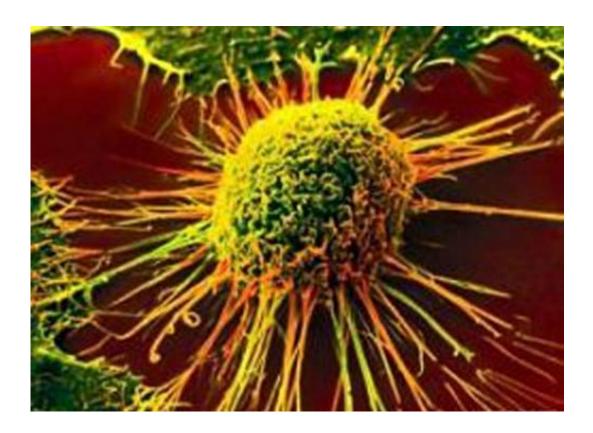


## New class of RNA tumor suppressors identified

November 23 2015



A pair of RNA molecules originally thought to be no more than cellular housekeepers are deleted in over a quarter of common human cancers, according to researchers at the Stanford University School of Medicine. Breast cancer patients whose tumors lack the RNA molecules have poorer survival rates than their peers.



The RNA molecules directly associate with and inhibit a well-known, <u>cancer</u>-associated protein called KRAS, the researchers found. In their absence, KRAS becomes hyperactive and issues continued signals to the cell to divide.

"This is the first time an RNA molecule in this class has been shown to act as a powerful <u>tumor suppressor</u>," said Paul Khavari, MD, PhD, professor and chair of dermatology at Stanford. "It does so by inhibiting the function of one of the most powerful cancer-causing proteins in the cell."

Khavari is the senior author of the study, which will be published online Nov. 23 in *Nature Genetics*. The lead author is Zurab Siprashvilli, PhD, a senior scientist at Stanford.

An oncogene is a gene that, when mutated, can cause cancer. The mutated gene creates a malfunctioning protein that encourages a cell to divide uncontrollably or enables it to sidestep the normal breakpoints that would halt cell division or launch a cellular suicide program to protect the organism.

The KRAS protein is a product of an oncogene. The protein sits on a cell's outer membrane and functions as an on-off switch to control cell division. Normally, it helps cells respond appropriately to external signals calling for cell growth. When mutated, however, it encourages the cell to undergo repeated rounds of cell division. KRAS mutation is an essential step in the development of many human cancers.

## **Deadly deletions**

The RNAs studied by the researchers are small, noncoding RNAs known as snoRNAs. Unlike the more familiar messenger RNA molecules that carry protein-making instructions from the DNA in the nucleus to the



outer cellular machinery called ribosomes, noncoding RNAs fulfill other necessary cellular functions. SnoRNAs are known to help assemble the ribosomes themselves, for example. Siprashvilli and his colleagues were interested in learning what role snoRNAs might play in the development of human cancers.

To do so, they compared 5,473 tumor genomes with the genomes obtained from surrounding normal tissue in 21 different types of cancer. In many ways, <u>cancer cells</u> represent biology's wild west. These cells divide rampantly in the absence of normal biological checkpoints, and, as a result, they mutate or even lose genes at much higher rate than normal. As errors accumulate in the genome, things go ever more haywire.

The researchers found that a pair of snoRNAs called SNORD50A/B had been deleted in 10 to 40 percent of tumors in 12 common human cancers, including skin, breast, ovarian, liver and lung. They also noted that <u>breast cancer patients</u> whose tumors had deleted SNORD50A/B, and skin cancer patients whose tumors made lower levels of the RNAs than normal tissue, were less likely than other similar patients to survive their disease.

"We were searching for areas of the genome that are highly abnormal in cancer cells," said Khavari, who is the Carl J. Herzog Professor of Dermatology. "We were very surprised to find SNORD50A/B so frequently deleted in so many different kinds of cancer. They are deleted as often as other very well-known tumor suppressor genes."

Because snoRNAs are best known for their role as housekeepers, it was surprising to find SNORD50A/B so directly implicated in human cancer. Khavari and his colleagues investigated to see if the RNAs were associated with any particular proteins in the cancer cells.



"Stunningly, we found that these RNAs associate with proteins in the RAS family, and specifically KRAS," Khavari said. "This is really last thing we would have expected. It was particularly surprising because my lab has been studying KRAS intensively for more than a decade, so it was quite a coincidence."

## Goading cancer cells to divide

Siprashvilli set out to find out more about the interaction between KRAS and SNORD50A/B. He found that when he deleted SNORD50A/B in human melanoma and lung cancer cells grown in the lab, the cells divided more quickly and displayed more cancerous traits than when SNORD50A/B was present.

Finally, they showed that when SNORD50A/B binds to KRAS, it inhibits the protein's ability to associate with an activating molecule called farnesyltransferase. Farnesyltransferase modifies the KRAS protein in such a way to allow it to travel to the cell's membrane to await external signals for growth and division.

"Normally, SNORD50A/B and farnesyltransferase work together to balance KRAS' function and allow it to respond appropriately to external signals," Khavari said. "When SNORD50A/B are missing, the balance is tilted toward KRAS hyperactivation."

In other words, when the genes for SNORD50A/B are lost from the genome, KRAS is free to goad the tumor cells to undergo repeated rounds of <u>cell division</u>.

Khavari pointed out that many pharmaceutical companies have been striving unsuccessfully to find a way to block farnesyltransferase's ability to activate KRAS. Understanding the role of the SNORD50A/B RNAs in this process could open new doors to blocking KRAS function in



cancer.

**More information:** The noncoding RNAs SNORD50A and SNORD50B bind K-Ras and are recurrently deleted in human cancer, *Nature Genetics*, DOI: 10.1038/ng.3452

## Provided by Stanford University Medical Center

Citation: New class of RNA tumor suppressors identified (2015, November 23) retrieved 19 April 2024 from <a href="https://medicalxpress.com/news/2015-11-class-rna-tumor-suppressors.html">https://medicalxpress.com/news/2015-11-class-rna-tumor-suppressors.html</a>

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.