MedicalXpress

Abnormalities in new molecular pathway may increase breast cancer risk

June 17 2013

A new molecular pathway involving the gene ZNF365 has been identified and abnormalities in that pathway may predict worse outcomes for patients with breast cancer, according to data published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"Genomic instability is an increased tendency for abnormal changes in DNA, like the addition of extra copies of chromosomes, DNA breaks and mutations," said Ji-Hye Paik, Ph.D., assistant professor in the Department of Pathology and Laboratory Medicine at Weill Cornell Medical College in New York, N.Y. "Because these genetic abnormalities increase the chances for developing a tumor, it is fundamentally important to understand the molecular basis of genomic instability in cancer for prognosis and therapy."

Telomeres are segments at the end of the chromosome that protect the chromosome from deterioration. As the length of the telomeres shortens, they activate cell death, mediated by the tumor suppressor gene, p53. This process is critical in the suppression of cancer, and dysfunctional telomeres can cause chromosomal abnormalities and cancer.

Using cells designed to be cancer-prone because of defective telomeres, Paik and colleagues demonstrated that p53 activates ZNF365 to maintain genomic stability. The researchers found that cells deficient in ZNF365 showed signs of incomplete doubling of DNA, causing abnormal cell division and unequally divided chromosomes. They concluded that

because ZNF365 promotes the timely resolution of cell division, its loss led to an abnormal number of chromosomes called aneuploidy, which is implicated in many diseases including cancer.

"Our study is the first to demonstrate molecular mechanisms underlying the p53–ZNF365–telomere pathway and to show how alterations in this pathway may lead to increased cancer risk," said Paik. "Understanding this pathway provides novel therapeutic opportunities for cancers."

To understand the role of ZNF365 in cancer, Paik and colleagues used data available from The Cancer Genome Atlas (TCGA) and analyzed the expression of ZNF365 in 49 triple-negative breast cancers (TNBCs)—the most aggressive form of breast cancer—and 300 non-TNBCs. They found that expression of ZNF365 was lowest in TNBCs, and it remained high in non-TNBCs.

Using data from a larger cohort of 2,978 women from TCGA, the researchers also found that among women who had a 10-year, relapse-free survival, those with a high expression of ZNF365 had a 26 percent higher survival advantage. Further, when the researchers analyzed for the presence of ZNF365 in a tissue microarray containing 18 normal breast tissues, 141 TNBCs and 145 non-TNBCs, ZNF365 was present in normal breast tissues and non-TNBCs, but its expression declined in TNBCs.

According to Paik, this study is the first to determine the expression of ZNF365 in different types of breast cancers, and because it predicts disease prognosis, ZNF365 may be a potential biomarker for patient stratification.

Provided by American Association for Cancer Research