Ultrathin films deliver DNA as possible gene therapy tool

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Gene therapy - the idea of using genetic instructions rather than drugs to treat disease - has tickled scientists' imaginations for decades, but is not yet a viable therapeutic method. One sizeable hurdle is getting the right genes into the right place at the right time.

Engineers at the University of Wisconsin-Madison are now developing a tool to tackle this problem. David M. Lynn and his colleagues have created ultrathin, nanoscale films composed of DNA and water-soluble polymers that allow controlled release of DNA from surfaces. When used to coat implantable medical devices, the films offer a novel way to route useful genes to exactly where they could do the most good.

Lynn, a UW-Madison professor of chemical and biological engineering, has used his nanoscale films to coat intravascular stents, small metal-mesh cylinders inserted during medical procedures to open blocked arteries. While similar in concept to currently available drug-coated stents, Lynn's devices could offer additional advantages. For example, Lynn hopes to deliver genes that could prevent the growth of smooth muscle tissue into the stents, a process which can re-clog arteries, or that could treat the underlying causes of cardiovascular disease.

Preliminary laboratory tests of the DNA-coated materials are promising. "The films survive basic mechanical forces associated with placement and expansion of stents," Lynn says. He and his colleagues have also demonstrated gene delivery to cells grown in a dish.

In preliminary experiments conducted in collaboration with Matthew Wolff, Timothy Hacker, and Jose Torrealba in the UW School of Medicine and Public Health, Lynn has shown that DNA film-coated stents can successfully deliver a gene encoding a fluorescent protein into a rabbit's artery, demonstrating that the films can also work in the complex environment of living tissue. Lynn presented a summary of the work at the annual spring meeting of the American Chemical Society in Chicago on Monday, March 26.

When placed in or near a body tissue, the films are designed to degrade and release the DNA. Large strands of DNA cannot normally penetrate cells, so Lynn constructs his films with special polymers designed to bundle the genes into small tight packages that cells can import. Once inside, the genes instruct the cells to make proteins.

Lynn and his colleagues create the films one layer at a time using a dip-coating method, dunking first in one solution, then another. The individual layers are so thin it would take roughly 10,000 of them to equal the thickness of a single sheet of paper.

As it turns out, making the DNA-containing films is relatively straightforward, Lynn says, but "getting [the DNA] back out of the films is the hard part."

The secret to films that release DNA is in the choice of the polymer and the layer-cake design. The researchers alternate layers of DNA with layers of a polymer that is stable when dry but that degrades when exposed to water. Because the polymers carry a positive electric charge that is attractive to DNA, each polymer layer also "primes" the surface to accept the next layer of DNA. While electrostatic forces between the layers keep the film stable in dry, room-temperature conditions, the polymers break down easily in a wet biological environment - like the inside of a patient's body.

Lynn's laboratory has engineered a whole toolbox of different polymers to fine-tune the DNA delivery properties of their films. Using the layering method, they can control the amount of DNA by adding more layers, or can even layer multiple ingredients in a specific order. Tweaking the polymer structure slightly can change how quickly the films erode and thus how long cells are exposed to the gene therapy. "We ultimately need an effect prolonged enough to be therapeutically relevant - whatever time scale that might turn out to be, " explains Lynn.

The films start to break down when they come into contact with water. "The architecture of the film determines the manner in which [DNA] is released," Lynn says. In his lab, they have developed some films that fall apart all at once, releasing all the ingredients simultaneously.

More recent designs erode like a bar of soap, with the effect that outer layers are released before inner layers. By placing one gene in the outer layers and another in the inner layers, they can deliver different products sequentially.

"This kind of control is extremely difficult to achieve using conventional materials," Lynn explains. A bigger arsenal of tools may allow researchers to tailor films for specific applications. In addition to delivering DNA from stents, Lynn envisions using these nanoscale films to deliver DNA from other implantable devices. The films may also improve methods for engineering lab-grown tissues, in which precisely controlled delivery of multiple DNA- or protein-based agents is required to coax cells to develop into functional tissues and organs. "Our long-term goal is to develop materials useful for localized gene therapy," he says.

Source: University of Wisconsin-Madison