Study pinpoints novel cancer gene and biomarker

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The ultimate goal of her work, says Lynda Chin, is translating discoveries into a form that is clinically useful for patients. Photograph by Sam Ogden/Dana-Farber Cancer Institute

(PhysOrg.com) -- Dana-Farber Cancer Institute scientists' discovery of a cancer-causing gene - the first in its family to be linked to cancer - demonstrates how the panoramic view of genomics and the close-up perspective of molecular biology are needed to determine which genes are involved in cancer and which are mere bystanders. The findings are reported in the June 25 issue of the journal *Nature*.

"In the coming years, we can expect genomic studies [which chart the activity of thousands of cell genes] to generate hundreds or thousands of genetic elements of interest in cancer research," says the study's senior author, Lynda Chin, MD, of Dana-Farber. "To narrow that group to the

genes that actually drive cancer growth and metastasis, it's necessary to do functional studies, which focus on what individual genes do to turn a cell cancerous, and mechanistic studies, which examine how they turn cells cancerous and in what setting. It is a long and intensive effort that will leverage knowledge from different fields and different model systems."

In the study, Chin, lead author Kenneth Scott, PhD, of Dana-Farber, and their colleagues worked their way through a series of experiments -- in yeast cells, multiple types of human cancer cells, laboratory cell cultures, and mouse models - to demonstrate that a surplus of a gene known as GOLPH3 can spur cancer cell growth in a variety of tissues. It is the first gene associated with the Golgi complex, a tiny packaging plant that prepares proteins for their journey within and outside the cell, which has been found to play a role in cancer. Chin's team also found that the protein made from GOLPH3 may serve as a biomarker for tumors that can be effectively treated with the chemotherapy drug rapamycin: tumors with a high level of the protein are more apt to shrink in response to the drug than those with low levels.

The study began with an observation made years ago that a section of chromosome 5p13 is often duplicated, or amplified, in cancers of the lung, ovary, breast, and prostate gland, as well as melanoma. The presence of this abnormality in so many different types of cancer led Chin and her associates to take a closer look at that stretch of chromosome to see what genes reside there.

Using a method called genomic qPCR that can pick out specific sequences of DNA, they found four genes in the amplified region, two of which, GOLPH3 and SUB1, were expressed at high levels, due to the increase in gene copy. To determine whether both, or either, of these genes are involved in cancer, they conducted "loss of function" tests, in which they lowered each gene's activity in a set of lab-grown tumor cells.

"When we 'knocked down' GOLPH3 expression [or activity] by 95 percent, it significantly inhibited the ability of these cell lines to grow in a semi-solid condition, a cancerous quality that normal cells do not typically share," Chin says. "Knocking down SUB1 to a comparable level had only a minimal effect."

Intriguing as this finding was, it was hardly enough to prove that GOLPH3 is an oncogene -- a contributor to cancer when overexpressed within a cell. Demonstrating that would require several experiments to ensure that GOLPH3 itself, and not a nearby "shadow" gene, is responsible for the effects. Next came gain-of-function studies to see whether revving up GOLPH3 activity can turn a non-cancerous cell cancerous. It did in both mouse and human cells.

"All these results enabled us to build a case that GOLPH3 is an oncogene," Chin states. But there was a problem. "This information wasn't very helpful for achieving our ultimate goal, which is the translation of our findings into a form that is clinically useful for patients."

Despite their discovery that GOLPH3 can promote cancer, researchers didn't know what the gene's role is in normal cells. "There was literally no information on what it does," Chin remarks. The only hint was that the protein it encodes -- designated GOLPH3 -- is found in the Golgi network.

The team's first attempt to uncover GOLPH3's role -- using gene expression profiling to see how protein levels track with various cell functions -- was fruitless. So the researchers ran experiments with yeast cells to see which proteins share GOLPH3's cell neighborhood and which proteins it interacts with.One such partner was found to be VPS35, a component of a structure called the retromer complex. The complex's job is to recycle the antenna-like receptors that dot the cell

surface.

From the many genetic screening tests that have been done in yeast, researchers knew that flaws in the retromer complex can cause cells to be vulnerable to rapamycin, just as excess GOLPH3 can. Rapamycin is known to interfere with a protein called TOR, whose job is to control yeast cell size. This suggested that the retromer complex in yeast is important for chemical signals sent to and from TOR.

Chin's team theorized that mammalian GOLPH3 also works with the retromer complex to control the activity of TOR in mammal cells (where it's known at mTOR). To test this idea, the investigators found that knocking down GOLPH3 reduced cell size just as rapamycin did. They followed those experiments with biochemical studies to explore how GOLPH3 affects cell size.

The team next sought to answer whether high GOLPH3 levels cause tumor cells to be more susceptible to rapamycin in animal studies. They took two sets of human melanoma skin cancer cells -- one of which had excess GOLPH3 and the other had normal levels -- implanted them in animals, allowed them to grow into tumors, then treated them with rapamycin. "In the animals where GOLPH3 was overexpressed, the cancer cells grew much faster, but the tumors were much more responsive to rapamycin," Chin notes, "suggesting the tumor-promoting effect of GOLPH3 is dependent on mTOR signaling."

Lastly, the team considered whether the same mechanism might be at work in human cancer cells. An experiment analyzing human tumor tissue for specific proteins suggested yes. The researchers found that non-small cell lung cancer cells with too many copies of the GOLPH3 gene also had abnormally high levels of mTOR activity. "The mechanistic relationship we'd identified in the mouse system is also at work in human tumors," says Chin, who is also an associate professor at Harvard

Medical School.

In addition to identifying GOLPH3 as a bona fide oncogene and an indicator of whether rapamycin is likely to be effective against specific tumors, the study points to the need to follow genomic studies with a rigorous examination of the biological purpose and operation of potential cancer genes, Chin concludes. "Only then can we turn our intriguing discoveries in the cancer genome into something that is useful to cancer patients."

Source: Dana-Farber Cancer Institute

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