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Bits of 'junk' RNA aid master tumor-suppressor gene

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Scientists have shown in literally thousands of studies that the p53 gene deserves its reputation as “the guardian of the genome.” It calls to action an army of other genes in the setting of varied cell stresses, permitting repair of damaged DNA or promoting cell death when the cell damage is too great. A key net effect of p53’s action is to prevent development of cancerous cells.

Now, University of Michigan Medical School scientists provide the most thorough evidence yet that p53 also regulates a trio of genes from the realm of so-called “junk” genes — the roughly 97 percent of a cell’s genetic material whose function is only beginning to be understood.

The study shows that “in the ‘junk’ lies treasure, in terms of critical knowledge about how normal cells stifle cancer or succumb to it,” says Guido Bommer, M.D., the lead author of results, published in a recent issue of the journal *Current Biology*.

“The findings in the study offer new insights into specific mechanisms by which the expression of hundreds to thousands of genes and proteins is altered in the roughly 50 percent of cancers that carry mutations in the p53 tumor suppressor gene,” says Eric Fearon, M.D., Ph.D., senior author of the study and deputy director of the U-M Comprehensive Cancer Center. Scientists continue to mine for details of what goes wrong when p53 is defective and cannot perform its tumor-fighting duties.

The U-M study is one of four recent studies from labs around the world showing that p53 normally gets support from members of a small family of micro RNA genes. The studies are part of a larger effort to understand the function of micro RNA (miRNA for short).

Scientists have long known the importance of messenger RNA (mRNA), which carries protein-making instructions. However, until recently, little was known about micro RNA genes. It is now well recognized that miRNAs regulate the levels of mRNAs, and/or the levels of the proteins produced from mRNAs.

The U-M research team studied the roles of the three genes that make up the miRNA34 family. They showed that the miRNA34 genes work in concert with p53, then went on to explore which other genes the family regulates. They found the miRNA34 genes showed pronounced effects on other genes that control the timing of cell proliferation and division. They also found that the miRNA34 gene family regulated the levels of the Bcl-2 protein, a key factor that enhances a cell's resistance to death-inducing stimuli.

The team went on to determine if expression of the miRNA34 genes was compromised in human lung cancer cells.

"We found that expression of two of the miRNA34 genes was lost in almost two-thirds of lung adenocarcinomas," says Bommer.

Adenocarcinomas represent the most common type of non-small cell lung cancer, which is the most frequently diagnosed type of lung cancer. When expression of the miRNA34 genes was restored in lung cancer cells, some of the aberrant growth properties were inhibited.

The discoveries of the role of micro RNAs in tumor suppression could have implications for future cancer therapies.

It's important to note that micro RNAs alone are not likely to offer new cancer treatment or prevention agents, says Fearon, who is the Emanual N Maisel Professor of Oncology, Professor of Internal Medicine, Professor of Pathology and Professor of Human Genetics at the U-M Medical School.

"However, because of the small size of mature miRNAs, there is optimism that it may be possible to deliver modified nucleic acids that might mimic the effect of the miRNAs," he says. If modified nucleic acids were to prove effective in more laboratory studies, he adds, they might be pursued further in clinical trials as anti-cancer agents, either alone or more likely in combination with other anti-cancer agents.

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