

Tiny genes may increase cancer susceptibility

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New evidence indicates that small pieces of noncoding genetic material known as microRNAs (miRNAs) might influence cancer susceptibility. Differences in certain miRNAs may predispose some individuals to develop cancer, say researchers collaborating in a joint study at the Kimmel Cancer Center at Jefferson in Philadelphia, Ohio State University Medical Center in Columbus and Roswell Park Cancer Institute in Buffalo.

MiRNAs play a number of roles in biological regulation, including development and cell differentiation, helping to determine what type a cell ultimately becomes. But when damaged, they can contribute to cancer by either turning on cancer-causing genes or by inhibiting tumor-blocking genes. The ways that MiRNAs are expressed have been used to profile tumor types in humans.

To see if miRNAs could affect cancer risk, Linda Siracusa, Ph.D., associate professor of microbiology and immunology at Jefferson Medical College of Thomas Jefferson University, research associate Cinzia Sevignani, Ph.D., and co-workers George Calin, M.D., Ph.D., and Carlo M. Croce, M.D., at Ohio State University in Columbus and Peter Demant, M.D., Ph.D., at Roswell Park Cancer Institute in Buffalo compared the mouse chromosome locations of genes known to affect cancer susceptibility – or "susceptibility loci" – in eight different types of tumors to the locations of mouse miRNAs.

Reporting in the journal *Proceedings of the National Academy of Sciences*, the team showed that overall, miRNAs were found 1.5 times

more likely to be in susceptibility regions than in non-susceptibility regions. "MiRNAs appear to be frequently located near places in the mouse genome that affect cancer susceptibility," the researchers say, suggesting that miRNAs could be "a new family of cancer tumor susceptibility genes."

Susceptibility loci are forms of the same gene. While one form may give a person a higher risk of developing a cancer, an alternate form may confer resistance to that particular type of cancer.

The researchers identified changes in the DNA sequences surrounding several miRNAs that were located at or near the susceptibility areas in mouse strains with a variety of tumor types. The team also looked at which mouse strains were cancer-resistant and which were susceptible to cancer, uncovering seven miRNAs that had genetic sequence differences between the two groups. Five of these miRNAs had changes within their predicted promoter regions, which turn on and potentially regulate the genes' expression levels.

"We have hypothesized that changes in the promoter regions could affect the levels of miRNAs, which could influence a person's lifetime risk of cancer," Dr. Siracusa notes.

Dr. Siracusa and her collaborators plan to examine miRNA expression levels among inbred mice strains. "Could the level of a particular miRNA affect the expression of other genes and regulate the stability of the RNA transcript" she asks. "Having a slightly lower level of a particular miRNA could make a person more susceptible to a particular cancer or the reverse, or a slightly increased level might protect that person."

Source: Thomas Jefferson University

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