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Researchers discover newborn rats hold secret to manufacturing human heart cells

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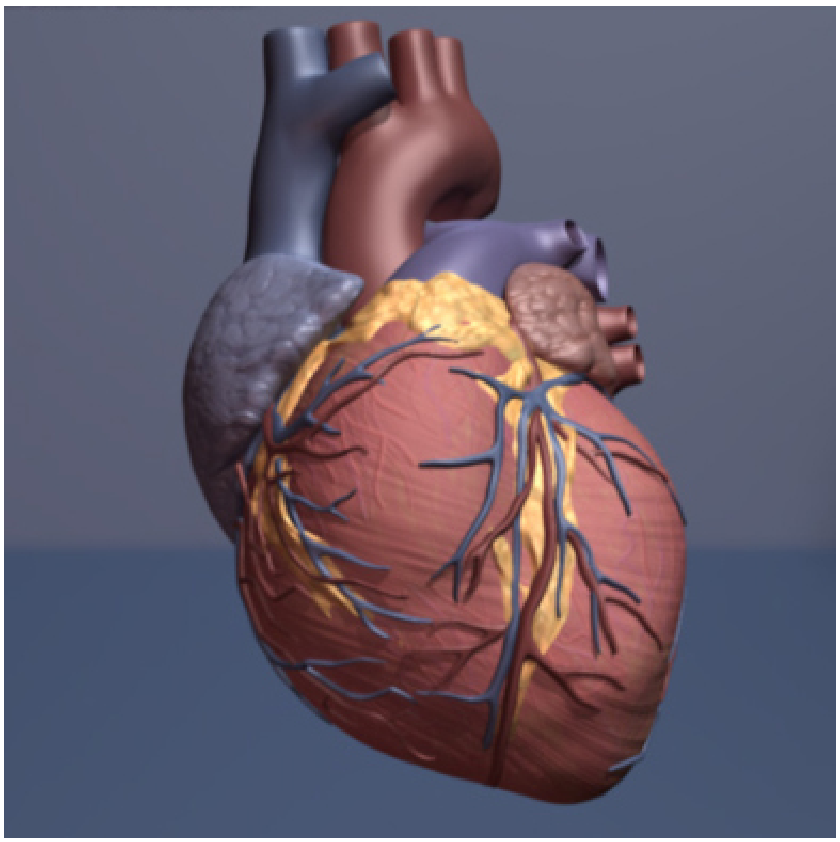

Human heart. Credit: copyright American Heart Association

Human heart muscle cells can be created in the lab, but researchers have been unable to grow the immature cells to the point where they could be useful.

It's a conundrum that's stumped researchers in regenerative medicine.

"You cannot really use them for regeneration. You cannot even use them for disease models," said Chulan Kwon, a professor at the Johns Hopkins School of Medicine.

But Kwon said he's discovered a solution for the problem in an unlikely place - newborn rats - and he published a study about his research in January in the journal *Cell Reports*.

When immature human heart cells are injected into baby rats, they match the rodents' rapid growth cycle and develop fully. These rats act as living incubators, said Dr. David Kass, a Hopkins professor and cardiologist who co-authored the study.

"The biological environment gives you whatever the magic juice is," Kass said. "There were a lot of people looking for this magic juice."

Researchers at the University of Washington, Harvard and Stanford universities and beyond have been working to solve this puzzle fundamental to regenerative medicine.

"Laboratories throughout the world are working on this," said Dr. Richard Lee, a Harvard professor of stem cell and regenerative biology. "We are all very excited that we can make heart cells, but they're heart cells like an infant's heart cells. We want to make heart cells like our patients, who are mostly adults."

Lee said his research team is working to unravel the conditions that stimulate cells to mature inside the body. He praised the Hopkins discovery.

"It's a very nice step forward," Lee said.

Dr. Charles Murry at the University of Washington also has tried to grow the cells to maturity.

"We tried a whole lot of things that didn't work," he said. "Sort of like Edison and the light bulb."

Murry has seen some positive signs when feeding the cells fat instead of sugar.

"But we haven't seen anything that works as well as putting them back into their natural environment, which is back into a heart," he said.

Soon after the late 1990s when researchers isolated embryonic stem cells , people in the field wondered if the process could be used to grow heart muscles in the lab and someday repair the lasting damage from heart attacks and disease. Researchers in 2007 developed methods to modify skin cells to behave as stem cells, and, about five years later, Murry's research team at the University of Washington developed techniques to activate these modified skin cells into early forms of heart muscle cells.

From there researchers have worked to fully develop them into heart cells, a feat that has proven elusive.

Kass, the Hopkins researcher, compares the cell to a car engine. In an undeveloped state, the engine parts are present but scrambled, so the engine doesn't function.

"When you look at a normal heart muscle cell, it's an exquisitely complicated and well organized engine. Every little protein has to be positioned precisely," Kass said. "This doesn't work if they're willy-nilly, oriented randomly and loosely around the cell."

These undeveloped cells have about 1 percent of the pumping force of an adult heart cell, Kwon said.

"The frustrating thing is even if you culture the dish for more than a year," he said, "they're just kind of stuck in embryonic stages."

Around the summer of 2013, he began experimenting with rats. He uses newborn rats engineered to have no immune system. This ensures the pups don't reject the foreign cells. Mouse hearts were too small.

He injects the rat hearts with as many as 200,000 human cells. These human cells are tagged with a protein that glows green or red under fluorescent light. After about a week, the cells remained immature. But after a month, they appeared developed. The researchers tested these cells and found they could contract or beat precisely like an adult heart cell.

The researchers suspect two forces at play: The rats faster life cycle quickens the cells' development. And the rats' biological cues cause the cells to leap the threshold into maturity.

"So the million dollar question would be: What are those cues?" Kwon said.

Their work was published Jan. 10 in *Cell Reports*, an open-access journal, and they're still trying to pinpoint the cues.

Further discoveries might allow them to replicate the cues in a petri dish and expedite cell growth by avoiding the delicate injections into rat hearts. While promising, their methods remain too small in scale to offer much help to patients. At least, not yet.

"It has to be a bit more practical," Kass said. "If you're injecting things into rat neonates, they're small. So how many cells can you really get in there, and how many can you actually find?"

The ability to culture larger quantities would allow doctors to test heart medicines on a patients' own cells, furthering the emerging trend of precision medicine.

In 2015, President Barack Obama announced a $215 million precision medicine initiative aimed at developing treatments that consider someone's genes, environment and lifestyle. The grant money funds efforts at the National Institutes of Health and the National Cancer Institute to advance such treatments.

Dr. Roberto Bolli at the University of Louisville School of Medicine sees potential in the rat method for screening patients with different medicines. Doctors could swab the cheek of a particular patient, modify the cheek cells to behave as stem cells, activate them into early heart cells, and inject them into the rats.

Once grown, the cells could be tested with various treatments.

"This would help tremendously to understand the mechanism or these hereditary diseases and also screen for drugs," Bolli said.

The Hopkins researchers are taking steps to produce more mature cells. Kwon said they will try the method with pig hearts, which are larger and can hold more implanted cells.

"If we can really scale this up," he said, "it has a lot of utilities."

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