Novel nanoparticle delivers powerful RNA interference drugs

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Silencing genes that have malfunctioned is an important approach for treating diseases such as cancer and heart disease. One effective approach is to deliver drugs made from small molecules of ribonucleic acid, or RNA, which are used to inhibit gene expression. The drugs, in essence, mimic a natural process called RNA interference.

In a new paper appearing today online in the journal, *ACS Medicinal Chemistry Letters*, researchers at Sanford-Burnham Medical Research Institute have developed nanoparticles that appear to solve a big challenge in delivering the RNA molecules, called small interfering RNA, or siRNA, to the cells where they are needed. By synthesizing a nanoparticle that releases its siRNA cargo only after it enters targeted cells, Dr. Tariq M. Rana and colleagues showed in mice that they could deliver drugs that silenced the genes they wanted.

"Our study describes a strategy to reduce toxic effects of nanoparticles, and deliver a cargo to its target," said Dr. Rana, whose paper, "In Vivo Delivery of RNAi by Reducible Interfering Nanoparticles (iNOPs)," also included contributions from researchers at the University of Massachusetts Medical School and the University of California at San Diego. "We've found a way to release the siRNA compounds, so it can be more effective where it's needed," Dr. Rana said.

In their experiment, the team synthesized what they call interfering nanoparticles, or iNOPs, made from repetitively branched molecules of a small natural polymer called poly-L-lysine. The iNOPs were specially

designed with positively charged residues connected by disulfide bonds and these iNOPS assemble into a complex with negatively charged siRNA molecules. It's the bonds that ensure that the siRNA molecules remain with the nanoparticle, named iNOP-7DS. However, once inside targeted cells, a naturally occurring and abundant antioxidant called glutathione breaks the bond, releasing the siRNA molecules. In their experiment, Dr. Rana and colleagues showed in the lab that iNOP-7DS is reducible – that is, the disulfide bonds holding the siRNA molecules can be broken.

They next showed that iNOP-7DS can be delivered effectively inside cultured murine liver cells, where the siRNA molecules silenced a gene called ApoB. This gene has been notoriously difficult to regulate in liver cells with small molecule drugs; high levels of the protein that ApoB encodes can lead to plaques that cause vascular disease.

Dr. Rana's lab further showed in tests that their nanoparticle remained stable in serum, suggesting that it is not degraded in the bloodstream. Finally, the researchers showed in tests with mice that their nanoparticle iNOP-7DS can be delivered effectively to the liver, spleen, and lung; and it suppressed the level of messenger RNA involved in the expression of the ApoB gene. In their in vivo experiment, they found that extremely small doses of siRNA were effective.

The next step, Dr. Rana said, is to increase the efficacy of iNOP-7DS in other in vivo experiments. "We would like to target not only ApoB, but cancer causing genes as well and in other tissues. That is the next goal." By marshaling the naturally occurring phenomenon of RNA interference, scientists are developing new ways to silence errant gene expression involved in illnesses. The nanoparticles developed by Dr. Rana and colleagues offer a potential new strategy for delivering this powerful therapeutic approach.

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