Two suppressor molecules affect 70 genes in leukemia

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By restoring two small molecules that are often lost in chronic leukemia, researchers were able to block tumor growth in an animal model. The research, using human chronic lymphocytic leukemia (CLL) cells, also showed that loss of the two molecules affects 70 genes, most of which are involved in critical functions such as cell growth, death, proliferation and metabolism.

The findings reveal how the two molecules, called miR-15a and miR-16-1, normally protect against cancer, and suggest a possible new treatment strategy for CLL.

The study, led by researchers at the Ohio State University Comprehensive Cancer Center, was published recently in the *Proceedings of the National Academy of Sciences*.

“These findings give us a signature of 70 deregulated genes that we believe finally explains at the molecular level how these two molecules contribute to CLL,” says principal investigator Carlo M. Croce, director of Ohio State’s human cancer genetics program.

“The identification of these genes could also have important significance for the development of new therapeutic approaches for chronic leukemias.”

The two molecules are forms of microRNA, tiny molecules that cells use to help regulate the type and amount of proteins they make.

In 2005, Croce and his colleagues first showed that these two microRNAs target a gene called Bcl2, which normally helps cells survive by protecting them from accidental self-destruction. In CLL, however, the gene behaves abnormally and helps the leukemic cells survive long after they should have died.

Croce and his colleagues believe that loss of the two molecules alters the gene's behavior.

For the new study, the investigators first injected mice with leukemia cells in which they had restored the two microRNAs. This completely suppressed tumor growth in three of five animals. Mice injected with leukemic cells that lacked the two molecules, on the other hand, developed significant tumors.

"This clearly showed that these two microRNAs can suppress tumor development," says coauthor Muller Fabrri, a researcher in Croce's laboratory.

Because each microRNA regulates many genes, the investigators wanted to learn which ones, in addition to Bcl2, are affected in cells lacking the two molecules.

First, they measured differences in gene activity in laboratory-grown CLL cells that had either high or low levels of the two molecules.

Next, they measured the levels of all the proteins in the two groups of cells. This proteomic analysis revealed 27 proteins with highly altered amounts. These were identified and shown to be involved in cell growth, cell death and cancer development.

Last, the researchers used human CLL cells from 16 patients to verify the gene targets.

“Together, these extensive experiments revealed the signature of 70 genes controlled by the two microRNAs,” Fabbri says. “They show that microRNAs can affect different biochemical pathways in different ways, and they explain at the molecular level what these two miRNAs do in this disease.”

Source: Ohio State University