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Researchers discover 'sticky' proteins fuse adult stem cells to cardiac muscle, repairing hearts

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Cardiologists are increasingly using adult stem cells in clinical trials to repair hearts following heart attacks, but no one has understood how the therapy actually works. Now, in animal experiments, researchers at The University of Texas M. D. Anderson Cancer Center have deconstructed the process, describing how the stem cells fuse with heart muscle cells to create new cells that repopulate the ailing organ.

In a paper posted Feb 15 at Online First of the journal *Circulation Research*, investigators found that this fusion is only possible if two cell adhesion proteins that stick to each other like Velcro are available to attach a stem cell to a heart muscle cell. They show in cell and mice studies that if either protein is blocked, the two cells don't blend.

The investigators also discovered that these new cells, once fused, divide again in an attempt to produce enough cells to help the heart contract.

"The accepted dogma is that heart cells cannot divide, but we show that fusing stem cells onto muscle cells bestows these cells with a new and wonderful ability to divide again to repair the heart," says the study's lead author Edward T. H. Yeh, M.D., professor and chair of the Department of Cardiology at M. D. Anderson Cancer Center.

"It is marvelous that adult stem cells can help heal a heart, and by understanding the mechanisms involved, we may be able to refine and

optimize the process," he says.

But there are not enough natural stem cells available in a body to mount an effective repair response to a heart attack, Yeh says, which is why researchers and clinicians are focused on boosting that response. And in the future, given what the researchers also have discovered about how stem cells can build new cells to line blood vessels, it may be possible to "choose to ether augment rebuilding of heart muscle or restoration of blood vessels, depending on what is therapeutically best for the patient."

This study is the latest undertaken in a focused research program conducted by Yeh and a team of researchers at M. D. Anderson, the Texas Heart Institute at St. Luke's Episcopal Hospital and The University of Texas Health Science Center at Houston to investigate stem cell repair of heart and vascular tissue. In an effort to understand and treat cardiotoxicity related to cancer treatment, M. D. Anderson has one of the largest cardiology programs at any cancer center.

In 2003, the researchers demonstrated that adult stem cells circulating in blood can be used to repair hearts, and that it is not necessary to take the stem cells from bone marrow. In 2004, they found stem cells use different methods to morph into the two kinds of cells needed to restore heart function. In animal studies, they showed that to make new heart muscle cells, the human stem cells fuse onto cardiac cells to produce new muscle (myocyte) cells. But to form new blood vessel cells, the stem cells "differentiate" or mature by themselves to provide new endothelial cells that patch vessel damage.

In this study, they looked into the mechanism by which stem cells fuse to cardiac myocytes. In laboratory experiments, they added adult human stem cells (those that express the CD34+ protein known to be associated with stem cells) to cardiac muscle cells from mice. After 24 hours, some fusion occurred spontaneously - cells were created that had both human

and murine protein signatures - but this occurred at a very low rate. They then created conditions that reflect an ongoing heart attack, such as exposing the cells to low oxygen, and saw production of two cytokine molecules, IL-6 and TNF-a, that are part of an inflammatory reaction and which are known to be released when a heart attack occurs. Next, the researchers exposed the cells to all three conditions simultaneously (hypoxia, and extra IL-6 and TNF-a) and found that cell fusion increased 10-fold. "It went from .2 percent of cells becoming fused to 2 percent," Yeh says.

The researchers noted that as a consequence of the experimental "heart attack," expression of two cell surface adhesion molecules was increased. Expression of the protein a4ß1 was induced in the mouse cardiac cells and VCAM-1 was expressed by human stem cells. "The two molecules act like a pair, and stick to each other," Yeh says. "This is the first step to the fusion process."

To double-check that production of a4ß1 and VCAM-1 were critical to cell fusion, the research team added antibodies to each protein into the cell culture, and found fusion couldn't occur.

They then tested the fusion process in mice that don't have an immune system, so they cannot reject the human stem cells. They induced a heart attack in the animals, injected stem cells and saw production of fused cells with signatures donated by each species. However, fusion was markedly reduced in mice given antibodies to a4ß1 and VCAM-1, Yeh says.

The researchers tested whether the adhesion molecules interrupted production of new blood vessel endothelial cells, and found that because fusion is not involved, formation of these cells was not affected. Then they blocked vascular endothelial growth factor (VEGF), a protein known to spur the formation of new blood vessels, and found that if

VEGF isn't available, stem cells will not differentiate into new endothelial cells.

Finally, Yeh tested the newly fused heart muscle cells to see what they did after they formed. Heart muscle cells do not divide, so the researchers did not know whether the new fused cells were an endpoint in themselves, designed to replace dying cardiac muscle, or whether they could give rise to other new cells. They discovered that fused cells took on some "stemness" - they divided, and continued to do so as long as new tissue is needed, but not long enough to produce a tumor. "In mice, we have found this process can continue for months," Yeh says.

"We show in these animal experiments that human adult stem cells can form new blood vessels and heart muscle cells, and knowing how these two different processes can be blocked could be very useful in determining the relative contribution of each toward heart repair," he said.

Source: University of Texas M. D. Anderson Cancer Center