MicroRNAs can convert normal cells into cancer promoters

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Unraveling the mechanism that ovarian cancer cells use to change normal cells around them into cells that promote tumor growth has identified several new targets for treatment of this deadly disease.

In the December issue of the American Association for Cancer Research journal *Cancer Discovery*, a team or researchers from the University of Chicago Medicine and Northwestern University Feinberg School of Medicine show that ovarian cancer cells induce nearby cells to alter their production of three microRNAs—small strands of genetic material that are important regulators of gene expression.

By changing gene expression, microRNAs can modify a cell's function. In this case, they convert normal, healthy fibroblasts into cancer-associated fibroblasts (CAFs). These CAFs pump out chemical signals telling cancer cells to multiply, invade healthy tissues and travel to distant sites in the abdomen. Importantly, by reversing the microRNA signals the researchers were able to cause CAFs to revert to normal fibroblasts.

"These cancer-supporting cells provide a novel and appealing treatment target," said one of the lead authors of the study Ernst Lengyel, MD, PhD, professor in the department of obstetrics and gynecology at the University of Chicago. "Cancer cells mutate rapidly, which enables them to develop drug resistance. But cancer-associated fibroblasts are genetically stable," he said. "Their harmful behavior is driven by the microRNAs. Inhibiting those signals is a new way to fight this disease. It

disrupts the cancer's support system and is unlikely to evolve resistance."

"With ovarian cancer," Lengyel added, "we desperately need new treatments. "There have been no new approaches introduced into the clinic for years, and thus no major improvements in patient survival."

Fibroblasts are the primary cellular component of connective tissue. They provide the structural framework for other tissues and aid in wound healing. When fibroblast-dense tissues are infiltrated by cancer cells, however, "intimate cross-talk between fibroblasts and cancer cells" can covert them to cancer-associated fibroblasts, Lengyel said, "shifting them into a new role."

"Only a few years ago scientists learned how to reprogram normal cells into cells that can give rise to any cell type in the body," said the second lead author on the study Marcus Peter, PhD, professor of medicine at Northwestern University Feinberg School of Medicine. "Our work demonstrates that cancer cells also have the ability to reprogram cells in their environment into cells that support their growth and that this process involves microRNAs."

The researchers found that cancer cells caused normal fibroblasts to reduce production of two microRNAs, miR-31 and miR-214, and to increase production of miR-155. Since microRNAs usually block gene expression, reduced levels increased expression of several of their target genes. Many of those genes are involved in the production of the chemical signals associated with CAFs.

The most highly upregulated such signal, known as CCL5, is a "key tumor-promoting factor," the authors show. When human ovarian cancer cells and CAFs were co-injected into mice, the tumor cells soon replaced normal ovarian structures. Antibodies that neutralized CCL5 inhibited this augmented growth.

"One strength of our study is that we used tumor cells and CAFs from patients, rather than cell lines," said Lengyel, a gynecologic oncologist who specializes in the surgical treatment of women with ovarian cancer. "Our model system is as close as possible to the real situation."

"Therapeutic approaches targeting microRNAs in cancer cells are under development," added Peter. "Our work suggests that it might be possible to modify microRNA expression in cancer-associated fibroblasts for therapeutic benefit."

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