MEDICAL RESEARCH

New Cell Transplants May Mend a Broken Heart

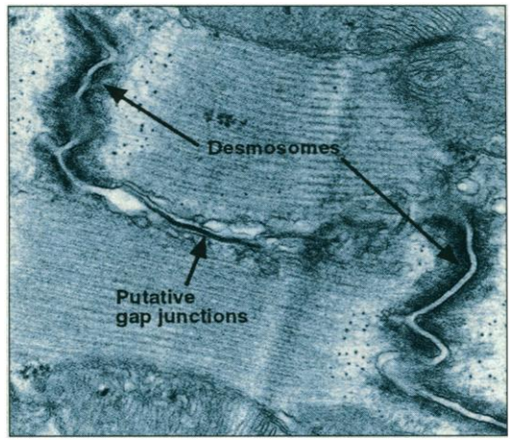
During a human life, the cells of the heart must accomplish a formidable task. They will have to contract 3 billion times in unison, exerting enough force to flush 5 liters of blood through the narrow confines of the arteries. Yet despite all the wear and tear this constant activity imposes on the heart's muscle cells, each must last as long as the person does, for heart muscle cells, unlike other muscle cells, lack the ability to divide. If the heart muscle is damaged—by a heart attack, say—the damaged area can't repair itself. Now, a research team from Indiana University School of Medicine in Indianapolis has made significant headway toward developing a new technique that might one day be used to mend crippled hearts.

On page 98, Mark Soonpaa, Gou Young Koh, Michael Klug, and Loren Field report the first successful attempt to transplant individual heart muscle cells into a live animal—a mouse—and have them form the tight bonds with the host heart cells needed for the transplants to contribute to pumping blood. "It's exciting. What it does is raise the possibility of cellular transplantation [in humans]," says cardiologist Jeffrey Leiden of the University of Chicago.

At this early, experimental stage, no one can say whether that possibility will ever be realized. But if it is, the impact on heart disease would be immense. Every year in the United States, 1.5 million people suffer heart attacks. A third of them die, and many of the survivors are left with disabling heart damage. Heart transplants are the most effective form of therapy for severe heart damage, but they are expensive, risky, and there is a chronic shortage of available hearts. But patients with severe damage from heart attacks or other conditions "could be ideal candidates for cardiac cell transplants," says cardiologist Elizabeth Nabel of the University of Michigan in Ann Arbor.

The implications of the Field team's work don't stop with damage repair. Their experiments also offer hope for gene therapy to prevent future heart attacks. Some researchers speculate that the transplanted cells could be genetically modified to manufacture growth factors that would encourage blood vessels to invade the heart muscle, enriching its blood supply, and possibly preventing repeat episodes.

For their transplant study, the Field team wanted to use muscle cells that are capable of dividing and making new attachments, on the assumption that such cells would be better able to invade the heart muscle. So they took cardiac muscle cells from mouse fetuses at the 15th day of gestation—before those cells lose their capacity to divide. To distinguish transplanted cells from those of the recipients, the donor mice had been genetically modified so that the nuclei of their cardiac muscle cells turn blue when appropriately stained. Some 10,000 cells from the donor mice were then injected into the wall of the left ventricle—the most powerful heart chamber—of each recipient mouse.



MARK SOONPAA

Bridging the gap? Transplanted fetal heart muscle cell (*above*) may form electrical links to host cells through gap junctions in addition to making physical connections through desmosomes.

After the mice had recovered from their operations, they seemed entirely normal—and so did their hearts, says Field. Their EKGs, for example, were completely normal. Two months later, when Field and his colleagues took a direct look at the heart muscle tissue of the recipient mice, the results were even more encouraging. They found that the transplanted cells were still there, having survived in the foreign tissue.

The transplanted cells have to do more than survive, however, to be of use to the heart. To be effective, heart muscle cells must all pull together like members of a tug-of-war team. And to do that, says Field, "muscles cells need to talk to one another and they need to be glued to one another."

When the Indiana workers examined the heart tissue from their transplant recipients under an electron microscope, they found that the transplanted cells were indeed firmly cemented to one another and to the host cells through connections called desmosomes. That tight connection represents a significant advance over previous transplant experiments by the Field group using genetically transformed adult skeletal or cardiac muscle cells. Those cells failed to fuse with the host cells. Field believes the fetal cells succeeded because they possessed all the surface characteristics needed for one cell to attach to another; the other cells had lost some of those characteristics during the laboratory manipulations.

Nonetheless, initially at least, the Field team's success seemed only partial, because even though the transplanted cells had fused to the recipients, the researchers could find no evidence that the two could actually communicate. Although the desmosomes were there, the researchers couldn't find any gap junctions, the communication pathways for the electrical messages that ensure that muscle cell contraction is coordinated.

But in the last few weeks, the Field team has had the first inkling that those gap junctions might be present after all. After further scrutiny of the electronmicrographs, Field, Soonpaa, Koh, and Klug have discovered a set of gap junctions between a transplanted and host cell. It suggests, says Field, that "the cells have the hard wiring necessary for the propagation of [the electrical messages]." But, he cautions, "we still need physiological proof," such as evidence of dye transfer, or the transmission of an electrical signal across the gap.

And that's only one of many barriers the Field team must overcome before they can think of testing the technique in humans. For example, the researchers must also show that they can transplant enough cells into an animal heart to boost its pumping ability. And they need to find out whether it's necessary to use dividing cells, as they now think. If it is, they will either have to use fetal cells, which could raise ethical objections, or they will need to find a way of triggering adult heart muscle cells to divide. And that, cautions Leiden, "is going to be very difficult" since so little is known about what stops adult heart muscle cells dividing in the first place.

Difficult or not, that's exactly what the Field team hopes to achieve—one day. "Somewhere, way down the road," says Soonpaa, "we hope to be able to alter adult [heart muscle] cells, so that they act like fetal cardiac muscle cells." With such a technique, tiny pieces of the healthy heart tissue remaining after a heart attack could be used to generate cells for transplantation. And that distant hope is a particularly bright one; it could alleviate not only the shortages of transplanted hearts but also—because the cells are the patient's own—the dangers involved in receiving foreign tissue.

–Rachel Nowak