

## Screening approach leads to discovery of gene linked to breast cancer

June 14 2007

---

Using a novel three-part screening process, scientists at Dana-Farber Cancer Institute have identified a gene that is made inappropriately in about a third of all breast cancers. The discovery, reached in collaboration with researchers at Brigham and Women's Hospital (BWH) and the Broad Institute of Harvard and MIT, is reported in the June 15, 2007 issue of the journal *Cell*.

Unlike breast cancer-susceptibility genes such as BRCA1 and BRCA2, the newly identified gene, called IKBKE, is not inherited in a mutated form that increases the risk of developing breast cancer at an early age. Rather, the mutation arises during a woman's life, causing an overproduction of the IKBKE protein. That, in turn, spurs cell growth and proliferation. The mutation is found in 30-40 percent of all breast cancers, making it a prime target for future drugs for the disease.

The method used to home in on the gene -- a combination of three existing experimental approaches -- offers an elegant solution to one of the major hurdles of genome-age research: how to sift through the multitude of genes identified by advanced screening technology as potential cancer-causers to find those with the most profound role in the disease. As such, the new approach can be used to discover genes associated with many types of cancers, the study's authors state.

"The genetic material within many human cancer cells is in such disarray that there can be numerous gene mutations," says the study's co-senior author, William Hahn, MD, PhD, of Dana-Farber, BWH, and the Broad

Institute. "Current technologies -- particularly 'microarray' sensors, which read the activity and changes in thousands of genes at a time -- enable us to locate dozens or even hundreds of gene abnormalities in cancer cells. The challenge is to winnow this group to find the genes most centrally involved in cancer initiation and maintenance.

"In the current study, we used several complementary approaches to identify an important breast cancer gene," he continues. "Each method helps 'filter' the information from the previous one, enabling us to zero in on the strongest candidate."

Hahn and his colleagues focused on a class of proteins known as kinases, which serve as molecular "starting guns" for chemical reactions within cells. Overproduction of certain kinases has been linked to a variety of cancers. To determine which, if any, kinases play a role in breast cancer, investigators conducted a sequence of experiments to refine their results.

They began with a cell protein called Ras, a courier of signals from the cell surface to the interior. Abnormalities in Ras or its partner proteins -- including kinases -- occur in the vast majority of "epithelial" cancers, which, like breast cancer, arise in the lining of bodily tissues. Ras transmits signals to a variety of "downstream" proteins -- among them, proteins called MEK or PI3K. When both of these become active at the same time, cells become cancerous, investigators found.

The team then created a set of 354 human kinases and injected each into normal epithelial cells to see if any mimicked PI3K's ability to transform them into cancer cells. They found five that did.

To narrow this field, investigators conducted a second group of screening procedures. Using a variety of genome-scale approaches, they sought to determine if genes for any of the five kinases were unusually abundant in cancer cells. They found extra copies of IKBKE, but not of

the other genes -- and correspondingly high levels of the IKBKE protein. This pointed to IKBKE's role as a breast cancer oncogene.

In the third part of the study, the investigators explored whether breast cancer cells depend on IKBKE for survival. In an earlier study, they had used a technique called RNA interference -- whose discovery was recognized with the Nobel Prize in Medicine and Physiology last year -- which uses bits of genetic material to systematically stifle certain genes. With a high-throughput version of this technique, they found that when IKBKE was switched off, the cancer cells tended to stop proliferating and died.

"This triple screening approach enabled us to study what happened to cells when IKBKE was turned on and when it was shut off, and to take a global look at the genetic alterations within breast cancer cell lines and tumors," Hahn says. "Integrating these techniques allowed us to identify a new breast cancer oncogene and show that it plays a crucial role in the formation and survival of tumors."

The discovery that mutated IKBKE helps sustain a sizable percentage of breast cancers may spur the development of new treatments for the disease, Hahn remarks. Drugs able to target the oncogene and shut it down could offer an effective therapy for women whose tumor cells harbor the mutation.

The three-stage approach to finding breast cancer genes may be used in other forms of cancer as well, Hahn continues. "Our study provides a framework for integrated genomic methods of oncogene discovery."

Source: Dana-Farber Cancer Institute

Citation: Screening approach leads to discovery of gene linked to breast cancer (2007, June 14)  
retrieved 23 April 2024 from  
<https://medicalxpress.com/news/2007-06-screening-approach-discovery-gene-linked.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.