Transplanted adult stem cells provide lasting help to injured hearts

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Human adult stem cells injected around the damage caused by a heart attack survived in the heart and improved its pumping efficiency for a year in a mouse model, researchers at The University of Texas MD Anderson Cancer Center report online ahead of publication in *Circulation Research*.

The study, with researchers at the Texas Heart Institute at St. Luke's Episcopal Hospital, used innovative imaging techniques developed by researchers at MD Anderson to track the stem cells' location and performance over time.

Injection of a patient's own adult stem cells into the heart has shown some efficacy in assisting recovery after a heart attack in early human clinical trials, said study senior author Edward T. H. Yeh, M.D., professor and chair of MD Anderson's Department of Cardiology.

"But nobody knows how they work, or how long the stem cells last and function in the heart," Yeh said. "This study shows how one type of adult stem cell works."

The team's research focused on adult stem cells - those that can differentiate into a limited variety of tissues - that circulate in the blood and are distinguished by the presence of the CD34 protein on the cell surface. These CD34-positive cells usually differentiate into blood vessel cells, also known as endothelial cells.

Earlier research by Yeh and colleagues showed CD34+ cells are capable of becoming heart muscle cells, called cardiomyocytes, blood vessel cells and smooth muscle cells.

A series of experiments showed:

- The CD34+ cells survived in the left ventricle of the heart for 12 months or longer.
- Left ventricular ejection fraction - a measure of how much blood is pumped from the heart to other organs at each contraction - improved in treated mice compared with controls for 52 weeks. LVEF went from 50 percent at baseline to 37 percent after heart attack and treatment, compared with 51 percent and 28 percent in untreated mice.
- This improvement was the result of increased blood vessel formation in and around the injured area, or paracrine signaling by the stem cells to other nearby cells, rather than formation of new heart muscle. Using an antibody technique developed by Yeh and colleagues, the team found that antibodies that blocked formation of new blood vessels completely negated the treatment benefit while antibodies that blocked heart muscle cell formation had no effect.

Ventricular ejection fraction measures the percentage of blood pumped from the heart at each contraction and is one of the most important measures of how the heart functions, Yeh said. LVEF normally is around 55 to 60 percent. Some cancer chemotherapies weaken the heart. "Oncologists pay very close attention to the ejection fraction in their patients, because when it drops, they won't give chemotherapy," Yeh said.

Multiple imaging methods pinpoint location, performance of transplanted stem cells

Developing and refining non-invasive monitoring of the heart is important for cancer patients, said senior co-author Juri Gelovani, M.D., Ph.D., professor and chair of MD Anderson's Department of Experimental Diagnostic Imaging.

"We need to develop methods for non-invasive monitoring by molecular-genetic and functional imaging of the fate of transplanted stem cells as they contribute regeneration of cardiac tissues and recovery of the heart's contractile function" Gelovani said. "We want to give the gift of sight to an otherwise very blind area of stem cell transplantation research."

After tying off an artery to the heart to induce a heart attack in the mice, the team then injected the mouse CD34+ cells around the damaged area in the treatment cohort. Before injection, a triple-fusion reporter gene was introduced via retrovirus into the CD34+ cells. The triple-fusion reporter allows for visualization of the stem cells using three different imaging methods after injection into the mice.

This triple reporter vector was invented by Gelovani and optimized for stem cells by senior research scientist Brian Rabinovich, Ph.D., of Experimental Diagnostic Imaging. The tri-fusion reporter gene delivers green fluorescence protein for imaging in tissue or cell culture, firefly luciferase for bioluminescent imaging, and the HSV1-tk gene, which is a reporter gene for positron emission tomography (PET) imaging. All three are expressed by the CD34+ cells and their progeny in the mouse hearts and provide the means for long-term monitoring of their fate by repetitive, multi-modal, non-invasive imaging.

Researchers used bioluminescence imaging to study how long the injected stem cells survived in the heart. PET/CT imaging coupled with magnetic resonance imaging (MRI), pinpointed the precise location of stem cells' in the heart muscle.

MRI also was used to measure ejection fraction and to assess the efficacy of the stem cell therapeutic approach for improving cardiac contractile function. This MRI technique relies on an innovative approach developed by co-author Jim Bankson, Ph.D., assistant professor in MD Anderson's Department of Imaging Physics, to match the MRI images to the motion caused by the beating heart, while associate professor Luc Bidaut, Ph.D., had optimized methods to overlay the PET/CT and MR images.

Bioluminescence imaging works well in small animals because the distance between detectors and the photon-emitting cells is short, it is unlikely to work in larger animals or humans for a variety of reasons. The PET/CT and MRI techniques used in the experiment are readily translatable into the clinic, Gelovani noted. The team used a new PET imaging agent called [18F]FEAU which, when acted upon by the HSV1-tk reporter gene, entrapped this radio-labeled PET agent inside the transplanted cells, enabling their detection in the heart by PET/CT imaging.

Gelovani said his team is developing an investigational new drug protocol for a Phase I human clinical trial using [18F]FEAU PET/CT imaging to monitor HSV1-tk or hTK2 reporter gene-labeled stem cells after transplantation in human patients.

Provided by University of Texas M. D. Anderson Cancer Center