MicroRNA regulates cancer stem cells

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One of the biggest stories in cancer research over the past few years has been, unexpectedly, stem cells. Not embryonic stem cells, but tumor stem cells. These mutated cells, which live indefinitely and can seed new tumors, are now suspected of causing many, if not all, cancers. What is worse, these persistent cells are not killed by chemotherapy or other current treatments. Their survival might explain why tumors frequently recur or spread after treatment.

Increasingly, researchers view the challenge of getting rid of these bad seeds as the key to treating cancer far more effectively. However, because they are extremely rare, even in large tumors, studying them has been difficult.

Now, researchers have devised a way to generate large numbers of human breast cancer stem cells in mice and have discovered a genetic switch that regulates critical properties of the cells. The regulator, which belongs to a class of molecules called microRNAs (microRNAs), pushes the stem cells to become more differentiated and less tumorigenic through its ability to switch off particular genes.

“People know that microRNAs are important regulators of cell differentiation, but nobody has shown that they regulate the critical properties of cancer stem cells, or any kind of stem cells,” says Judy Lieberman, an investigator at the Immune Disease Institute and Harvard Medical School professor of pediatrics at Children’s Hospital Boston. Lieberman and Erwei Song, a former postdoc in her lab now working as a breast cancer surgeon at Sun Yat-Sen University in Guangzhou, China,

are the senior investigators on the work, which appears in the Dec. 14 issue of *Cell*.

By showing that microRNAs can rein in tumor stem cells, the work suggests a novel way to target these cells to treat cancer with therapeutic RNAs, a promising new class of medicine under development for many diseases.

In the study, Song and first author Fengyan Yu started working in China to isolate breast cancer stem cells from freshly removed tumors. Because cancer stem cells resist chemotherapy, the researchers predicted that breast tumors from women who had received such treatment before surgery might be enriched with stem-like cells, and their experiments confirmed this idea. In tumors from untreated women, less than 1 in 250 cells had the cell surface markers and growth characteristics of stem cells; in treated tumors, the number rose to 1 in 17.

The finding gave Song and Yu the idea of trying to generate larger quantities of tumor stem cells by growing human breast cancer cells in immunosuppressed mice dosed with a chemotherapeutic agent. After three months of such a regimen, nearly 75 percent of the cells in the retrieved tumors displayed the properties of stem cells: they had the expected cell surface markers, were highly tumorigenic and metastatic in mice, were relatively drug resistant, and could be induced to differentiate into multiple kinds of breast tissue cells.

With a ready supply of cancer stem cells, the researchers were able to measure levels of microRNAs, small gene regulators that are known to influence a gene's ability to create proteins important for cell growth and differentiation. They found that cancer stem cells contained low amounts of several microRNAs compared to more mature tumor cells or stem cells that had differentiated in culture.

They zeroed in on a tumor-supressing microRNA called let-7. When the team activated let-7 in the stem cells, they lost their ability to self-renew and began to differentiate. The cells also became less able to form tumors in mice or to metastasize. Further studies showed that let-7 did this by switching off two cancer-related genes: the oncogene Ras, and HMG2A, which when switched off caused the cells to differentiate.

If this finding applies to other tumor types, let-7 may offer a unique opportunity to attack tumor stem cells using therapeutic RNA. Delivery of the let-7 RNA to tumors could potentially deplete stem cells by pushing them down the path of differentiation. Using small RNAs to treat disease is a topic Lieberman is quite familiar with—in 2003, her lab was the first to show therapeutic RNAs could work in an animal model of liver disease, and their work has since focused on devising methods for targeting RNAs to all kinds of cells. Yu, now a visiting student in the Lieberman lab, is looking at ways to deliver the let-7 RNA mimics to stem cells.

“One of the fundamental problems of all the therapies that we have is that they are not doing anything to these cells,” Lieberman says. “If those turn out to be the cells that go on and form metastases and are resistant to chemotherapy and are responsible for relapses, and if your therapy isn’t dealing with those cells and is, in fact, selecting for them, that is very worrisome.”

Source: Harvard Medical School