Overcoming cancer drug resistance with nanoparticles

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One of the ways in which cancer cells evade anticancer therapy is by producing a protein that pumps drugs out of the cell before these compounds can exert their cell-killing effects. A research team at Northwestern University has found that biocompatible iron oxide-titanium dioxide nanoparticles can bypass this pump and enable DNA-damaging anticancer drugs to reach the cell nucleus.

Gayle Woloschak, a member of the Northwestern University Center for Cancer Nanotechnology Excellence, led the research team that developed this nanoparticle. She and her collaborators reported their findings in the journal *Cancer Research*.

The goal of this work was two-fold: identify a nanoparticle that would overcome pump-related drug resistance which could simultaneously serve as a tumor imaging agent. The researchers chose a nanoparticle with an iron oxide core surrounded by a titanium dioxide shell. The iron oxide core serves as a powerful magnetic resonance imaging (MRI) contrast agent, while the titanium dioxide shell can bind to anticancer agents such as doxorubicin through a chemical bond that will break in the acidic conditions inside a cancer cell.

The investigators treated drug-resistant ovarian cancer cells with a doxorubicin-loaded nanoparticle and showed that the nanoparticle was readily transported into the cells. More importantly, the nanoparticles released their drug payload, enabling doxorubicin to reach the cell nucleus. Doxorubicin kills cells through a process that involves binding

to DNA in the nucleus. When compared to doxorubicin alone, the resistant cells accumulated up to 6 times more drug then when administered using the nanoparticle-drug combination. Interestingly, the researchers found that when they co-administered even empty nanoparticles (no doxorubicin) with transferrin, a molecule involved in iron transport, they saw increased cell uptake of transferrin. This observation is important since many research groups are developing nanoparticles that incorporate transferrin on the surface to stimulate cell uptake. In this scenario, it could be beneficial to co-treat with this type of empty particle.

This work, which is detailed in a paper titled, "Nanocarriers enhance doxorubicin uptake in drug-resistant ovarian cancer cells," was supported in part by the NCI Alliance for Nanotechnology in Cancer, a comprehensive initiative designed to accelerate the application of nanotechnology to the prevention, diagnosis, and treatment of cancer. An abstract of this paper is available at the journal's website.

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