'Good cholesterol' nanoparticles seek and destroy cancer cells

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High-density lipoprotein's hauls excess cholesterol to the liver for disposal, but new research suggests "good cholesterol" can also act as a special delivery vehicle of destruction for cancer.

Synthetic HDL nanoparticles loaded with small interfering RNA to silence cancer-promoting genes selectively shrunk or destroyed ovarian cancer tumors in mice, a research team led by scientists from The University of Texas MD Anderson Cancer Center and the University of North Texas Health Science Center reports in the April edition of *Neoplasia*.

"RNA interference has great therapeutic potential but delivering it to cancer cells has been problematic," said Anil Sood, M.D., the study's senior author and MD Anderson's director of Ovarian Cancer Research and co-director of the Center for RNA Interference and Non-Coding RNA at MD Anderson. "Combining siRNA with HDL provides an efficient way to get these molecules to their targets. This study has several important implications in the ability to fight certain cancers."

Sood and Andras Lacko, Ph.D., professor of Molecular Biology and Immunology at UNT Health Science Center, jointly developed the nanoparticles, which build on Lacko's original insight about HDL's potential for cancer drug delivery.

The next step is to prepare for human clinical trials, the two scientists said. "If we can knock out 70, 80 or 90 percent of tumors without drug

accumulation in normal tissues in mice, it is likely that many cancer patients could benefit from this new type of treatment in the long run," Lacko said.

Only cancer and liver cells express HDL receptor

Previous studies have shown that cancer cells attract and scavenge HDL by producing high levels of its receptor, SR-B1. As cancer cells take in HDL, they grow and proliferate. The only other site in the body that makes SR-B1 receptor is the liver. This selectivity for cancer cells protects normal, healthy cells from side effects.

Previous attempts to deliver siRNA by lipsomes and other nanoparticles have been hampered by toxicity and other concerns. The tiny bits of RNA, which regulate genes in a highly targeted fashion, can't simply be injected, for example.

"If siRNA is not in a nanoparticle, it gets broken down and excreted before it can be effective," Sood said. "HDL is completely biocompatible and is a safety improvement over other types of nanoparticles."

The team developed a synthetic version of HDL, called rHDL, because it's more stable than the natural version.

Fewer and smaller tumors, less toxicity

Using rHDL as a delivery method has other advantages as well. rHDL has not shown to cause immunologic responses, helping to minimize potential side effects, Lacko said, and it exhibits longer time in circulation than other drug formulations or lipoproteins. Also, because SR-B1 is found only in the liver, an rHDL vehicle will help block and

treat metastasis to that organ.

Researchers first confirmed the distribution of SR-B1 and the uptake of rHDL nanoparticles in mice injected with cancer cells. They found that siRNA was distributed evenly in about 80 percent of a treated tumor. As expected, the nanoparticles accumulated in the liver with minimal or no delivery to the brain, heart, lung, kidney or spleen. Safety studies showed uptake in the liver did not cause adverse effects.

Using siRNA tailored to the individual gene, the researchers separately shut down the genes STAT3 and FAK in various types of treatment-resistant ovarian cancer tumors. STAT3 and FAK are important to cancer growth, progression and metastasis; however, they also play important roles in normal tissue so targeting precision is vital.

The siRNA/rHDL formulation alone reduced the size and number of tumors by 60 to 80 percent. Combinations with chemotherapy caused reductions above 90 percent.

Conventional approaches to target STAT3 have met limited success, Sood said. FAK, which is over expressed in colorectal, breast, ovarian, thyroid and prostate cancers, is particularly aggressive in ovarian cancer and one reason for its poor survival rate. While previous attempts have targeted FAK with liposomal nanoparticles or small molecule inhibitors, these methods are not tumor-specific and are more likely to harm normal cells, the scientists noted.

Next Step: Clinical Studies

"In order to help expedite the study's progress to a clinical setting, we have identified 12 genes as biomarkers for response to STAT3-targeted therapy," Sood said. "Next, we'll work with the National Cancer Institute Nanoparticle Characterization Lab to develop a formulation of the

HDL/siRNA nanoparticle for human use."

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