

Novel Mechanism Through Which Normal Stromal Cells Become Cancer-promoting Stromal Cells Identified

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- Change in three microRNAs' expression converted normal fibroblasts to cancer-associated fibroblasts.
- Restoring the pattern of microRNA expression reduced cancer-promoting qualities.
- Cytokines regulated by these specific microRNAs represent potential new targets for ovarian cancer treatment.

PHILADELPHIA — New understanding of molecular changes that convert harmless cells surrounding ovarian cancer cells into cells that promote tumor growth and metastasis provides potential new therapeutic targets for this deadly disease, according to data published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

“New approaches for treating patients with ovarian cancer are desperately needed,” said Ernst Lengyel, M.D., Ph.D., professor in the department of obstetrics and gynecology at the University of Chicago. “There have been no new approaches introduced into the clinic for quite some time, and we have seen no major improvements in patient survival over the years.”

According to Lengyel, greater understanding of the biology of ovarian cancer should provide new therapeutic targets. He and his colleagues set out to learn how normal stromal cells are transformed into cancer-associated fibroblasts, which are found in the tissue immediately surrounding the ovarian cancer cells. Intimate cross talk between cancer-associated fibroblasts and cancer cells boosts tumor growth and metastasis.

“The strength of our study lies in the fact that we used cells from patients, rather than cell lines,” said Lengyel. “This means that our model system reflects as closely as possible the clinical situation in patients.”

Initial analysis indicated that cancer-associated fibroblasts from patients with ovarian cancer had altered patterns of expression of small molecules called microRNAs compared with normal and tumor-adjacent fibroblasts.

MicroRNAs are important regulators of gene expression because they help direct that cell's function. Thus, modified patterns of microRNA expression change cell function.

Lengyel and colleagues further studied the microRNA most upregulated in cancer-associated fibroblasts and the two microRNAs most significantly downregulated. When they changed the pattern of expression of these three microRNAs in normal fibroblasts to mimic the pattern they had seen in cancer-associated fibroblasts, they found that the normal fibroblasts were converted into cells with in-vitro characteristics of cancer-associated fibroblasts. Moreover, the cells reprogrammed to become cancer-associated fibroblasts by altering microRNA expression enhanced the growth of tumor cells in a mouse model of ovarian cancer.

Conversely, restoring the pattern of expression of the three microRNAs to normal in cancer-associated fibroblasts reduced their cancer-promoting characteristics.

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

Lengyel added that treatments targeting microRNAs in cancer-associated fibroblasts may be particularly effective because these cells are genetically stable, unlike cancer cells, therefore, the risk that cancers will become unresponsive to these treatments is less than for treatments targeting cancer cells.

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