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Common cancer gene sends death order to tiny killer

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Scientists at Johns Hopkins have discovered one way the p53 gene does what it's known for—stopping the colon cancer cells. Their report will be published in the June 8 issue of Molecular Cell.

The research team identified a tiny bit of genetic code, a microRNA called miR-34a that participates in p53's uncanny ability to kill cells likely to become malignant because of damaged genes in their nuclei. MicroRNAs are small chains of ribonucleic acid (RNA) made by the same machinery that produces other types of RNA in the cell, such as the messenger RNAs that carry the instructions to make proteins. Once produced, microRNAs stick to messenger RNAs and, like crumpled paper jammed in a copy machine, prevent proteins from being made.

Josh Mendell, M.D., Ph.D., an assistant professor in the McKusick-Nathans Institute of Genetic Medicine, suspected that p53 activates microRNAs like miR-34a because a number of studies have demonstrated that these tiny RNA molecules are frequently abnormal in cancer cells.

"P53 is one of the most commonly mutated genes in human cancers," says Mendell. "And there is now a great deal of evidence that microRNAs themselves can act to either promote cancer or to stop cancer spread."

To test their idea, the team first chemically damaged the DNA of two sets of colon cancer cells, one missing p53 and the other containing

healthy p53. They then looked for any of the 500 known human microRNAs that are activated only in cells containing p53.

It turned out that the miR-34a gene is turned on by p53, and in fact, experiments demonstrated that p53 binds directly to the genetic material near miR-34a to promote its activation.

Concluding that p53 controls miR-34a, they next teamed up with Charlie Lowenstein, M.D., and his colleagues in Hopkins's department of medicine to put miR-34a into colon cancer cells. Doing this killed cells that contained p53, but fewer were killed in cells lacking p53, further suggesting that this microRNA gets its kill orders from p53.

When researchers examined pancreatic cancer cells known to contain damaged or missing p53, they found that those cells had limited or zero miR-34a.

"With no p53 gene or miR-34a to stem tumor development, there's no brake in pancreatic cells and uncontrolled growth leads to cancer," says Anirban Maitra, M.B.B.S., associate professor of pathology, oncology and genetic medicine.

Mendell and his team are looking for missing miR-34a in other cancers. If it's a widespread phenomenon, the work could lead to treatments that aim to restore the missing microRNA to cancer cells.

Source: Johns Hopkins Medical Institutions