EphA2-targeted therapy delivers chemo directly to ovarian cancer cells

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With a novel therapeutic delivery system, a research team led by scientists at The University of Texas M. D. Anderson Cancer Center has successfully targeted a protein that is over-expressed in ovarian cancer cells. Using the EphA2 protein as a molecular homing mechanism, chemotherapy was delivered in a highly selective manner in preclinical models of ovarian cancer, the researchers report in the July 29 issue of the *Journal of the National Cancer Institute*.

EphA2 is attractive for such molecularly targeted therapy because it has increased expression in ovarian and other cancers, including breast, colon, prostate and non-small cell lung cancers and in aggressive melanomas, and its expression has been associated with a poor prognosis.

"One of our goals has been to develop more specific ways to deliver chemotherapeutic drugs," said senior author Anil K. Sood, M.D., professor and in the Departments of Gynecologic Oncology and Cancer Biology at M. D. Anderson. "Over the last several years we have shown that EphA2 is a target that is present quite frequently in ovarian and other cancers, but is either present in low levels or is virtually absent from most normal adult tissues. EphA2's preferential presence on tumor cells makes it an attractive therapeutic target."

The researchers used a carrier system to deliver chemotherapy directly to ovarian cancer cells. The immunoconjugate contains an anti-EphA2 monoclonal antibody linked to the chemotherapy drug monomethyl

auristatin phenylalanine (MMAF) through the non-cleavable linker maleimidocaproyl. Research has shown that auristatins induce cell cycle arrest at the G - M border, disrupt microtubules and induce apoptosis (programmed cell death) in cancer cells.

The investigators evaluated the delivery system's specificity in EphA2-positive HeyA8 and EphA2-negative SKMel28 ovarian cancer cells through antibody-binding and internalization assays. They also assessed viability and apoptosis in ovarian cancer cell lines and tumor models and examined anti-tumor activity in orthotopic mouse models with mice bearing HeyA8-luc and SKOV3ip1 ovarian tumors.

According to Sood, who is also co-director of both the Center for RNA Interference and Non-Coding RNA and the Blanton-Davis Ovarian Cancer Research Program at M. D. Anderson, the immunoconjugate was highly specific in delivering MMAF to the tumor cells that expressed EphA2 while showing minimal uptake in cells that did not express the protein. In the models, the therapy inhibited tumor growth in treated mice by 85 percent - 98 percent compared to control mice.

"Once we optimized the dosing regimen, the drug was highly effective in reducing tumor growth and in prolonging survival in preclinical animal models," Sood said. "We actually studied bulkier masses because that is what one would see in a clinical setting where there are pre-existent tumors, and even in this setting the drug was able to reduce or shrink the tumors."

As for future research with the EphA2-silencing therapy, Sood said, "We are gearing up to bring it to phase I clinical trials. A lot of the safety studies are well under way or nearing completion and we anticipate that this drug will enter clinical trials within the next few months."

He added that his group is simultaneously conducting preclinical testing

on other chemotherapy drugs to determine which agents might combine well with the immunoconjugate used in the current study.

"There is growing interest in molecularly targeted therapy so that we are not indiscriminately killing normal cells," Sood noted. "The goal is to make the delivery of chemotherapy more specific. The immunoconjugate we used is in a class of drugs that is certainly quite attractive from that perspective."

Source: University of Texas M. D. Anderson Cancer Center (news : web)