Heart attack damage reduced by shielded stem cells

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Samira Aghlara-Fotovat, a bioengineering graduate student at Rice University, with a vial of stem cell-loaded capsules she formulated to repair damage caused by heart attacks. Credit: Jeff Fitlow/Rice University

Bioengineers and surgeons from Rice University and Baylor College of

Medicine (BCM) have shown that shielding stem cells with a novel biomaterial improves the cells' ability to heal heart injuries caused by heart attacks.

In a study using rodents, a team led by Rice's Omid Veiseh and Baylor's Ravi Ghanta showed it could make capsules of wound-healing mesenchymal stem cells (MSCs) and implant them next to wounded hearts using minimally invasive techniques. Within four weeks, heart healing was 2.5 times greater in animals treated with shielded stem cells than those treated with nonshielded stem cells, the researchers found.

The study is available online in the Royal Society of Chemistry journal *Biomaterials Science*.

Someone has a heart attack every 40 seconds in the United States. In each case, an artery that supplies blood to the heart becomes blocked and heart muscle tissue dies due to lack of blood. Hearts damaged by heart attacks pump less efficiently, and scar tissue from heart attack wounds can further reduce heart function.

"What we're trying to do is produce enough wound-healing chemicals called reparative factors at these sites so that damaged tissue is repaired and restored, as healthy tissue, and dead tissue scars don't form," said Veiseh, an assistant professor of bioengineering and CPRIT Scholar in Cancer Research at Rice.

Ghanta, associate professor of surgery at Baylor, a cardiothoracic surgeon at Harris Health's Ben Taub Hospital and co-lead author of the study, said prior studies have shown that MSCs, a type of adult stem cell produced in blood marrow, can promote tissue repair after a heart attack. But in clinical trials of MSCs, "cell viability has been a consistent challenge," Ghanta said.

"Many of the cells die after transplantation," he said. "Initially, researchers had hoped that stem cells would become heart cells, but that has not appeared to be the case. Rather, the cells release healing factors that enable repair and reduce the extent of the injury. By utilizing this shielded therapy approach, we aimed to improve this benefit by keeping them alive longer and in greater numbers."

A few MSC lines have been approved for human use, but Veiseh said transplant rejection has contributed to their lack of viability in trials.

"They're allogenic, meaning that they're not from the same recipient," he said. "The immune system perceives them as foreign. And so very rapidly, the immune system starts chewing at them and clearing them out."

Veiseh has spent years developing encapsulation technologies that are specifically designed not to activate the body's immune system. He co-founded Sigilon Therapeutics, a Cambridge, Massachusetts-based biotech company that is developing encapsulated cell therapeutics for chronic diseases. Trials of Sigilon's treatment for hemophilia A are expected to enter the clinic later this year.

"The immune system doesn't recognize our hydrogels as foreign, and doesn't initiate a reaction against the hydrogel," Veiseh said. "So we can load MSCs within these hydrogels, and the MSCs live well in the hydrogels. They also secrete the same reparative factors that they normally do, and because the hydrogels are porous, the wound-healing factors just diffuse out."

In previous studies, Veiseh and colleagues have shown that similar capsules can keep insulin-producing islet cells alive and thriving in rodents for more than six months. In the heart study, study co-lead author Samira Aghlara-Fotovat, a Rice bioengineering graduate student

in Veiseh's lab, created 1.5-millimeter capsules that each contained about 30,000 MSCs. Several of the capsules were placed alongside wounded sections of heart muscle in animals that had experienced a heart attack. The study compared rates of heart healing in animals treated with shielded and unshielded stem cells, as well as an untreated control group.

"We can deliver the capsules through a catheter port system, and that's how we imagine they would be administered in a human patient," Veiseh said. "You could insert a catheter to the area outside of the heart and inject through the catheter using minimally invasive, image-guided techniques."

Veiseh said capsules in the study were held in place by the pericardium, a membrane that sheaths the heart. Tests at two weeks showed that MSCs were alive and thriving inside the implanted spheres.

More than 800,000 Americans have hearts attacks each year, and Ghanta is hopeful that encapsulated MSCs can one day be used to treat some of them.

"With further development, this combination of biomaterials and stem cells could be useful in delivering reparative therapy to heart attack patients," he said.

Veiseh said the pathway to regulatory approval could be streamlined as well.

"Clinical grade, allogenic MSCs are commercially available and are actively being used in patients for a range of applications," he said.

Veiseh credited Aghlara-Fotovat with doing much of the work on the project.

"She basically executed the vision," he said. "She developed the hydrogel formulation, the concept of how to package the MSCs within the hydrogel, and she did all the in vitro validation work to show that MSCs remained viable in the capsules."

Aghlara-Fotovat is co-mentored by Ghanta and worked in his lab at Baylor alongside research assistant Aarthi Pugazenthi, including assisting in rodent surgeries and experiments.

"What attracted me to the project was the unmet clinical need in (heart attack) recovery," Aghlara-Fotovat said. "Using hydrogels to deliver therapeutics was an exciting approach that aimed to overcome many challenges in the field of drug delivery. I also saw a clear path to translation into the clinic, which is the ultimate goal of my Ph.D."

"I think one of the things that attracts students to my lab in particular is the opportunity to do translational work," Veiseh said. "We work closely with physicians like Dr. Ghanta to address relevant problems to human health."

More information: Ravi K. Ghanta et al, Immune-modulatory alginate protects mesenchymal stem cells for sustained delivery of reparative factors to ischemic myocardium, *Biomaterials Science* (2020). DOI: 10.1039/D0BM00855A

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