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# Research finding suggests way to make bladder cancer cells more susceptible to chemotherapy

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Researchers at the UC Davis Cancer Center have discovered a way of sensitizing muscle-invasive bladder cancer cells so that they succumb to the toxic effects of chemotherapy. The finding adds to mounting evidence that tiny strands of RNA — called microRNA — play key roles in some of the deadliest types of cancer.

In the current study, published online June 28 in *International Journal of Cancer*, researchers boosted the production of a microRNA found in bladder cancer cell lines — encoded for by the gene miR-34a — and found that this resulted in more of the cells being killed by cisplatin, a chemotherapy drug used to treat many types of cancer.

"When we took the bladder cancer cell lines and activated miR-34a, they were more responsive to chemotherapy," said Ralph deVere White, UC Davis Cancer Center director and professor of urology.

The study establishes, for the first time, a link between sensitivity of bladder cancer cells to chemotherapy and the expression of miR-34a. It suggests that miR-34a may be used as a predictor of response to chemotherapy, as well as a target for new drugs.

Currently, about 50 percent of patients with advanced bladder cancer will survive five years after diagnosis. Although clinical trials have demonstrated that chemotherapy before surgery can improve survival

rates, it is rarely used because fewer than 50 percent of patients will respond favorably. Without knowing which patients will improve as a result of chemotherapy, physicians are generally reluctant to use a treatment that can cause their patients to suffer significant side effects.

"So, now we have to prove that it works to predict chemotherapy response in patients," deVere White said. To that end, UC Davis has entered into a partnership with Israel-based Rosetta Genomics to develop a microRNA profile for muscle-invasive bladder cancer that may be used to predict response to chemotherapy.

As part of the current study, deVere White and his colleagues studied 27 patients and found that many who expressed lower levels of miR-34a subsequently did not respond to the combined chemotherapy-surgery treatment. Because the finding was not statistically significant, however, further work in this area is needed.

The team also studied tumor samples taken from eight of the patients who did not respond to chemotherapy. They compared the expression of miR-34a before and after chemotherapy.

"We wanted to see, if you looked at the patient's tissue before chemotherapy, were there differentially expressed microRNAs in the patients who responded to the drugs versus those that didn't respond," deVere White explained.

The team found that expression of miR-34a increased after treatment in only two of the eight cases, suggesting that gene expression levels remained low during treatment and confirming the link between low gene expression and failure to respond to treatment.

"The combined data indicate that the elevation of miR-34a expression levels prior to chemotherapy would be of benefit to muscle-invasive

bladder cancer patients, particularly in a setting of low mi-R-34a expression," the authors write.

Since their discovery in 1993, microRNAs have been found to be involved in a number of types of cancer, heart disease and diseases of the nervous system. In 2007, deVere White was part of a team that identified miR-125b, a gene that encodes for a microRNA that jump starts prostate cancer cell growth midway through the disease process, eventually causing it to become fatal.

The microRNA studied here was also recently found to play a role in medulloblastoma, an aggressive type of brain cancer. MicroRNAs, which are usually 22 to 33 nucleotides in length, are known as post-transcriptional regulators. That means they work by turning genes on or off during the part of the protein synthesis process that involves making a strand of RNA from a DNA template. The human genome encodes for an estimated 1,000 microRNAs.

According to the authors, future studies involving miR-34a will focus on testing its ability to increase sensitivity to chemotherapy and analysis of miR-34a expression in patients with muscle-invasive bladder cancer. With the currently low chemotherapy success rate and poor five-year survival rate for patients with this disease, "such studies are clearly warranted," the authors write.

"If we can prove what is causing chemotherapy resistance in patients with muscle-invasive bladder cancer, American ingenuity will come up with ways to overcome it," predicted deVere White.

Provided by University of California - Davis Health System

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