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In blood vessel stents, innovative materials allow better control, delivery of gene therapy

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Before gene therapy becomes practical for treating human diseases, researchers must master the details of safe and effective delivery. Cardiology researchers at The Children's Hospital of Philadelphia have advanced delivery techniques by creating a versatile synthetic material that can bind to a variety of gene therapy vectors and can be custom-designed for controlled local release of therapeutic genes at a disease site.

In an animal study, the research team used their new synthetic formulation to bind adenoviruses to bare metal stents, tiny metal scaffolds inside the carotid arteries of rats. Adenovirus served as a gene therapy vector to carry genes for an enzyme that significantly reduced restenosis, the hazardous narrowing of a blood vessel that often occurs despite the presence of a stent designed to hold it open.

Although the materials are in an early stage, the hope is that this method may help to treat artery disease in people. "We developed a synthetic gene delivery system that can be used for any gene therapy vector, not just adenoviruses," said study leader Robert J. Levy, M.D., the William J. Rashkind Chair of Pediatric Cardiology at The Children's Hospital of Philadelphia. "Furthermore, this new formulation allows us to increase the dosage of gene therapy vectors delivered, and we can tune the materials for sustained release over a longer time period."

Levy's group reported its study this week in the online version of the journal *Circulation*, published by the American Heart Association.

Over the past decade, stents have become increasingly useful in treating constricted blood vessels in heart disease and in peripheral artery disease. Stents, which expand partially blocked blood vessels to improve circulation, may be made of bare metal or may have a coating of polymers that release drugs.

Neither type is ideal. Polymer coatings cause inflammation in vessels, which may lead to new bottlenecks at the same time the coating releases drugs meant to reduce vessel injury. Bare metal stents produce less inflammation, but without the benefit of drug delivery. Previously, in a proof-of-principle study in animals, Levy's group attached to stents an extremely thin layer of protein, one molecule thick, containing adenovirus vectors that delivered genes that successfully inhibited restenosis. However, that method had serious limitations; it operated only within a narrow range of temperatures and acidity levels, and was useable only with adenovirus vectors.

The new formulation, said Levy, is more robust, more controllable and adaptable to any virus used as a gene therapy vector, not just adenoviruses. His team synthesized three components into a complex that tethers viral vectors to stent surfaces. One of the three components is an amplifier that increases the dose of gene vector more than fourfold over the previous formulation.

In addition, by varying another component, the stent can be tuned to release vector at a controlled rate that can theoretically be tailored to a schedule appropriate for the particular treatment. "Prior studies have shown that 90 percent of the gene vector is released within 12 to 24 hours, after which vessel blockages regrow," said Levy. "In this study, the stents had significant coverage of the vector seven days later—and less restenosis. Our goal is to customize the materials to allow peak release of the vector when it can have the maximum benefit."

The adenovirus vector carries genes that code for inducible nitric oxide synthase (iNOS), a protein that controls cell damage in blood vessels. In the current study, the iNOS reduced restenosis by 56 percent in the carotid arteries of treated rats, as compared with control animals.

Although this particular study used adenovirus vectors, said Levy, the synthetic formulation could tether any other type of viral gene therapy vector to the metal stents. It might also carry other therapeutic agents in addition to gene vectors. Further studies, he added, will refine these methods and investigate them in larger animal models that more closely simulate human vessel disease.

Source: Children's Hospital of Philadelphia

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