MedicalXpress

# Scientists show lab-made heart cells ideal for disease research, drug testing

April 18 2012

Heart-like cells made in the laboratory from the skin of patients with a common cardiac condition contract less strongly than similarly created cells from unaffected family members, according to researchers at the Stanford University School of Medicine. The cells also exhibit abnormal structure and respond only dully to the wave of calcium signals that initiate each heartbeat.

The finding used induced pluripotent stem, or iPS, cell technology to create heart-muscle-like cells from the skin of patients with dilated cardiomyopathy, which is one of the leading causes of heart failure and heart transplantation in the United States. It adds to a growing body of evidence indicating that iPS cells can faithfully reflect the disease status of the patients from whom they are derived.

Using the newly created diseased and normal cells, the researchers were able to directly observe for the first time the effect of a common beta blocker drug, as well as validate the potential usefulness of a gene therapy approach currently in clinical trials.

"Primary human cardiac cells are difficult to obtain and don't live long under laboratory conditions," said Joseph Wu, MD, PhD, associate professor of cardiovascular medicine. Instead, researchers have relied on studies of cells from rodent hearts, which beat much more quickly, to understand more about human heart disease. "Now we've created heart cells from iPS cells derived from skin that allow us to study in detail the mechanisms of a common cardiac disease and how these cells respond to

clinical interventions."

Wu is the senior author of the research, which will be published April 18 in *Science Translational Medicine.* Postdoctoral scholar Ning Sun, MD, PhD, is the first author. The work is the latest in a type of research that's sometimes referred to as "disease-in-a-dish" studies. Using iPS technology, other researchers have created stem cells from patients with Parkinson's disease, Marfan syndrome and amyotrophic lateral sclerosis, among others.

The implications of such research are huge. According to Wu, one of the major reasons cardiac drugs are pulled from the market is unexpected cardiac toxicity — that is, they are damaging the very hearts they're meant to help. Currently, such drugs are pre-screened for toxic effects on common laboratory cell lines derived from either hamster ovaries or human embryonic kidney cells. Even though these ovarian and kidney cells have been artificially induced to mimic the electrophysiology of human heart cells, they are still very different from the real thing. A reliable source of diseased and normal human heart cells on which to test the drugs' effect prior to clinical use could improve drug screening, save billions of dollars and improve the lives of countless patients.

Dilated cardiomyopathy occurs when a portion of the heart muscle enlarges and begins to lose the ability to pump blood efficiently. Eventually, the enlarged muscle begins to weaken and fail, requiring either medication or even transplant. Although many cases occur sporadically and without an apparent cause, dilated cardiomyopathy can also be inherited via a variety of genetic mutations.

Wu and Sun performed skin biopsies on seven members of three generations of a family with the inherited form of the condition (called familial dilated cardiomyopathy). Four of the family members had inherited a specific genetic mutation — in a gene called TNNT2 — that

causes the disease; the other three had not. The researchers used iPS technology to convert skin cells from the affected and unaffected family members into stem cells, which they then coaxed to become heart muscle cells for further study. They then compared cells from unaffected family members with those who had the disease.

"We didn't know exactly how the mutation carried in this family would impact the contractility of the cells," said Sun. "Other studies had indicated that this mutation decreased calcium sensitivity in rodent cells, but we had no direct biochemical data on human cells. We were able to show that the force of contraction was lower in cells from patients with the mutation. We also saw that, as predicted in the rodent model, they were less responsive to calcium signaling." (In a normal heart, rapid, periodic increases in calcium levels inside heart cells trigger each contraction.)

Wu and Sun also saw that the diseased cells exhibit structural differences and are more susceptible to mechanical stress than unaffected cells.

When the researchers treated the diseased cells with metoprolol, a beta blocker commonly used to treat cardiomyopathy, they found that it decreased the frequency of contractions as expected. It also increased the responsiveness of the cells to calcium and, over time, helped resolve some of the structural differences between affected and unaffected cells.

Finally, they showed that adding a protein called Serca2a, which may inhibit the deleterious effect of the mutated TNNT2 gene, significantly improved the contraction forcefulness of the diseased cells. Serca2a is currently in clinical trials as a possible gene therapy for dilated cardiomyopathy.

"Next, we'd like to continue looking at cells from patients with other mutations associated with this disorder," said Wu. "How do they behave

in culture? Do they respond in the same way? What is the mechanism for their response? What changes if we selectively introduce different mutations into these cells? And how do we scale up drug screening using cardiac specific iPS cell lines?"

Provided by Stanford University Medical Center