Normal stem cells made to look and act like cancer stem cells

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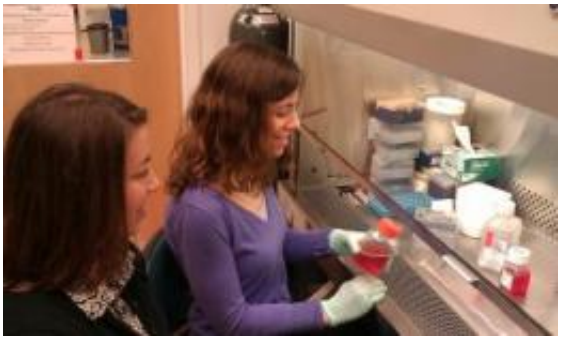

From left to right are study co-first authors Nicole Vincent Jordan and Amy N. Abell, Ph.D. Credit: Photo by Les Lang/UNC School of Medicine

Researchers at the University of North Carolina at Chapel Hill School of Medicine, after isolating normal stem cells that form the developing placenta, have given them the same properties of stem cells associated with an aggressive type of breast cancer.

The scientific first opens the door for developing novel targeted therapies aimed at triple negative breast cancer. Known also as TNBC, this is a highly recurrent tumor that spreads aggressively beyond its original site in the breast and carries a poor prognosis for patients who have it.

The study will be published online Friday, May 6, by the journal *Cell Stem Cell*.

"We changed only one amino acid in normal tissue stem cells, trophoblast stem cells. While they maintained their self-renewal, these mutant stem cells had properties very similar to what people predict in cancer stem cells: they were highly mobile and highly invasive," said Gary Johnson, PhD, professor and chair of pharmacology at UNC and senior study author. "No one has ever isolated a stem cell like that." Johnson is also a member of the UNC Lineberger Comprehensive Cancer Center.

In normal development, epithelial stem cells called trophoblasts are involved in the formation of placental tissue. To do so, they must undergo a conversion to tissue-like cells. These then travel to the site in the uterus where they revert to a noninvasive tissue cell. "But the mutant trophoblast stem cells made in our lab, which would normally invade the uterus and then stop, just keep going," Johnson said.

The study led by the first authors, research assistant professor Amy N. Abell, PhD and graduate student Nicole Vincent Jordan, both working in Johnson's lab, showed that similar to triple-negative breast cancer stem cells, normal tissue stem cells also go through the same program of molecular changes during organ development called epithelial mesenchymal transition, or EMT. This suggests that breast cancer cells utilize this tissue stem cell molecular program for tumor metastasis, or cancer spread.

The discovery was made using a unique mouse model of tissue stem cell EMT developed in the Johnson laboratory. The study identified two proteins that regulate the expression of specific genes in tissue stem cells during organ development that control normal EMT. Inactivation of the proteins MAP3K4 and CBP in trophoblast stem cells causes them to become hyperinvasive.

In collaboration with Aleix Prat, PhD and Charles Perou, PhD in the

UNC Lineberger Comprehensive Cancer Center, the research team made another discovery: an overlap between the gene expression signature of the mutant tissue stem cells properties during EMT and the triple-negative human breast cancer gene signature that's predictive of invasiveness. The same genes were downregulated.

"This significant genetic intersection between tissue stem cells and TNBC has identified previously unrecognized genes that likely contribute to breast cancer metastasis," said Johnson. "This newly identified gene signature is currently being investigated in different models of breast cancer with the goal of developing new therapeutic interventions for the treatment of TNBC."

Provided by University of North Carolina School of Medicine