Subtle changes in PTEN tumor suppressor gene can determine cancer susceptibility

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It is an accepted fact that genetics play a key role in a person's susceptibility to cancer, and that throughout life, mutations can cause damage to tumor suppressor genes (TSGs) further increasing the chances of developing cancerous tumors.

Now a new study led by scientists at Beth Israel Deaconess Medical Center (BIDMC) demonstrates that even subtle changes in expression of the PTEN tumor suppressor gene can significantly increase cancer susceptibility in specific tissues, suggesting that environmental factors, such as diet or exposure to carcinogens, may have a more dramatic influence on tumor development than previously recognized. Appearing in this week's Advance On-line issue of Nature Genetics, the findings propose a new model for the role of tumor suppressor genes in the onset of cancer and could prove valuable in the development of diagnostic tests targeted to these gene alterations.

"More than 30 years ago, it was proposed that a person's susceptibility to cancer was dependent on a 'two-hit' model," explains Pier Paolo Pandolfi, MD, PhD, Director of the Cancer Genetics Program at BIDMC and George C. Reisman Professor of Medicine at Harvard Medical School. This meant that there had to be two genetic alterations of a single tumor suppressor gene (TSG) to activate tumor development - one gene would be missing from birth, while the second would be lost to other factors during one's lifetime.

"Our study adds another dimension to this Knudsonian model [so-named

for its creator, cancer geneticist Alfred Knudson] demonstrating that cancer susceptibility can be driven in specific tissues by a progressive -- but slight -- continuum reduction in tumor suppressor levels," explains Pandolfi. "Consequently, subtle modulation of TSG levels can result in increased cancer susceptibility. This implies that any factor that affects PTEN levels - chemicals, diet, other carcinogens - could increase tumor susceptibility, even in the absence of a full blown genetic mutation."

Tumor suppressor genes function to slow down cell division, repair DNA and help alert damaged cells when it is time to die, and PTEN is one such example. (In addition to preventing uncontrolled cell growth, PTEN is also responsible for controlling cell movement or migration, controlling the adhesion of cells to surrounding tissues and helping to control the formation of new blood cells.) But, when TSGs are absent or malfunctioning - as is the case of a genetic mutation - cells can multiply too quickly, growing out of control and leading to the development of cancerous tumors.

In recent years, with the advent of functional genomics, the idea that subtle changes in TSG levels could influence tumor development had been proposed but not formally investigated. To test this hypothesis, the Pandolfi team created a mouse model of PTEN that expressed the gene at approximately 80 percent of total levels. Next, they used a gene targeting approach which drives a transcriptional interference of the PTEN gene, resulting in inefficient protein production. The authors report that the presence of one targeted allele resulted in approximately 80 percent of PTEN expression relative to the normal level of PTEN expressed in specific tissues - in this case, mammary gland tissue. And, as predicted, the scientists subsequently identified an increased incidence of mammary tumors in these mice, and through a careful histopathological and molecular analysis were able to demonstrate that mammary tumors maintained both the targeted and wild-type PTEN alleles intact.

"These mice showed mammary cancer at a high incidence and in the absence of further alterations to the PTEN gene," explains Pandolfi. "This confirms that the PTEN gene is a 'quasi-insufficient' tumor suppressor, such that even a subtle 20 percent decrease in gene expression is sufficient to impair its full tumor-suppressive activity."

This discovery, say the authors, is tremendously relevant for how genetic alterations in cancer are detected, studied, evaluated and treated. "From a diagnostic perspective, our findings encourage the implementation of quantitative methods to evaluate cancer gene expression levels, and the design of therapies oriented to target these alterations," they write. Adds Pandolfi, "Our immediate aim is to develop a genetic test to be used for the screening of patients at risk of developing breast cancer. Such a test might also be useful in predicting the outcome of certain treatments [i.e. Trastuzumab] for breast cancer patients."

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