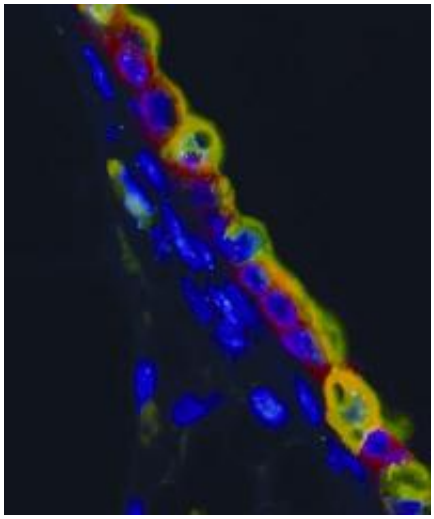
New insights on control of pituitary hormone outside of brain has implications for breast cancer

1 October 2012



Turning on Akt1 in breast epithelial cells (red, yellow) of a virgin mouse for 96 hours causes them to to terminally differentiate and produce milk (green, yellow). Nuclei are shown in blue. Credit: Chien-Chung Chen, Lewis Chodosh, Perelman School of Medicine, University of Pennsylvania

The hormone prolactin is produced by the pituitary gland in the brain and then travels via the bloodstream to cells throughout the body, where it exerts multiple reproductive and metabolic effects, most notably on the breast where it is the master regulator of lactation. In recent years researchers have found that prolactin is also produced by some tissues outside the brain, however little is known about the functions of extra-pituitary prolactin or how its production is regulated in these tissues.

Now, the laboratory of Lewis A. Chodosh, MD, PhD, chair of the Department of Cancer Biology at the Perelman School of Medicine, University of Pennsylvania, reports in *Genes & Development* that activation of the PI3K-Akt oncogenic signaling pathway in the mammary glands of mice rapidly induces cells in the breast itself to produce prolactin. This, in turn, triggers Stat5 activation, mammary epithelial differentiation and milk production in virgin mice within a matter of hours.

"Remarkably, these changes occur in the absence of any of the complex hormonal changes or developmental programs that normally accompany pregnancy" explains Chodosh.

Consistent with a physiological role for prolactin outside of the brain, the Penn team found that mice bearing mutant Akt genes fail to activate Stat5 or initiate lactation when they give birth due to an inability to synthesize and secrete prolactin in the mammary gland, despite normal levels of circulating prolactin in the blood.

These findings provide the first demonstration that the synthesis and secretion of mammary gland prolactin is regulated by PI3K-Akt signaling and identify a physiological function for extra-pituitary prolactin during a critical developmental stage that is essential for the survival of mammalian offspring.

What's more, prolactin has long been thought to play a role in human breast cancer, however this has typically been assumed to be due to circulating prolactin produced by the pituitary. Since the PI3K-Akt signaling pathway is commonly activated in human cancers, this new finding suggests the important possibility that prolactin produced by the breast itself may play a role in breast cancer. In fact, mammary prolactin has been detected in some human breast cancers. As such, investigators have proposed that prolactin produced by the mammary gland – rather than by the pituitary – may play a direct role in the development of breast cancer, for example by providing pro-growth or pro-survival signals to cancer cells in the breast. Accordingly, anti-cancer drugs aimed at blocking

the effects of prolactin are currently under development.

"Since the PI3K-Akt pathway is one of the most commonly activated oncogenic pathways in human cancer, its identification as an upstream regulator of prolactin production in the mammary gland has intriguing potential implications for understanding the pathology of human breast cancer and as well as improving its treatment," notes Chodosh.

Provided by University of Pennsylvania School of Medicine