MicroRNA undermines tumor suppression

March 17 2009, by Nicole Giese

A small piece of RNA, or microRNA (miRNA), ratchets down the activity of the tumor-suppressor gene p53, according to a study by Whitehead Institute and National University of Singapore researchers.

While p53 functions to suppress tumor formation, the p53 gene is thought to malfunction in more than 50% of cancerous tumors.

The study published online March 17 in Genes *and Development* reports the first time that a miRNA has been shown to directly affect the p53 gene, although researchers have previously identified other genes and miRNAs that regulate p53's activity indirectly.

"For critical genes like p53, it's important that they are maintained at the right level in the cell," says Beiyan Zhou, a postdoctoral researcher in the lab of Whitehead Member Harvey Lodish and mentor to the paper's first author, Minh Le. "Le's work describes one more layer of regulatory mechanism that balances p53 gene expression."

miRNAs, short snippets of RNA, usually reduce how often a certain gene is translated into a protein. When a miRNA matches with and binds to a given messenger RNA coding for a specific protein, thereby preventing that messenger RNA from acting as a template for protein creation.

To investigate whether any miRNAs directly affect p53, Le, who is a joint graduate student in Lodish's lab and in the lab of Bing Lim at the National University of Singapore, searched the p53 gene for any sites

that matched with known miRNAs from two databases. Only miRNA125b potentially has p53 target sites in humans, in zebrafish, and in many other vertebrates, indicating that it was important enough in cellular processes to be conserved through evolution.

Le tested miRNA125b's effects on several types of cells known to express p53, including human neural and lung cells. When Le reduced the amount of miRNA125b in the cells, p53 levels and the number of cells undergoing apoptosis (a type of programmed cell death that can be triggered by p53) both increased, whereas an increase in miRNA125b levels decreased levels of p53 and the number of apoptotic cells.

To confirm that miRNA125b played a similar role in developing organisms, Le changed the miRNA125b levels in zebrafish embryos. When she reduced miRNA125b levels in the embryos, cellular p53 levels and apoptosis both increased.

"Taking all of this data together, the p53 pathway is a major target of miRNA125b," says Lodish, who is also a professor of biology and bioengineering at MIT. "Most miRNAs have multiple targets, but there are a few cases that a miRNA has one major target and this is one of them."

More information: "MicroRNA-125b is a novel negative regulator of p53" *Genes & Development*, online March 18, 2009

Source: Whitehead Institute for Biomedical Research (news : web)

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