Destined for disease: Breast cancer mutation regulates cell fate

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A new study sheds light on why individuals who inherit a particular family of mutations have a high risk of developing a very aggressive form of breast cancer. The research, published by Cell Press on February 4th in the journal *Cell Stem Cell*, shows that breast tissue cells from these individuals make abnormal cell-fate decisions even before cancer develops and provides exciting new insights into the mechanisms behind one of the most lethal types of breast cancer.

There are many forms of human breast cancer. Mutations in the BRCA1 tumor suppressor gene are associated with the development of the "basal-like" subtype of breast cancer which exhibits a very poor prognosis. "Recent evidence has indicated that BRCA1 might regulate breast cell differentiation," explains senior study author Dr. Charlotte Kuperwasser, Associate Professor in anatomy and cellular biology from Tufts University School of Medicine and member of the Sackler School of Graduate Biomedical Sciences at Tufts. "We wanted to examine whether BRCA1's role in differentiation was associated with the increased development of basal-like breast cancer."

Dr. Kuperwasser's group examined disease-free breast tissues from patients with normal or mutant BRCA1 genes. Using an ingenious strategy that allowed them to mimic the environment of intact human breast tissue, they transplanted the human cells into mice and looked at the types of tumors that formed after the cells were exposed to additional cancer-promoting signals. Although the cells with normal BRCA1 grew into different kinds of breast cancer, the cells from

women with BRCA1 mutations mostly formed the aggressive basal-like tumors. Importantly, molecular analysis of disease-free breast cells with mutated BRCA1 revealed that even before tumors developed, the mutant cells were more likely to remain immature and contain elevated levels of a protein called Slug. The researchers showed that when Slug is present in the breast, cells are unable to undergo proper maturation and are stalled in a premature state of development. This premature state of development is subsequently retained in basal-like breast cancers.

These findings show that BRCA1 mutations significantly impact breast cell maturation even before the patients manifest an increased risk for breast cancer. In a sense, the BRCA1 mutation "stacks the deck" towards a basal-like tumor phenotype by biasing differentiation towards this state. "Future studies will be necessary to fully dissect the precise domains and mechanisms by which BRCA1 regulates breast epithelial differentiation," concludes Dr. Kuperwasser. "In addition, further experiments will be needed to determine whether certain mutations in BRCA1 affect differentiation and regulate cell fate differently and whether different mutations alter the propensity for the development of basal-like tumors."

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