New collagen patch speeds repair of damaged heart tissue in mice

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You can't resurrect a dead cell anymore than you can breathe life into a brick, regardless of what you may have gleaned from zombie movies and Dr. Frankenstein. So when heart cells die from lack of blood flow during a heart attack, replacing those dead cells is vital to the heart muscle's recovery.

But muscle tissue in the adult human heart has a limited capacity to heal, which has spurred researchers to try to give the healing process a boost. Various methods of transplanting healthy cells into a damaged heart have been tried, but have yet to yield consistent success in promoting healing.

Now, researchers at the Stanford University School of Medicine and Lucile Packard Children's Hospital have developed a patch composed of structurally modified collagen that can be grafted onto damaged heart tissue. Their studies in mice have demonstrated that the patch not only speeds generation of new cells and blood vessels in the damaged area, it also limits the degree of tissue damage resulting from the original trauma.

The key, according to Pilar Ruiz-Lozano, PhD, associate professor of pediatrics, is that the patch doesn't seek to replace the dead heart-muscle cells. Instead, it replaces the epicardium, the outer layer of heart tissue, which is not muscle tissue, but which protects and supports the heart muscle, or myocardium.

"This synthetic tissue has the mechanical properties of the embryonic

epicardium," said Ruiz-Lozano, who is the senior author of a study that describes the researchers' findings. The study will be published online Aug. 29 in *Biomaterials*. Vahid Serpooshan, PhD, a postdoctoral scholar in cardiology, is the lead author.

Embryonic epicardium is significantly more flexible than adult epicardium, but more rigid and structured than existing materials, making it more conducive to growth of new tissue. "We paid tremendous attention to the physical properties of the materials and how their elasticity could modify the function of the heart," Ruiz-Lozano said.

The epicardium - or its artificial replacement - has to allow the cell migration and proliferation needed to rebuild damaged tissue, as well as be sufficiently permeable to allow nutrients and cellular waste to pass through the network of blood vessels that weaves through it. The mesh-like structure of collagen fibers in the patch has those attributes, serving to support and guide new growth. Like sugar snap pea vines climbing a garden trellis, blood vessels spread through the interlacing fibers of the patch, blossoming new muscle cells like peapods as they proliferate.

Collagen is a fibrous protein found in connective tissue, including skin, bone, cartilage and tendons, as well as in the epicardium. Because the patch is made of acellular collagen, meaning it contains no cells, recipient animals do not need to be immunosuppressed to avoid rejection. With time, the collagen gets absorbed into the organ.

Compared with control mice that received no patch, mice that were given the patch promptly after experiencing a surgically induced heart attack showed significant improvement in overall cardiac function in echocardiograms two weeks later. The patched hearts showed more migration of cells to the site of the injury four weeks after patch implantation. The new cells were present both in the patch and in the adjacent damaged heart tissue.

The patched hearts also had greater development of new blood vessels, which appeared to have improved delivery of oxygen and nutrients to the tissue, thus reducing the number of cells that perished compared to unpatched hearts.

In addition to helping heart tissue regenerate, the patch could be used as a delivery system for getting medications or stem cells into a patient, Ruiz-Lozano said.

Daniel Bernstein, MD, professor of pediatric cardiology and a co-author of the paper, said the potential of the patch as a delivery system could make it useful in treating children with heart problems.

"For pediatric patients with congenital heart disease, or who have heart damage from a viral infection or other heart injury, we could use this to introduce growth factors directly to the heart in a way that would persist for a long period of time," he said.

Ruiz-Lozano and her colleagues are already at work on studies to explore the use of the patch as a delivery system, along with conducting studies of how the patch will perform in larger animals.

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