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Researchers identify and shut down protein that fuels ovarian cancer

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A protein that stimulates blood vessel growth worsens ovarian cancer, but its production can be stifled by a tiny bit of RNA wrapped in a fatty nanoparticle, a research team led by scientists at The University of Texas M. D. Anderson Cancer Center reports in the *Journal of the National Cancer Institute*.

"The protein interleukin-8 (IL-8) is a potential therapeutic target in ovarian cancer," said senior author Anil Sood, M.D., professor in the M. D. Anderson Departments of Gynecologic Oncology and Cancer Biology.

The paper demonstrates that high IL-8 expression in tumors is associated with advanced tumor stage and earlier death for ovarian cancer patients. Lab experiments and research in a mouse model show that short interfering RNA (siRNA) can cut IL-8 expression, reducing tumor size by attacking its blood supply.

"This comprehensive analysis - with human data, animal data and lab experiments to highlight the molecular mechanisms involved - helps us develop the new targets needed for a more effective approach against ovarian cancer," Sood said.

Interleukin-8 is overexpressed in many types of cancer and has previously been shown to promote tumor growth, new blood vessel growth known as angiogenesis, and metastasis, the spread of cancer to other organs. "In the long run, this research will have applications in

other cancers as well," Sood said.

His research focuses on ovarian cancer, for example, while senior co-author Menashe Bar-Eli, Ph.D., professor in M. D. Anderson's Department of Cancer Biology, examines IL-8's role in melanoma.

Ovarian cancer is often detected in late stages. Initial treatment includes surgery and taxane- or platinum-based chemotherapy regimens that keep the cancer at bay for a time in most patients. Recurrence is common and often lethal.

To examine IL-8's role in ovarian cancer, the researchers analyzed tumors from 102 patients diagnosed and treated between 1988 and 2006 at M. D. Anderson and the University of Iowa. Of those, 43 had tumors with high levels of IL-8 and 59 had low levels. The median survival of those with high IL-8 tumors was 1.62 years, compared with 3.79 years for those with low expression of the protein.

All 43 tumors with high expression of IL-8 were of high grade and 42 of 43 were advanced, either stage III or IV tumors. By comparison, 10 of 59 tumors with low IL-8 expression were early stage tumors and six were of low grade.

Genes transcribe single strands of RNA that in turn are "read" by ribosomes to produce proteins. siRNAs are short, double-stranded bits of RNA capable of halting that process. The team confirmed in a lab experiment that a specific siRNA silences IL-8 and then tested it against two lines of ovarian cancer in a mouse model.

Sood, Gabriel Lopez-Berestein, M.D., professor in M. D. Anderson's Department of Experimental Therapeutics, and colleagues are building an arsenal of siRNAs capable of silencing genes that produce cancer-promoting proteins. They packaged siRNA that stymies IL-8 into a small

ball of fat known as a liposome, a combination they developed to overcome a problem - siRNA is hard to deliver to tumors.

Tumors shrank by a median of 32 percent and 52 percent in the two cancer lines among mice that received injections of the IL-8 siRNA liposome compared to those receiving control siRNA or empty liposomes.

Mice that got both the IL-8 siRNA plus the taxane-based chemotherapy drug docetaxel had median tumor weight reduction of 90 percent and 98 percent in the two cell lines. Mice with control siRNA plus docetaxel saw reductions of 67 and 84 percent.

Finally, they tested the approach in mice with an ovarian cancer cell line known to be resistant to taxane-based drugs such as docetaxel. IL-8 siRNA alone reduced the size of these tumors by 47 percent, and when combined with docetaxel reduced tumor size by 77 percent, suggesting that the combination re-sensitizes a resistant tumor to taxanes.

The team gauged the impact of IL-8 siRNA on tumor blood supply by measuring the density of blood vessels in the tumor. The IL-8 siRNA alone reduced blood vessel density by 34 percent and 39 percent in two cancer lines.

"These are encouraging results. We want to move one of our siRNA agents into the clinic to test its potential for therapy," Sood said, "and then in the longer term, we'll consider moving additional siRNA agents into the clinical arena."

The IL-8 siRNA liposome is the third developed by Sood's and Lopez-Berestein's team. Two others target the oncoproteins FAK and EphA2. The EphA2 siRNA liposome is closest to Phase I clinical trial, with required toxicology studies nearly complete. A clinical trial could begin

within a year.

Methods used to inject siRNA in high volumes for research purposes are impractical for human therapy. Sood and Lopez-Berestein developed the liposomal approach to ensure that the siRNA reaches the cell intact so it can silence the targeted gene. Their research has shown that the liposome penetrates deeply into cells to deliver its siRNA.

Source: University of Texas