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MicroRNA suppresses prostate cancer stem cells and metastasis

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A small slice of RNA inhibits prostate cancer metastasis by suppressing a surface protein commonly found on prostate cancer stem cells. A research team led by scientists at The University of Texas MD Anderson Cancer Center reported today in an advance online publication at *Nature Medicine*.

"Our findings are the first to profile a microRNA expression pattern in prostate cancer stem cells and also establish a strong rationale for developing the microRNA miR-34a as a new treatment option for prostate cancer," said senior author Dean Tang, Ph.D., professor in MD Anderson's Department of Molecular Carcinogenesis.

MicroRNAs, or miRNAs, are short, single-stranded bits of RNA that regulate the messenger RNA expressed by genes to create a protein.

Cancer stem cells are capable of self-renewal, have enhanced tumor-initiating ability and are generally more resistant to treatment than other cancer cells. They are associated with tumor recurrence and metastasis, the lethal spreading of cancer to other organs. These capacities are more prevalent in cancer cells that feature a specific cell surface protein called CD44, Tang said.

"CD44 has long been linked to promotion of tumor development and, especially, to cancer metastasis," Tang said. "Many cancer stem cells overexpress this surface adhesion molecule. Another significant finding from our study is identifying CD44 itself as a direct and functional

target of miR-34a."

MicroRNA goes up, CD44 and cancer stem cells fall

In a series of lab experiments with cell lines, human xenograft tumors in mice and primary human prostate cancer samples, the researchers demonstrated that miR-34a inhibits prostate cancer stem cells by suppressing CD44.

- miR-34a is greatly reduced in prostate cancer cells that express high levels of CD44 on the cell surface. In 18 human prostate tumors, the microRNA was expressed at 25 to 70 percent of the levels found in cells without CD44.

- Prostate tumors in mice that also received miR-34a treatment were one third to half the average size of those in control group mice.

- In CD44-positive prostate cancer cell lines, treatment with miR-34a resulted in greatly reduced tumor incidence. Most dramatically, in one cell line, tumor regeneration was blocked in all 10 treated animals, while tumors formed in all 10 animals treated with the control miRNAs.

- Many characteristics of cancer stem cells – formation of self-renewing cells, clonal growth capacity and formation of spheres – were suppressed when miR-34a was overexpressed in prostate cancer cell lines.

- Most significantly, intravenous treatment of tumor-bearing mice with synthetic miR-34a reduced tumor burden by half in one tumor type. It also steeply reduced lung metastases in another

tumor type, resulting in increased animal survival.

- Interestingly, the researchers observed a consistent, inverse relationship between miR-34a levels and CD44, the surface marker used to enrich prostate cancer stem cells. For example, the CD44 protein and CD44-expressing cancer cells were reduced in tumors treated with the microRNA. Tumors with miR-34a blocked had higher levels of CD44 protein and messenger RNA.

- Finally, knocking down CD44 with a short hairpin RNA produced the same results as treating cells with miR-34a did – reduced tumor development, tumor burden and metastases.

"There are many companies developing microRNA-based drugs," Tang said. "Delivery of miRNAs is a challenge, but the field is moving fast through the preclinical stage."

Scientists from Austin-based Mirna Therapeutics collaborated on the study. Mirna has eight microRNAs in preclinical development, including miR-34a.

Provided by University of Texas M. D. Anderson Cancer Center