Medical Xpress

Technique could help identify patients who would suffer chemo-induced heart damage

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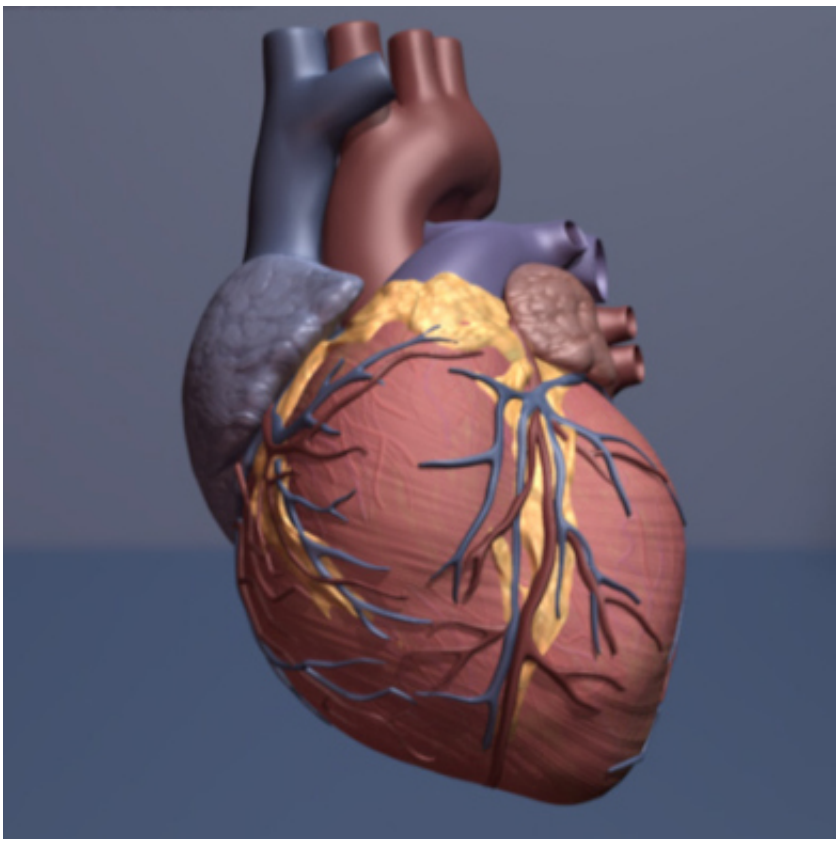

Human heart. Credit: copyright American Heart Association

Cancer patients who receive a particular type of chemotherapy called doxorubicin run a risk of sustaining severe, lasting heart damage. But it is not possible to predict who is likely to experience this serious side effect. It is also unknown exactly how the drug damages heart muscle.

Now, researchers at the Stanford University School of Medicine have shown that heart muscle cells made from the skin cells of breast cancer patients who suffered cardiac side effects after receiving doxorubicin respond more adversely to the drug than cells made from patients who did not.

These cells provide researchers with a sorely needed platform to study the effects of doxorubicin exposure on human heart muscle cells, and may allow them to one day predict which patients should avoid the drug. Until now, researchers have relied primarily on animal models to investigate the phenomenon because heart muscle tissue is difficult to obtain from living patients.

"In the past, we've tried to model this doxorubicin toxicity in mice by exposing them to the drug and then removing the heart for study," said Joseph Wu, MD, PhD, director of the Stanford Cardiovascular Institute and a professor of cardiovascular medicine and radiology. "Now we can continue our studies in human cells with iPS-derived heart muscle cells from real patients. One day we may even be able to predict who is likely to get into trouble."

Wu is the senior author of the research, which will be published online April 18 in *Nature Medicine*. Former Stanford Cardiovascular Institute instructor Paul Burridge, PhD, is the lead author of the study. Burridge is now an assistant professor of pharmacology at Northwestern University.

The research relies on induced pluripotent stem cells, or iPS cells, derived from patients' own skin cells to make heart muscle cells. IPS cells are stem cells that can be coaxed to develop into nearly any tissue in the body. The technique gives researchers access to a variety of human cell types, such as brain and heart muscle cells, that are typically difficult to obtain for study.

Toxic side effect

About 8 percent of cancer patients treated with doxorubicin will experience heart damage, which can be severe enough to require a heart transplant. The failing heart function is due to the death of the cells in the organ's muscle tissue. This dilemma places patients in a medical Catch-22, having been cured from cancer but later suffering heart disease as a result of the chemotherapy. Advanced prediction of which patients are susceptible to doxorubicin's heart damage would greatly benefit cancer patients.

For the study, the researchers collected skin cells from 12 women, eight of whom had been treated at Stanford for breast cancer. Four of the eight had experienced heart damage in response to the drug while the other four did not. Another group of four women served as healthy control subjects. The researchers used the study participants' own skin cells to create iPS cells, which they then grew in the lab into heart muscle cells.

"We found that cells from the patients who had experienced doxorubicin toxicity responded more negatively to the presence of the drug," said Burridge. "They beat more irregularly in response to increased levels of doxorubicin, and we saw a significant increase in cell death after 72 hours of exposure to the drug when we compared those cells to cells from healthy controls or patients who didn't have heart damage."

Some researchers have proposed that the particular sensitivity of heart muscle cells to the drug might be because they have more mitochondria than other cells in the body. Mitochondria serve as a cell's energy factories, and continuously beating heart muscle cells need a lot of energy throughout their lifetimes. But they also produce small amounts of damaging molecules called reactive oxygen species as a byproduct of this energy-making process, and these molecules can harm cell

membranes and DNA.

Mitochondrial mystery

The researchers found that the doxorubicin-sensitive cells experienced higher levels of DNA damage and of reactive oxygen species in the presence of doxorubicin. These cells were also significantly more likely than cells from healthy controls or from patients who didn't sustain heart damage to initiate a program of cellular suicide, which can be triggered by damage to the mitochondrial membrane. But the researchers made another telling discovery.

"We had assumed, based on our hypothesis, that the doxorubicin-sensitive cells would experience a more severe loss in mitochondrial capacity," said Burridge. "And that was true. But we also observed that cells made from patients who had experienced damage appeared to have slightly different baseline mitochondrial function even before the drug was applied."

It is possible that heart muscle cells from these patients are fundamentally different than others, perhaps due to genetic variation, according to the researchers. This genetic difference could cause their heart muscle cells to respond negatively to doxorubicin.

The next step is to learn more about what causes the sensitivity, which the Stanford researchers hope to do by combining their studies of the iPS-derived cells with existing genome-wide association studies attempting to pinpoint DNA mutations that might cause compromised heart function.

"Doxorubicin and other similar drugs are used to treat many types of cancers, including lymphomas and leukemias," said Melinda Telli, MD, assistant professor of oncology at Stanford. Telli is a co-author of the

study and helped recruit breast cancer patients for inclusion in the study. "But we don't want to cure any of these patients of their cancers only to leave them with another life-threatening problem."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

More information: Human induced pluripotent stem cell–derived cardiomyocytes recapitulate the predilection of breast cancer patients to doxorubicin-induced cardiotoxicity, *Nature Medicine*, DOI: 10.1038/nm.4087

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