A transcription factor called SLUG helps determines type of breast cancer

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During breast-tissue development, a transcription factor called SLUG plays a role in regulating stem cell function and determines whether breast cells will mature into luminal or basal cells.

Studying factors, such as SLUG, that regulate stem-cell activity and breast-cell identity are important for understanding how breast tumors arise and develop into different subtypes. Ultimately, this knowledge may help the development of novel therapies targeted to specific breast-tumor subtypes.

Stem cells are immature cells that can differentiate, or develop, into different cell types. Stem cells are important for replenishing cells in many tissues throughout the body. Defects that affect stem-cell activity can lead to cancer because mutations in these cells can cause uncontrollable growth. Some transcription factors regulate the differentiation or "programming" of breast stem cells into the more mature cells of the breast tissue. Abnormal expression of these transcription factors can change the normal programming of cells, which can lead to imbalances in cell types and the over-production of cells with enhanced properties of stem cells.

Breast tissue has two main types of cells: luminal cells and basal cells. Transcription factors, like SLUG, help control whether cells are programmed to become luminal cells or basal cells during normal breast development. In cancer, transcription factors can become deregulated, influencing what type of breast tumor will form. In aggressive basal-type

breast tumors, SLUG is often over-expressed.

Previous work led by Charlotte Kuperwasser, principal investigator and senior author, determined that some common forms of breast cancer originate from luminal cells, whereas rare forms of breast cancer originate from basal cells. This difference in origins suggests that genes that affect the ability of a cell to become luminal or basal may also affect the formation of breast tumors. Because SLUG can regulate breast-cell differentiation, Kuperwasser's team investigated SLUG's role in breast-cell differentiation and tumor growth.

How the Study Was Conducted: The research team reduced the expression of the SLUG gene in human-derived breast cells and then used cell-sorting techniques to separate the cells into groups of luminal, basal, and stem cells. Next, they used mathematical modeling to measure the rate and frequency that each of the three cell types changed into another cell type. By comparing the rates between control cells and cells in which SLUG was reduced, the team was able to determine the role of SLUG in luminal-, basal-, and stem-cell transitions.

To test the result of their mathematical model, the research team examined and compared breast-tissue samples from mice in two groups: a control group with normal SLUG and an experimental group that did not express SLUG. Mammary glands from the experimental and control groups were analyzed for changes in structure, the amount and distribution of luminal and basal cells in the gland, and whether these cells had stem-cell activity.

The SLUG-deficient mice exhibited defects in breast-cell differentiation. The mammary glands of these mice had too many luminal cells and defective basal cells that had luminal-cell characteristics. The control group of normal mice had a normal ratio of luminal to basal cells.

The SLUG-deficient mice showed defects in stem-cell function: Specifically, tumor formation and tissue regeneration was inhibited, an indication of defective stem cells, suggesting that SLUG was necessary to maintain normal luminal and basal cells within the mammary gland.

Additionally, SLUG-deficient cells when transplanted could not regenerate the mammary gland of the mouse, suggesting that SLUG is necessary for mammary stem-cell function. Tumor formation was also inhibited in SLUG-deficient mice, suggesting that SLUG may affect stem-cell activity necessary for tumor formation.

First author Sarah Phillips, a Ph.D. student in genetics at the Sackler School of Graduate Biomedical Sciences at Tufts University: "The study gives us insight into a potential source of cellular imbalance in breast tissues that can become cancerous. It also builds on the relationship between the levels of SLUG and the levels of cells that are associated with aggressive cancers. Breast cancer is very complex biologically, but any information we can find that could reduce this cellular over-growth could eventually be another tool to treat breast cancer at its sources."

More information: Phillips et al., Cell-State Transitions Regulated by SLUG Are Critical for Tissue Regeneration and Tumor Initiation, *Stem Cell Reports* (Available online 24 April 2014 In Press, Corrected Proof) dx.doi.org/10.1016/j.stemcr.2014.03.008

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