Nanoparticles deliver one-two therapeutic punch to kill tumor cells

December 17 2010

The standard approach to cancer therapy today is to mix and match chemotherapy drugs in order to attack tumors in multiple ways. Now, two separate teams of investigators have demonstrated that using nanoparticles to deliver multiple drugs simultaneously can produce a synergistic effect that boosts the cell-killing ability of both drugs.

In one study, a team of investigators at Northwestern University has shown that they can combine two powerful but extremely toxic anticancer agents - cisplatin and doxorubicin - in one polymer nanoparticle, producing a substantial boost in their ability of the combination to destroy tumors. In addition, the two-in-one nanoparticle reduces the amount of both drugs needed to kill cancer cells, which presumably would reduce the toxic side effects associated with these drugs.

SonBinh Nguyen and Thomas O'Halloran led this study, which was published in the Journal of the American Chemical Society. Dr. O'Halloran is the co-principal investigator of one of 12 Cancer Nanotechnology Platform Partnerships funded by the National Cancer Institute Alliance for Nanotechnology in Cancer. He is also a member of the Northwestern University Center for Cancer Nanotechnology Excellence (CCNE), which is also part of the Alliance for Nanotechnology in Cancer.

Though originally designed to carry arsenic trioxide to solid tumors, the nanoparticles used in this study are proving to be quite versatile in their

ability to ferry a wide range of cargos to malignancies. In this study, the investigators wanted to see if delivering two drugs in one nanoparticle offered any advantages of delivering them without the nanoparticle or in separate nanoparticles. The nanoparticles, which the researchers call nanobins, are made by encasing a liposome inside a pH-responsive polymer cage. In this case, doxorubicin is entrapped within the liposome's core, while cisplatin was entrapped in the polymer cage.

In an initial set of experiments, the investigators determined that a 5 to 1 ratio of cisplatin to doxorubicin was the most effective at treating ovarian tumors when the two drugs were combined in the same nanoparticle. When the two drugs were administered at this ratio but with each in its own nanoparticle, the combination was not only less effective at killing malignant cells, but the two drugs appeared to be interfering with each other, a phenomenon often observed in clinical practice. Administering the two drugs in the same nanoparticle ensures that the drugs are hitting their intracellular targets at the same time, which is what likely leads to the synergism observed in this study.

Meanwhile, Mansoor Amiji and Zhenfeng Duan, co-principle investigators of the Cancer Nanotechnology Platform Partnership at Northeastern University, have shown that a different type of polymer nanoparticle can also deliver two anticancer agents simultaneously and as a result can kill cancer cells that have become resistant to drug therapy. In this case, the researchers synthesized biocompatible polymer nanoparticles that entrapped paclitaxel and lonidamine and that targeted the epidermal growth factor receptor (EGFR) that is overexpressed on highly aggressive tumors. When added to tumor cells growing in culture, the nanoparticle containing both drugs was far more effective at killing the drug-resistance cells than when the two drugs were co-administered in separate nanoparticles. The investigators reported their findings in the journal *Molecular Pharmaceutics*.

In a separate set of experiments, the results of which were published in the journal *Angewandte Chemie International Edition*, Drs. Nguyen and O'Halloran, joined by Thomas Meade, another member of the Northwestern CCNE, demonstrated that nanobins can also co-deliver a therapeutic and magnetic resonance imaging agent to tumors. In this study, the researchers loaded the anticancer agent gemcitabine into the nanobin's core and added a gadolinium magnetic resonance contrast agent to the nanobin's surface. When added to mouse tumor cells, the nanobins were taken up rapidly and the nanobins were clearly visible in magnetic resonance images. In addition, the nanoparticles released their gemcitabine payload once the nanobins were taken up by the cultured cells.

More information: This work, which is detailed in three papers, was supported in part by the NCI Alliance for Nanotechnology in Cancer. Abstracts of the papers are available at the journals' websites.
Journal of the American Chemical Society paper
Molecular Pharmaceutics paper
Angewandte Chemie International Edition paper

Provided by National Cancer Institute