

Cancer cells need normal, nonmutated genes to survive

May 28 2009

Corrupt lifestyles and vices go hand in hand; each feeds the other. But even the worst miscreant needs customary societal amenities to get by. It's the same with cancer cells. While they rely on vices in the form of genetic mutations to wreak havoc, they must sustain their activity, and that requires equal parts vice and virtue.

According to a new study in the May 29 issue of *Cell*, [cancer cells](#) rely heavily on many normal proteins to deal with stress and maintain their deviant state. Researchers at Harvard Medical School and Brigham and Women's Hospital used a technique called [RNA interference](#) (RNAi) to dial down the production of thousands of proteins and determine which were required for cancer cell survival.

"Cancer cells actually leverage many genes that don't harbor mutations to maintain their malignant lifestyles," says first author and postdoctoral researcher Ji Luo. "These genes probably help them deal with the problems that develop as a result of the inappropriate presence of growth and survival signaling in tumor cells."

Being a cancer cell isn't easy. Think of all the [DNA replication](#) and [protein production](#) involved, not to mention the abnormal architecture of a tumor, which deprives cells of oxygen. Survival requires a complete kit of [stress response](#) tools.

"Researchers often characterize cancer cells as oncogene addicts, but they're just as reliant on normal genes that alleviate stress," explains

senior author Stephen Elledge, a professor at HMS and Brigham and Women's Hospital. "These stress management genes deserve attention as potential therapeutic targets."

In recent years, the National Cancer Institute has supported an ambitious effort to understand the molecular basis of cancer by sequencing cancer genomes. Elledge and Luo note that this Cancer Genome Atlas project would miss the stress management genes.

"If these genes are intact, they won't stand out when you compare the [DNA sequences](#) of cancer cells with normal cells," says Luo.

So the team took a different approach to test their "non-oncogene addiction" hypothesis. They acquired two human cell lines, identical in every way except for one—the presence or absence of a Ras oncogene. Ras mutations are prevalent in many deadly cancers, and researchers have not been successful in developing drugs against the dangerous gene.

The team used molecules called shRNAs to interfere with the production of thousands of normal, healthy proteins in the two cell lines. They gave the cells time to divide and sifted through the data to determine which proteins were required for survival. (In the past, labs relied on large robots to complete these types of screens, but Elledge and others have refined the technology in an effort to make RNAi affordable and accessible. Luo conducted his genome-wide screen in test tubes without the aid of a robot.)

Despite their similarities, the two cell lines responded differently to a number of shRNAs. That is, normal cells tolerated low levels of a particular protein while cells with the Ras mutation perished. Luo validated 50 of these hits in a second pair of cell lines. Dozens of these represent brand new therapeutic targets.

"This opens the door to using a drug cocktail approach to treat tumors driven by Ras mutations," says Elledge, who is also an investigator with Howard Hughes Medical Institute. "We might be able to tinker with the levels of these proteins and cripple cancer cells without hurting normal [cells](#) in the body, though this needs to be tested in tumor models."

"This type of functional approach complements the physical mapping of cancer genomes, but provides a much more direct path to new anti-cancer drug targets," adds Luo. "The genes that are critical for maintaining the malignant state will really crystallize when we combine forces."

Source: Harvard Medical School ([news](#) : [web](#))

Citation: Cancer cells need normal, nonmutated genes to survive (2009, May 28) retrieved 19 April 2024 from

<https://medicalxpress.com/news/2009-05-cancer-cells-nonmutated-genes-survive.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.