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MicroRNA "Safety Switch" Prevents Spread of Cancer

Researchers have found a tiny snippet of RNA that acts as a molecular safety switch, to prevent the spread of many cancers. Without the RNA switch keeping it in check, a cancer-promoting enzyme is freed to trigger the spread of prostate cancer. Researchers suspect the RNA may have similar effects on breast, brain, ovarian, lung, and colon cancers.

Diagnostic tests for levels of this safety switch, called microRNA-101 (miR-101), in tumors might predict the likelihood that cancer will spread. It might even be possible to revert tumors to a less aggressive state by reintroducing miR-101 into cells, the researchers said.

"For treatment purposes, our studies suggest that replacing miR-101 in solid tumors that have lost it could reduce their metastatic properties."

— **Arul M. Chinnaiyan**

Led by Howard Hughes Medical Institute investigator Arul Chinnaiyan, the researchers published their findings November 13, 2008 in *Science Express*, the early online version of the journal *Science*. Chinnaiyan is at the University of Michigan Medical School, and other co-authors were from the Michigan Center for Translational Pathology, the National Cancer Centre in Singapore, and the Genome Institute of Singapore.

The discovery of the microRNA switch sprang from the researchers' interest in an enzyme called EZH2. The Chinnaiyan laboratory and others had previously established that EZH2 levels are elevated in aggressive metastatic prostate cancers and other types of cancer. The enzyme triggers a genetic program that promotes the survival and spread of tumor cells. The enzyme does this by repressing the activity of certain genes by attaching methyl groups to the packaging proteins known as histones, which control access to DNA. The attachment of methyl group can activate or silence the expression of genes.

Because of the importance of EZH2 in cancer progression, we began looking for a control mechanism that might explain how or why it is dysregulated in cancer, said Chinnaiyan. We looked at obvious mechanisms, like

amplification of the gene, but we couldn't find anything suggesting that EZH2 itself was aberrant in cancer. So, since microRNAs have been implicated in the regulation of many genes, including some cancer genes, we began to look for evidence of that mechanism of control, he said.

MicroRNAs are tiny segments of RNA far shorter than the messenger RNA (mRNA) molecules that serve as blueprints for proteins in the cell. MicroRNAs control gene activity by attaching themselves to target mRNAs, suppressing or activating their function.

To pinpoint a potential microRNA controller of EZH2, Chinnaiyan and his colleagues used computer programs to identify microRNAs that are likely to target a given gene. These programs yielded two candidates. One of them, miR-101, had been associated with prostate cancer progression in studies by other researchers, who found that low levels of miR-101 correlated with more aggressive cancers.

When they tested miR-101 in the lab, Chinnaiyan and his colleagues found that it attaches directly to the regulatory segment of the EZH2 gene.

They also found that adding extra miR-101 to breast and prostate cancer cells reduced the level of EZH2, as well as the proliferation and invasiveness of those cells. Both of those characteristics help researchers categorize the aggressiveness of the cancer. Reducing miR-101 had the opposite effects. They also found that enhancing miR-101 suppressed EZH2's ability to repress genes by attaching methyl groups to histones.

When Chinnaiyan's team compared how enhancing miR-101 or suppressing EZH2 influenced broad patterns of gene activity, they found very similar effects. This demonstrated that miR-101 and EZH2 were operating as part of the same gene control program, Chinnaiyan explained.

The researchers also explored the role of miR-101 in human tumors. Interestingly, we found a significant association in prostate cancers between the loss of miR-101 and prostate cancer progression, said Chinnaiyan. We saw that as we went from benign prostate tissue to clinically localized disease to metastatic cancers, miR-101 expression tended to be lost and EZH2 elevated.

By analyzing published genetic data, the group found evidence that the gene for miR-101 is frequently compromised in prostate, breast, ovarian, and colon cancers, as well as specific forms of brain and lung cancers and leukemia.

The findings could have important implications for diagnosing and treating cancers, said Chinnaiyan. For prognostic purposes, if you could measure the level of miR-101 in solid tumors, you might be able to distinguish those likely to aggressively metastasize from those that would tend to remain localized, he said. And for treatment purposes, our studies suggest that replacing miR-101 in solid tumors that have lost it could reduce their metastatic properties.

Chinnaiyan and his colleagues now plan to look for other targets of miR-101 regulation, especially those that play a role in cancer progression.