

Guinea pig hearts beat with human cells

Cardiac cells derived from human stem cells can integrate into injured hearts.

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Damaged skin and liver can often repair themselves, but the heart rarely heals well and heart disease is the world's leading cause of death. Research published today raises hopes for cell therapies, showing that heart muscle cells differentiated from human embryonic stem cells can integrate into existing heart muscle[1].

"What we have done is prove that these cells do what working heart muscles do, which is beat in sync with the rest of the heart," says Chuck Murry, a cardiovascular biologist at the University of Washington in Seattle, who co-led the research.

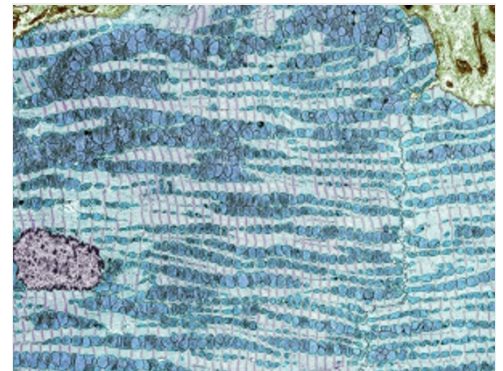
It has been difficult to assess cell therapies in animal models because human cells cannot keep up with the heart rates of some small rodents. Cardiomyocytes derived from human embryonic stem (ES) cells typically beat fewer than 150 times a minute. External electrical stimulation can increase that rate, but only up to about 240 beats per minute, says Michael LaFlamme, a cardiovascular biologist at the University of Washington and the other co-leader on the project. Rats and mice have heart rates of around 400 and 600 beats per minute, respectively.

However, guinea pigs have a heart rate of 200–250 beats per minute, near the limit for human cardiomyocytes. After working out ways to suppress guinea pigs' immune systems so that they would accept human cells, Murry, LaFlamme and their co-workers began transplantation experiments. They also devised a way to make assessing electrical activity straightforward: using recent genetic-engineering technology, they inserted a 'sensor' gene into the human ES cells so that cardiomyocytes derived from them would fluoresce when they contracted.

From the first experiment with the sensor in guinea pigs, it was obvious that the transplanted cells were beating in time with the rest of the heart, says LaFlamme. When he looked into the chest cavity, the heart "was flashing back at us", he says.

Healing heart

The human cells seemed to aid healing: four weeks after the researchers killed regions of the guinea pigs' hearts to simulate a heart attack, the hearts of animals that received cardiomyocytes exhibited stronger contractions than those that received other cell types. And cardiomyocyte transplants did not seem to cause irregular heartbeats, a common concern for cell-replacement therapy in the heart. In fact, the transplants seemed to suppress arrhythmias.



MEDIMAGE / SPL

When transplanted into guinea pig hearts, human heart muscle cells (pictured) can beat in time with resident cells.

But it will be a long road from demonstrating this sort of integration to demonstrating possible therapeutic benefits, says Glenn Fishman, a cardiologist at New York University Langone School of Medicine, who was not involved in the work. “The conclusion that the human cells can connect with the guinea pig tissue is true,” he says, “but the clinical implications are a bit of a stretch.”

Cardiomyocytes engrafted in only a tiny percentage of scar tissue, Fishman explains, and the area seems too small to produce much additional pumping force. He suspects that the benefits seen stem from the 'paracrine effect', in which transplanted cells secrete factors that rejuvenate damaged host tissue. In fact, many researchers are exploring such strategies to prompt damaged heart tissue to restore itself, he says.

Extrapolating from results in guinea pigs is difficult, adds Ronald Li, who leads a programme in cardiac stem-cell engineering at Mount Sinai Hospital in New York City. Li says that his recent unpublished work in dogs and pigs shows that transplanting cardiomyocytes derived from human ES cells can cause arrhythmias.

Both Murry and LaFlamme agree that much more work needs to be done before transplantable cardiomyocytes are ready for human trials. The more immediate goal, says LaFlamme, is to hunt for experimental conditions that allow cells to engraft in scar tissue more thoroughly. It's exciting “to see that the cells can couple electrically”, he says. “Now we can test new strategies to make more couple.” And although cell transplants to humans might be a long way off, he adds, “I think it's a nut we can crack.”

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References

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1. Shiba, Y. *et al. Nature* <http://dx.doi.org/10.1038/nature11317> (2012).