

MicroRNA convicted of triggering metastasis

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The jury is in: microRNAs can cause tumors to metastasize. These tiny molecules fine-tune protein production and play a powerful role in biological processes ranging from development to aging. Now scientists have proved that they can prompt otherwise sedentary cancer cells to move and invade other tissues.

Labs have been probing the relationship between aberrant microRNA levels and cancer for several years. They've shown that some microRNAs cause normal cells to divide rapidly and form tumors, but they've never demonstrated that microRNAs subsequently cause cancer cells to metastasize.

Now, working in the lab of Whitehead Member Robert Weinberg, postdoctoral fellow Li Ma has coaxed cancer cells to break away from a tumor and colonize distant tissues in mice by simply increasing the level of one microRNA. Her results appear online in *Nature* on September 26.

“Li has shown that a specific microRNA is able to cause profound changes in the behavior of cancer cells, which is striking considering that 10 years ago no one suspected microRNAs were involved in any biological process,” says Weinberg, who is also an MIT professor of biology.

Ma began with a list of 29 microRNAs expressed at different levels in tumors versus normal tissue. She examined their production in two groups of cancer cells—metastatic and non-metastatic. Metastatic cancer cells (including those taken directly from patients) contained much

higher levels of one microRNA called microRNA-10b.

Next, Ma forced non-metastatic human breast cancer cells to produce lots of microRNA-10b by inserting extra copies of the gene. She injected the altered cancer cells into the mammary fat pads of mice, which soon developed breast tumors that metastasized.

So what caused this stunning metamorphosis?

MicroRNAs typically disrupt protein production by binding to the messenger RNAs that copy DNA instructions for proteins and carry them to “translators.” Ma used a program developed in the lab of Whitehead Member David Bartel to search for the target of microRNA-10b. She identified several candidates, including the messenger RNA for a gene called HoxD10.

Generally involved in development, Hox proteins control many genes active in an embryo. Some Hox proteins have also been implicated in cancer. HoxD10, for example, can block the expression of genes required for cancer cells to move—essentially applying the brakes to a migration process.

To test whether she had removed the brakes during her experiment, awakening the dormant migration process, Ma boosted the level of HoxD10 in the cancer cells with artificially high levels of microRNA-10b. The cells lost their newly acquired abilities to move and invade.

“I was able to fully reverse microRNA-10b induced migration and invasion, suggesting that HoxD10 is indeed a functional target,” Ma explains.

“During normal development, this microRNA probably enables cells to

move from one part of the embryo to another,” adds Weinberg. “Its original function has been co-opted by carcinoma cells.”

Source: Whitehead Institute for Biomedical Research

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