'Basal-like' breast cancer does not originate from basal stem cells

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New research uncovers a case of mistaken identity that may have a significant impact on future breast cancer prevention and treatment strategies. The study, published by Cell Press in the September 3rd issue of the journal *Cell Stem Cell,* suggests that despite their "stem cell-like" characteristics, most aggressive breast tumors are not derived from normal mammary gland stem cells.

The glandular tissue of the breast contains two main cell types, outer "basal" cells and inner "luminal" cells. The basal layer consists mostly of differentiated cells with a small population of mammary stem cells. The luminal layer contains differentiated cells and several types of cells which are intermediates between the luminal cells and stem cells. The different cell types can be identified and separated on the basis of specific molecular markers.

"In breast cancer, it has been proposed that different tumor subtypes may originate from different stem and intermediate cells, with more aggressive 'basal-like' breast cancers originating from basal stem cells and less aggressive breast cancers from the luminal intermediates," explains senior study author, Dr. Matthew J. Smalley from The Breakthrough Breast Cancer Research Centre at the Institute of Cancer Research in London. "Strikingly, the vast majority of breast tumors with mutations in BRCA1, a breast cancer susceptibility gene, have basal-like characteristics, suggesting a stem cell origin."

More recently, however, it was demonstrated that increases in abnormal

luminal intermediate cells are associated with BRCA1 mutations and that there are similarities between the genes switched on in normal human luminal intermediate cells and basal-like breast cancer cells. "To resolve the true origin of BRCA1 breast cancer, we designed the first direct comparison of the effects of creating identical BRCA1-associated tumor predisposing events in basal stem versus luminal intermediate cells," says Dr. Smalley.

Specifically, the researchers deleted the BRCA1 gene in mouse basal stem cells or luminal intermediate cells. They discovered that although BRCA1 deletion caused tumors to form from both basal stem cells and luminal intermediate cells, only the latter had features that were identical to both human BRCA1 tumors and the majority of human basal-like breast cancers not associated with BRCA1 mutations.

Taken together, these findings suggest that the majority of so-called basal-like breast cancers are derived from luminal intermediate cells and not from basal stem cells as was originally expected. "Our results highlight luminal intermediate cells as a key to understanding the origins of basal-like breast cancer," concludes Dr. Smalley. "This has important implications for treatment and prevention strategies for this aggressive disease."

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