Study links microRNA to shut-down of DNA-repair genes

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New research shows for the first time that molecules called microRNA can silence genes that protect the genome from cancer-causing mutations.

The study, led by researchers at the Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, shows that microRNA-155 (miR-155) can inhibit the activity of genes that normally correct the damage when the wrong bases are paired in DNA.

The loss or silencing of these genes, which are called mismatch repair genes, causes inherited cancer-susceptibility syndromes and contributes to the progression of colorectal, uterine, ovarian and other cancers.

"This is the first evidence that deregulation of microRNAs can cause genomic instability, a characteristic of cancer cells," says principal investigator Dr. Carlo M. Croce, professor of Molecular Virology, Immunology and Medical Genetics, and director of Ohio State's Human Cancer Genetics program.

"We discovered that miR-155 targets and downregulates mismatch repair genes and that overexpression of miR-155 results in an increase in genomic alterations that contribute to cancer pathogenesis," he says.

The study was published recently in the Proceedings of the National Academy of Sciences and shows the following:

- Overexpression of miR-155 reduced the expression of the human mismatch repair genes MLH1, MSH2 and MSH6 by 72 percent, 42 percent and 69 percent, respectively, in a colorectal cancer cell line.

- High expression of miR-155 in human colorectal tumors correlates with low expression of MLH1 and MSH2.

- Human tumors that feature unexplained mismatch repair inactivation showed miR-155 overexpression.

The third finding may explain a colon-cancer conundrum. About five percent of colorectal cancer cases feature a genomic marker called microsatellite instability that signals the loss of mismatch repair ability and the presence of an inherited cancer predisposition condition. These cases also show no expression of mismatch genes. Yet, the genes themselves show no alterations that explain the loss of expression.

"This study describes a totally new mechanism that might explain those cases of colorectal cancer that display microsatellite instability but no mutations or epigenetic inactivation of the mismatch repair genes," says co-author Muller Fabbri, a research scientist with the OSUCCC-James.

Overall, Croce says, "Our findings suggest that miR-155 expression might be an important stratification factor in the prognosis and treatment of cancer patients and provide an additional analytical test for exploring the etiology of microsatellite-instability tumors when the standard tests do not provide a conclusive diagnosis."

Provided by The Ohio State University