchers found that the protein kinase Akt1 rises in concentration during pregnancy and lactation, suggesting a potential developmental role for the kinase in milk production. Another study showed that permanent activation of Akt1 in the mammary glands of mice leads to early lipid accumulation during pregnancy, raising the possibility that the gene might be important in the increased synthetic demand for lipid during lactation.

To further investigate, in the current study, the researchers examined mice lacking either Akt1 or the related gene Akt2, which are expressed in the same areas of the mammary gland at distinct developmental stages. While Akt1 protein increases during pregnancy and lactation, Akt2 levels decline.

Indeed, the researchers found that the mammary gland cells of Akt1-deficient mice failed to engage critical metabolic pathways during the transition from pregnancy to lactation, which in turn led to other deficiencies. Specifically, the mammary cells failed to increase their uptake of glucose, cells' primary energy source, and their synthesis of lipid. The cells also did not lower the level of enzymes that break down lipids.

As early as two days after birth, pups nursed by mice lacking Akt1 weighed significantly less than those nursed by normal mothers. That difference in weight only grew more exaggerated with time. In contrast, the researchers reported, the offspring of Akt2-deficient mice gained weight normally.

The researchers further showed that the mice without Akt1 displayed a four-fold reduction in milk secretion compared to either normal mice or mice lacking Akt2.

The findings represent some of the first to reveal functional differences between Akt1 and Akt2, the researchers said. The new findings show that Akt1 is uniquely essential for lactation and establish a role for the isoform in glucose metabolism, a function earlier linked almost exclusively to Akt2, they said.

The findings may have important implications for cancer therapy, as the Akt pathway is also one of the most commonly activated in cancer, Chodosh said.

"The metabolic demands of the lactating mammary epithelial cell bear many similarities to those of tumor cells in that pathways controlling energy generation as well as carbohydrate, protein, and lipid synthesis must be coordinated to support the anabolic processes central to growth," the researchers wrote. "In this regard, Akt1's ability to act as a central

regulator of nutrient uptake and utilization is consistent with the frequent observation of constitutive activation of the PI3K/AKT pathway in a wide range of human cancers, including those of the breast."

Cancer cells also commonly exhibit increased rates of glucose uptake as part of a shift toward a greater reliance on that sugar's breakdown for energy, a phenomenon known as the Warburg effect. Such increased glycolytic metabolism in tumors is associated with increased tumor aggressiveness and poor prognosis, the researchers said.

"Our findings demonstrating a physiological requirement for Akt1 in the control of glucose and lipid metabolism further implicate Akt1 activation as a potential mediator of the Warburg effect and reinforce the importance of efforts to design pharmacologic agents that will inhibit this pathway in tumors."

Source: Cell Press

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