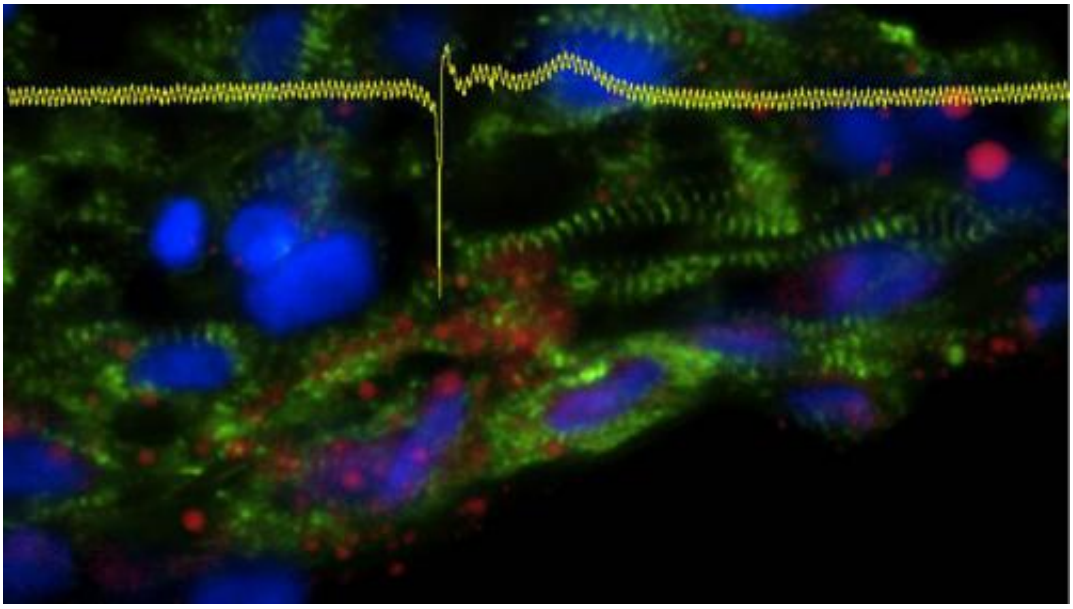
Patients' skin cells transformed into heart cells to create 'disease in a dish'

January 27 2013



In this study, researchers used an ARVD/C patient's skin cells to make induced pluripotent stem cells. Then they used those stem cells to generate ARVD/C patient-specific heart cells (shown here in green). These heart cells provide a valuable ?disease in a dish? model that can be used to study ARVD/C and test new treatments. Credit: Sanford-Burnham Medical Research Institute

Researchers use skin cells from patients with an inherited heart condition to recreate the adult-onset disease in a laboratory dish—producing the first maturation-based disease model for testing new therapies.

Most patients with an inherited heart condition known as arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) don't know they have a problem until they're in their early 20s. The lack of symptoms at younger ages makes it very difficult for researchers to study how ARVD/C evolves or to develop treatments. A new stem cell-based technology created by 2012 Nobel Prize winner Shinya Yamanaka, M.D., Ph.D., helps solve this problem. With this technology, researchers can generate heart muscle cells from a patient's own skin cells. However, these newly made heart cells are mostly immature. That raises questions about whether or not they can be used to mimic a disease that occurs in adulthood.

In a paper published January 27 in *Nature*, researchers at Sanford-Burnham Medical Research Institute and Johns Hopkins University unveil the first maturation-based "disease in a dish" model for ARVD/C. The model was created using Yamanaka's technology and a new method to mimic maturity by making the cells' metabolism more like that in adult hearts. For that reason, this model is likely more relevant to human ARVD/C than other models and therefore better suited for studying the disease and testing new treatments.

"It's tough to demonstrate that a disease-in-a-dish model is clinically relevant for an adult-onset disease. But we made a key finding here—we can recapitulate the defects in this disease only when we induce adult-like metabolism. This is an important breakthrough considering that ARVD/C symptoms usually don't arise until young adulthood. Yet the stem cells we're working with are embryonic in nature," said Huei-Sheng Vincent Chen, M.D., Ph.D., associate professor at Sanford-Burnham and senior author of the study.

To establish this model, Chen teamed up with expert ARVD/C cardiologists Daniel Judge, M.D., Joseph Marine, M.D., and Hugh Calkins, M.D., at Johns Hopkins University. Johns Hopkins is home to

one of the largest ARVD/C patient registries in the world.

"There is currently no treatment to prevent progression of ARVD/C, a rare disorder that preferentially affects athletes. With this new model, we hope we are now on a path to develop better therapies for this life-threatening disease," said Judge, associate professor and medical director of the Center for Inherited Heart Disease at the Johns Hopkins University School of Medicine.

Disease in a dish

To recreate a person's own unique ARVD/C in the lab, the team first obtained skin samples from ARVD/C patients with certain mutations believed to be involved in the disease. Next they performed Yamanaka's technique: adding a few molecules that dial back the developmental clock on these adult skin cells, producing embryonic-like induced pluripotent stem cells (iPSCs). The researchers then coaxed the iPSCs into producing an unlimited supply of patient-specific heart muscle cells. These heart cells were largely embryonic in nature, but carried along the original patient's genetic mutations.

However, for nearly a year, no matter what they tried, the team couldn't get their ARVD/C heart muscle cells to show any signs of the disease. Without actual signs of adult-onset ARVD/C, these young, patient-specific heart muscle cells were no use for studying the disease or testing new therapeutic drugs.

Speeding up time

Eventually, the team experienced the big "aha!" moment they'd been looking for. They discovered that metabolic maturity is the key to inducing signs of ARVD/C, an adult disease, in their embryonic-like

cells. Human fetal heart muscle cells use glucose (sugar) as their primary source of energy. In contrast, adult heart muscle cells prefer using fat for energy production. So Chen's team applied several cocktails to trigger this shift to adult metabolism in their model.

After more trial and error, they discovered that metabolic malfunction is at the core of ARVD/C disease. Moreover, Chen's team tracked down the final piece of puzzle to make patient-specific heart muscle cells behave like sick ARVD/C hearts: the abnormal over-activation of a protein called PPAR. Scientists previously attributed ARVD/C to a problem in weakened connections between heart muscle cells, which occur only in half of the ARVD/C patients. With the newly established model, they not only replicated this adult-onset disease in a dish, but also presented new potential drug targets for treating ARVD/C.

What's next?

Chen's team was recently awarded a new grant from the California Institute for Regenerative Medicine to create additional iPSC-based ARVD/C models. With more ARVD/C models, they will determine whether or not all (or at least most) patients develop the disease via the same metabolic defects discovered in this current study.

Together with the Johns Hopkins team, Chen also hopes to conduct preclinical studies to find a new therapy for this deadly heart condition.

Provided by Sanford-Burnham Medical Research Institute