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New findings may improve treatment of inherited breast cancer

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Scientists have identified some of the elusive downstream molecules that play a critical role in the development and progression of familial breast cancer. The research, published by Cell Press in the October 10th issue of the journal *Molecular Cell,* also identifies a compound found in grapes and red wine as an excellent candidate for treatment of some forms of breast cancer.

About 8% of breast cancer cases are caused by mutations in tumor suppressor genes, such as breast cancer associated gene-1 (BRCA1). BRCA1 is the most frequently mutated tumor suppressor gene found in inherited breast cancers and BRCA1 mutation carriers have a 50-80% risk of developing breast cancer by age 70.

"Although work with animal models of BRCA1 mutation has provided some insight into the many biological processes linked with BRCA1, very little is known about the downstream mediators of BRCA1 function in tumor suppression," says lead study author Dr. Chu-Xia Deng from the Genetics of Development and Diseases Branch at the National Institutes of Health.

Dr. Deng and colleagues were interested in investigating the relationship among BRCA1, SIRT1 and Survivin. SIRT1 is a protein and histone deacetylase involved in numerous critical cell processes including metabolism, DNA repair and programmed cell death, known as apoptosis. Although SIRT1 has been implicated in tumorigenesis, no concrete role in cancer initiation or progression has been identified.

Survivin is an apoptosis inhibitor that is dramatically elevated in many types of tumors. Research has suggested that Survivin may serve to maintain the tumor and promote growth.

The researchers found that BRCA1 functioned as a tumor suppressor by maintaining SIRT1 expression, which in turn inhibited Survivin expression. When BRCA1 was not functioning properly, SIRT levels decreased and Survivin levels increased, allowing BRCA1-deficient cells to overcome apoptosis and undergo malignant transformation.

They went on to show that the compound resveratrol strongly inhibited BRCA1-mutant tumor growth in cultured cells and animal models. Resveratrol is an important constituent of traditional Japanese and Chinese medicine that has recently been shown to inhibit some types of cancer by inducing apoptosis with very little associated toxicity. In the current paper, resveratrol enhanced SIRT1 activity, this leading to reduced Survivin expression and subsequent apoptosis of BRCA1 deficient cancer cells.

These findings identify SIRT1 and Survivin as downstream mediators of BRCA1-regulated tumor suppression and identify resveratrol as a potent inhibitor of BRCA1-mutant cancer cells. "Resveratrol may serve as an excellent compound for targeted therapy for BRCA1 associated breast cancers," says Dr. Deng.

Source: Cell Press