Researchers renew obsolete concept by using folate for cancer drug delivery

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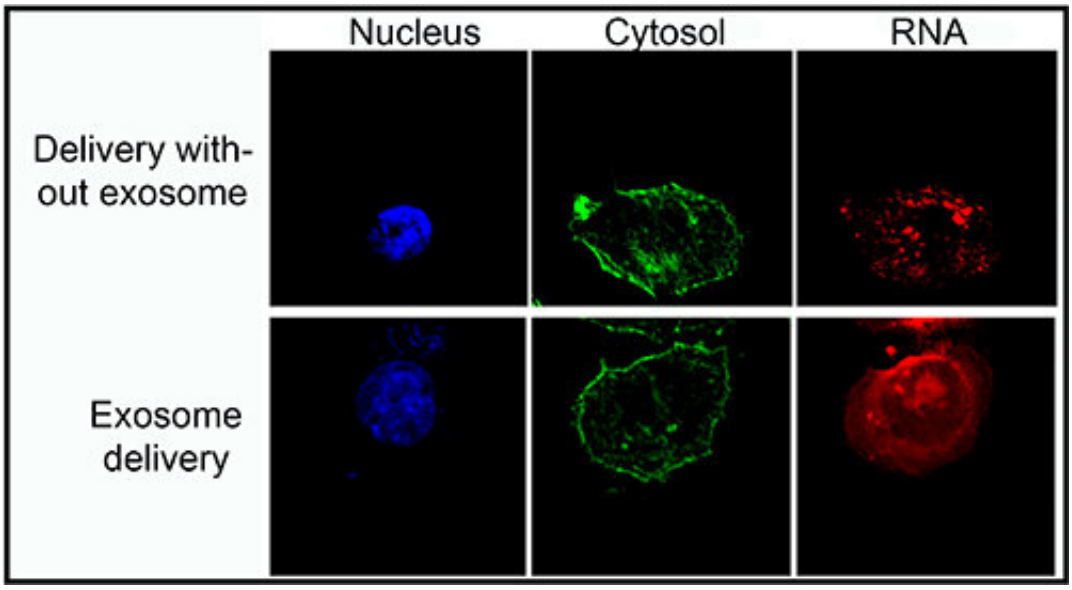

Images of cancer tumor cells taken with a confocal laser scanning microscope. The top row of images show that the anti-cancer formulation delivered directly becomes trapped within endosomes inside the cell (bright spots in the first row of images). The bottom row shows effective delivery of the exosome formulation of the anti-cancer treatment with interfering RNA. Credit: Guo Lab, OSU

NIBIB-funded biomedical engineers at the Ohio State University (OSU) have demonstrated a new method for delivering an anti-cancer drug in a study that tested the effect in animal models. When formulated within a membrane sac, called an exosome, and when paired with the B-vitamin

folate, the anti-cancer drug can enter the cell without being sealed off within the cell by another sac, called an endosome. Endosome trapping has been a formidable challenge to overcome in drug delivery.

The approach, developed with support from the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and the National Cancer Institute (NCI), both at NIH, works on the principle that receptors for folate are expressed in abundance on cancer cells, but to a more moderate degree on healthy cells. In their report in the August 22, 2019 online *Journal of Controlled Release*, the authors suggest that their approach, tested on mice, will renew the interest in folate as a broad target for human cancer therapy.

"Folate targeting has been an elusive approach to cancer therapy," said David Rampulla, Ph.D., director of the NIBIB Division of Discovery Science and Technology. "This team has demonstrated an efficient drug delivery system and shown how a nanoparticle combined with folate can efficiently target cancer cells. It is the kind of advance that could represent the basis for much-needed cancer therapies."

Folate is a B-vitamin required for synthesis and cell division. Because of the heightened expression of folate receptors on cancer cells, folate has been widely proposed for targeted cancer therapy for 25 years, having been tested extensively in studies with breast, lung, ovarian, colorectal, and head and neck cancers. Typical approaches pair folate with an anti-cancer drug, such as a nanoparticle of interfering RNA, which has the potential to disrupt the genetic machinery within cancer cells.

Ideally, folate is recognized by receptors on the cell membrane, which allows the anti-cancer nanoparticle to gain access to the cell. However, researchers have encountered the challenge that therapeutics delivered via the folate receptor pathway become trapped within the endosome sac. Thus, in the past, the use of folate for specific drug delivery has not

been successful.

The OSU team, led by senior author Peixuan Guo, Ph.D., the Sylvan G. Frank Endowed Chair in Pharmaceutical Drug Delivery, applied an alternate approach to delivering the interfering RNA to the cell. They put interfering RNA nanoparticles into an exosome with folate on its surface. Upon contact with the cancer cell membrane, the exosome specifically binds to and fuses with the cancer cell's membrane, releasing its therapeutic contents into the watery component of the cytoplasm (cytosol).

The research team had previously demonstrated that the approach could be effective in impeding breast, colorectal, and prostate cancers in mice. That study was published Dec. 11, 2017, in *Nature Nanotechnology*.

In their present study, the researchers took the next step, conducting tests to further elucidate the treatment delivery method. To show that folate receptors enhance delivery of the interfering RNA nanoparticles when they are delivered as a component of the exosome, they paired folate with an interfering RNA called survivin siRNA, which disrupts a protein in cancer cells that can inhibit cell death. Cancer occurs when cells do not die and proliferate out-of-control. They used optical fluorescent imaging technology to capture the effect of the treatment delivery via exosome compared to delivery of the survivin siRNA without an exosome. The imaging showed that the exosome delivery permitted the treatment to be distributed throughout the cell.

To determine whether folate receptors on cancer cells can be specifically targeted, the team applied the treatment in cervical cancer in mice. Those mice treated with folate and survivin siRNA bound within an exosome had reduced tumor growth, confirming the effectiveness of the new cancer treatment approach."The therapeutic effect is surprisingly high," Guo said. "This finding will be a revolution to renew an obsolete

concept in using folate as a specific targeting agent in cancer therapy."

More information: Zhen Zheng et al. Folate-displaying exosome mediated cytosolic delivery of siRNA avoiding endosome trapping, *Journal of Controlled Release* (2019). DOI: 10.1016/j.jconrel.2019.08.021

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