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Lactation protein suppresses tumors and metastasis in breast cancer, scientists discover

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A protein that is necessary for lactation in mammals inhibits the critical cellular transition that is an early indicator of breast cancer and metastasis, according to research conducted at the University at Buffalo and Princeton University and highlighted as the cover paper in November issue of *Nature Cell Biology*.

"This is the first confirmed report that this protein, called Elf5, is a tumor suppressor in breast cancer," explains Satrajit Sinha, PhD, associate professor of biochemistry in the UB School of Medicine and Biomedical Sciences and a corresponding author on the paper with Yibin Kang, PhD, in the Department of Molecular Biology at Princeton University.

The researchers say the findings provide new avenues to pursue in treating and diagnosing breast cancer and possibly cancers of other organs as well. The paper includes findings from both animal and human breast cancer models.

Under normal circumstances, Elf5 is a transcription factor that controls the genes that allow for milk production.

But when the researchers used knockout mice developed at UB, in whom Elf5 was removed, they found more than just an inability to produce milk. They found that epithelial cells in the mammary glands also

became more mesenchymal, that is, more like stem cells, an early harbinger of cancer, Sinha says.

"We found that when Elf5 levels are low or absent, epithelial cells become more like stem cells, morphing into mesenchymal cells, changing their shape and appearance and migrating elsewhere in the body," says Sinha. "This is how cancer spreads."

The UB-Princeton collaboration began when lead author Rumela Chakrabarti, PhD, originally a postdoctoral researcher in Sinha's laboratory at UB, took a position in the laboratory of Yibin Kang, PhD, Warner-Lambert/Parke-Davis Professor of Molecular Biology at Princeton, whose research focus is breast cancer metastasis. This allowed Chakrabarti to harness the expertise of the two laboratories to generate such a breakthrough finding.

"Elf5 keeps normal breast cells in their current shape and restricts their movement," says Chakrabarti. She found that the protein accomplishes this by suppressing the epithelial-mesenchymal transition by directly repressing transcription of Snail2, a master regulator of mammary stem cells known to trigger the EMT.

"Elf5 keeps Snail2 repressed, but once Elf5 is lost, then there is nothing to repress Snail 2," she explains.

The paper notes that Elf5 loss is frequently detected early in the disease at the breast hyperplasia stage, when the number of cells increases. In experiments conducted by the Princeton scientists, the researchers also found that little or no Elf5 in human breast cancer samples correlated with increased morbidity.

"It seems that loss of Elf5 is an initial event in the disease, so it could also be an important diagnostic tool," Sinha notes, which is a current

focus of the UB and Princeton team.

"We want to know, how early does the loss of Elf5 occur? Could we use loss of Elf5 as a reliable diagnostic tool?" he asks.

The finding reveals the complex pathways through which breast cancers develop, he says, while also providing new avenues to pursue for diagnostics and treatments.

"Our research shows that the EMT-Snail 2 pathway is a valuable one to target for early breast cancer intervention," says Sinha, "possibly by designing something to recapture the repressive effect of Elf5 or a drug that could mimic Elf5 activity. And this is just one molecule, part of a big network. That's why we are now creating a detailed map of this molecule and its associated partners in order to give us a better idea of what to look for."

Provided by University at Buffalo