'Connectosomes' create gateway for improved chemo delivery, fewer side effects

October 4 2016

Engineering researchers at The University of Texas at Austin have developed a new method that delivers chemotherapy directly and efficiently to individual cells. The approach, described in the Sept. 8 edition of the *Journal of the American Chemical Society*, could provide a faster means of targeting and killing cancer cells with significantly lower doses of chemo than conventional drug delivery methods, which could decrease side effects for patients.

For this method, the researchers developed and utilized a new type of nanoparticles, which they call "connectosomes," that are equipped with gap junctions—a pathway that allows for the rapid movement of molecules between two cells. The gap junctions allow the connectosomes to create a direct channel to deliver drugs to each individual cell.

The researchers believe their approach is a major step forward in realizing the advantages of nanoparticle-based drug delivery materials and improving the effectiveness of treatments.

Avinash Gadok, a doctoral student in the Cockrell School of Engineering, and biomedical engineering Assistant Professor Jeanne Stachowiak collaborated with Professor Hugh Smyth and postdoctoral fellow Silvia Ferrati, both from the College of Pharmacy at UT Austin, on the research.

According to their study, the team's new delivery method, which harnesses gap junctions to deliver chemotherapy directly and efficiently,

has led to a significant decrease in the dose required to kill a cancer cell. Driving down the dosage of chemo could lessen potential side effects, from nausea and hair loss to infertility and heart damage, that patients experience. In addition, having a direct route to a cell could provide more effective treatment for later-stage tumors that have metastasized, which are often out of reach of current chemotherapy delivery methods.

"Gap junctions are the cells' mechanism for sharing small molecules between neighboring cells. We believed that there must be a way to utilize them for better drug delivery," Stachowiak said. "The big challenge was in making the materials efficiently and showing that the drugs are delivered through the gap junctions and not some other component."

To form the connectosomes, Gadok used a chemical process to derive liposomes from donor cells that were engineered to over-produce gap junctions, which are made of proteins. She then loaded the connectosomes with the chemotherapy drug doxorubicin.

The team's connectosomes address a main challenge in chemotherapeutics—getting a concentrated dose of drugs to cross through the cell's plasma membrane barrier and reach its target inside of the cell.

Even highly membrane-permeable drugs, such as doxorubicin, have limited transport rates across the plasma membrane, so they require higher doses to be effective. And when the drug is freely delivered, doxorubicin kills healthy cells along with cancerous cells, resulting in harmful side effects.

In in-vitro tests with human cells, the researchers found that chemo delivered through connectosomes is 10 times as efficient at killing cancer cells as freely delivered doxorubicin. Connectosomes are also 100

to 100,000 times as efficient as conventional nanoparticles in delivering chemo, because a drug can diffuse more efficiently through a gap junction than across the oily lipid membrane.

"Connectosomes could open doors for the improved utilization of nanoparticles to deliver other types of therapies," Gadok said. "A huge advantage of nanoparticles is that they can target cells, which helps protect off-target tissues."

In two related projects, the researchers are seeing whether connectosomes can biochemically target tumor cells, and they are also researching to see whether they could be useful in inhibiting the migration of tumor cells. In particular, gap junctions are known to suppress cell migration, creating the potential for connectosomes to help control the movement of tumor cells out of the tumor and into the bloodstream.

"We would like to see whether this approach could delay metastasis while treating the tumor," Stachowiak said. "It would be nice to have a multipronged approach where you have a particle that slows down metastasis, rapidly delivers drugs and turns off expression of genes that are promoting the migration of tumor cells."

Provided by University of Texas at Austin