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Researchers zero in on the tiniest members in the war on cancer

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Researchers from the University of Pennsylvania and Johns Hopkins University have uncovered another reason why one of the most commonly activated proteins in cancer is so dangerous. As reported in *Nature Genetics* this week, the Myc protein can stop the production of at least 13 microRNAs, small pieces of nucleic acid that help control which genes are turned on and off.

Furthermore, in several instances, re-introducing repressed miRNAs into Myc-containing cancer cells suppressed tumor growth in mice, raising the possibility that a gene-therapy approach could be an effective therapy for treating certain cancers.

Andrei Thomas-Tikhonenko, an associate professor in the Department of Pathobiology in Penn's School of Veterinary Medicine, and a research team led by Joshua Mendell, assistant professor at the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins, analyzed more than 300 miRNAs in both human and mouse lymphoma cells.

Mendell's team had previously found that Myc could turn on one particular group of growth-promoting miRNAs called the miR-17-92 cluster in lymphoma cells. In those cells that had high amounts of Myc protein, the researchers found significant changes in the quantities of at least 13 miRNAs.

"The surprising aspect, considering our miR-17-92 results," Tsung-Cheng Chang and Duonan Yu, lead co-authors on the study, wrote, "is

that lots of Myc turns everything off, not on."

When they looked closer at the DNA of the lymphoma cells, the team also found that Myc was directly attaching to the DNA at the miRNA genes.

"This was further evidence that the decrease in miRNA levels was directly due to the action of Myc," says Chang said.

"This study expands our understanding of how Myc acts as such a potent cancer-promoting protein," Mendell said. "We already knew that it can directly regulate thousands of genes. Through its repertoire of miRNAs, Myc likely influences the expression of thousands of additional genes. Activation of Myc therefore profoundly changes the program of genes that are expressed in cancer cells."

"Still, we needed to determine whether any of these Myc-regulated microRNAs played a direct role in cancer," Thomas-Tikhonenko said.

The Penn team individually reintroduced several of the repressed miRNAs into mouse lymphomas that also had high levels of Myc and measured the effect on lymphoma progression in animals. They found that at least five of the miRNAs could stop cancer growth.

"While this result was not entirely surprising, we had no idea that cancer suppression by microRNAs could be so powerful," Thomas-Tikhonenko said.

Mendell also notes that RNA-based therapies have had some success in animal models, and researchers might potentially find a wide range of miRNAs that can stop cancers in their tracks.

Source: University of Pennsylvania