MedicalXpress

A new molecular mechanism in breast cancer development

November 15 2011

About 10% of breast cancers are due to mutations in genes called BRCA1 and BRCA2. However, the molecular mechanism by which alteration of these genes greatly increases the risk of cancer is not fully understood. In a new study, published Nov. 15 in the online, open-access journal *PLoS Biology*, an international team led by Miquel Àngel Pujana, of Bellvitge Biomedical Research Institute (IDIBELL) and the Catalan Institute of Oncology (ICO), and Christopher Maxwell, now at the Child and Family Research Institute, has made an important step towards revealing the underlying pathways.

The researchers found a key interaction between BRCA1 and another protein called RHAMM (encoded by the HMMR gene). These two proteins act on a previously unknown molecular mechanism that regulates epithelial cell polarity. The researchers have shown that BRCA1 and RHAMM control the normal development of breast epithelial cells. If one or both of these genes have mutations, then the normal architecture and development of breast cells is altered in ways that increase the risk of a specific tumor type appearing.

"BRCA1 mutation carriers are at high risk for breast cancer," said Pujana, "but these mutations exhibit variable penetrance, which can be in part explained by other genetic factors such as the identified variant in HMMR." A common genetic variant of HMMR slightly increases (approximately 1.1-fold) the risk of breast cancer in women carrying BRCA1 mutations. "Therefore, by itself, this variant does not justify a genetic analysis," explains Pujana.

But as shown by other CIMBA (Consortium of Investigators of Modifiers of BRCA1 and BRCA2) investigators, if other mutations are added which also slightly modify the risk -- and about twenty are known now -- then "it may vary considerably the risk of developing breast cancer in these women. Depending on the combination of genetic modifier variants that are inherited, the risk of developing cancer might be increased or decreased. " The researchers initially discovered the effect of HMMR by genetic analysis of affected families. Then they went on to analyse the roles of these genes in breast cells and their effects when mutated or functionally perturbed. They found that RHAMM and BRCA1 interact with proteins known to control key aspects of cell polarity and the cell division cycle, perhaps explaining why certain types of breast cancer have characteristic cell morphology and cell proliferation characteristics.

The investigation of these genetic variants is directed towards developing more accurate genetic models that can predict the risk of cancer in women who carry BRCA1 or BRCA2 mutations, and thus to help them to take appropriate preventive measures. Variants are also associated with different types of tumors, with important implications for patient prognosis.

More information: Maxwell CA, Benìtez J, Gòmez-Baldò L, Osorio A, Bonifaci N, et al. (2011) Interplay between BRCA1 and RHAMM Regulates Epithelial Apicobasal Polarization and May Influence Risk of Breast Cancer. PLoS Biol 9(11): e1001199. doi:10.1371/journal.pbio.1001199