Renegade RNA -- Clues to cancer and normal growth

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Researchers at Johns Hopkins have discovered that a tiny piece of genetic code apparently goes where no bit of it has gone before, and it gets there under its own internal code.

A report on the renegade ribonucleic acid, and the code that directs its movement, will be published Jan. 5 in *Science*.

MicroRNAs, already implicated in cancer and normal development, latch on to and gum up larger strands of RNA that carry instructions for making the proteins that do all the cell's work. They are, says Joshua Mendell, M.D., Ph.D., an assistant professor in the McKusick-Nathans Institute of Genetic Medicine at Hopkins, like "molecular rheostats that fine-tune how much protein is being made from each gene."

That's why normally microRNAs always have appeared to stick close to the cell's protein-making machinery.

But during a survey of more than 200 of the 500 known microRNAs found in human cells, Mendell's team discovered one lone microRNA "miles away" --- in cellular terms --- from all the others.

"It was so clearly in the wrong place at the wrong time for what we thought it was supposed to be doing that we just had to figure out why," says Hun-Way Hwang, a graduate student in human genetics and contributor to the study.

Consisting of only 20 to 25 nucleotide building blocks (compared to other types of RNA that can be thousands of nucleotides long), each microRNA has a different combination of blocks. Mendell's team realized that six building blocks at the end of the wayward miR-29b microRNA were noticeably different from the ends of other microRNAs.

Suspicious that the six-block end might have something to do with miR-29b's location, the researchers chopped them off and stuck them on the end of another microRNA. When put into cells, the new microRNA behaved just like miR-29b, wandering far away from the cell's protein-making machinery and into the nucleus, where the cell's genetic material is kept.

The researchers then stuck the same six-block end onto another type of small RNA, a small-interfering RNA or siRNA that turns off genes. This also forced the siRNA into the nucleus.

According to Mendell, these results demonstrate for the first time that despite their tiny size, microRNAs contain elements consisting of short stretches of nucleotide building blocks that can control their behavior in a cell. Mendell hopes to take advantage of the built-in "cellular zip code" discovered in miR-29b as an experimental tool. For example, he plans to force other microRNAs and siRNAs into the nucleus to turn off specific sets of genes.

Mendell's team is actively hunting for additional hidden microRNA elements that control other aspects of their behavior in cells. They also are curious to figure out what miR-29b is doing in the nucleus. Because microRNAs have been implicated in cancer as well as normal development, Mendell hopes that further study of miR-29b will reveal other, hidden functions of microRNAs.

Source: Johns Hopkins Medical Institutions