Scientists to study role-switching cells in heart failure

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The National Institutes of Health has awarded more than $2 million to a team of scientists from Washington University in St. Louis and InvivoSciences, a biotechnology startup with WUSTL roots, to construct artificial tissue models that will allow the rapid testing of new drugs for heart failure.

According to the Centers for Disease Control, about 5.8 million people in the United States have heart failure, and many of them will die of their disease.

Drugs used to treat heart failure, such as the ACE inhibitors or beta blockers, improve the symptoms and allow patients to live longer and feel better. They may even reverse pathological changes in the heart tissue to some degree.

But heart failure is still the leading hospital discharge diagnosis and trials for several promising drugs for this disease have been spectacular and costly failures.

The WUSTL research focuses on the role in heart disease of role-switching cells called myofibroblasts that proliferate in over-stressed or injured hearts. In response to a heart attack, fibroblasts convert to this cell type, which secretes collagen and contracts the matrix of fibers around the injured heart tissue to repair the defect.

But heart cells never truly regenerate in the damaged tissue, and

myofibroblasts compensate for their absence by forming a stiff, collagenous scar that interferes with the heart's ability to maintain stable heart rhythms and to expand and contract forcefully to pump blood.

Fibroblasts also convert to myofibroblasts in response to high blood pressure, or hypertension. The resulting diffuse invasion of myofibroblasts also interferes with the electrical and mechanical functions of the tissue, and can lead to heart failure.

"Drugs that block the effects of myofibroblasts on the electrical or mechanical properties of heart tissue or that coax them to revert to fibroblasts might be more effective than current therapies," says Guy M. Genin, PhD, associate professor of mechanical engineering and materials science in WUSTL's School of Engineering & Applied Science, who is one of three co-primary investigators (PI) on the grant.

A wound-healer run amok

In the 1970s, a scientist at the University of Geneva in Switzerland discovered cells in healing wounds that seemed to be intermediate in character between fibroblasts, which secrete fibers such as collagen that make up the matrix that holds cells together in tissues, and smooth muscle cells, like those in the intestines and blood vessels.

These cells, which were named myofibroblasts to reflect their double nature, secrete fibers to fill in a wound and then contract to bring together its edges. And after the wound is healed, they disappear, either by committing cell suicide or perhaps by reverting to their original cell type.

But not always.

The heart is made up predominantly of two types of cells, Genin says:

the fibroblasts, which maintain the collagen and other structural proteins within the heart, and the cardiomyocytes, which do the pumping.

After a heart attack, some of the fibroblasts will convert to myofibroblasts to restore tissue integrity, and many persist even after their work is done. If blood pressure is high enough to provoke fibroblasts to become myofibroblasts, the cells also may get stuck in their helper state.

The cardiomyocytes don't proliferate, but the myofibroblasts keep dividing, gradually replacing healthy tissue with fiber-stiffened (fibrotic) tissue.

This phenomenon is not limited to the heart. Myofibroblasts can proliferate elsewhere in the body as well — although they may arise from different cell types in different tissues — and fibrotic remodeling of the kidney, liver (cirrhosis of the liver) and lungs follows a similar progression, Genin says.

The severe consequences of myofibroblast dysfunction motivate the effort to better understand these enigmatic cells.

Artificial heart tissue

"There's a lot we don't understand about what these cells do in the heart," Genin says.

"We don't know why conversion of fibroblasts to the contractile phenotype is sometimes helpful and sometimes harmful. We don't know how these cells alter the electrical and mechanical properties of heart tissue, or the degree to which these changes are to blame for the ultimate shutdown of the heart.

"We think that a therapy that would control the number and properties of myofibroblasts in the heart might be useful, but we don't know that for sure," Genin adds. "Nor do we know how to reverse the transition to this cell phenotype once it has occurred."

Many of these questions would be very difficult to sort out in real tissue, so the scientists use model tissues invented at WUSTL in Eliot Elson's lab. Elson, PhD, the Alumni Endowed Professor of Biochemistry and Molecular Biophysics in the Department of Biochemistry and Molecular Biophysics at WUSTL's School of Medicine, is the second of three co-PIs on the grant.

To make the tissues, the scientists crack open fertilized chicken eggs, pull fibroblasts and muscle cells out of the embryos' hearts, and mix them together with collagen.

"Over the course of time, the cells interact with each other and the collagen to form pieces of artificial heart that beat on their own in a Petri dish," Elson says.

The scientists can control the number of myofibroblasts in the tissue (most fibroblasts convert to myofibroblasts when they are plated out) and their distribution. In this way, they can mimic the fibrotic changes characteristic of a heart attack and those characteristic of hypertension.

"For a model of myocardial infarction, we want to create an island of wound-healing cells inside a patch of heart tissue, and for hypertension, we try to create what's called interstitial fibrosis, in which the myofibroblasts are interspersed between the contractile cells," Genin says.

The electrical and mechanical activity of the manufactured tissues then can be investigated with the help of a variety of sophisticated imaging

and force measurement techniques, many developed at WUSTL in the laboratories of Elson and Genin, and of Igor Efimov, PhD, the Lucy and Stanley Lopata Distinguished Professor of Biomedical Engineering in the School of Engineering & Applied Science.

At the same time, the scientists are developing computer models that are digital analogs of the artificial tissues, including electrophysiological models pioneered by Yoram Rudy, PhD, the Fred Saigh Distinguished Professor of Engineering in the School of Engineering & Applied Science. The back and forth between the tissue models and the computer models will allow them to test basic biophysical theories explaining their experimental observations.

Drug screening with tissue constructs

Once they understand the basic cellular biophysics of failing heart tissue, they will transfer their work to tissue models that will make it much faster and safer to test drugs for heart failure and hypertensive heart disease, the scientists say.

They plan to make the transition to drug screening with the help of InvivoSciences, whose chief scientist Tetsuro Wakatsuki, PhD, the third PI on the grant, earned a doctorate in biophysics and a master's degree in mechanical engineering at Washington University.

InvivoSciences makes engineered heart tissues from mouse embryonic stem cells and stem cells from differentiated adult tissues in humans, such as fat and skin. The company then uses biochemical methods to convert these undifferentiated cells to tissue- or organ-specific cells, such as cardiomyocytes and fibroblasts, and to generate artificial tissues from them.

"We'll develop the science on the much less expensive chicken egg

tissues and then we'll start our own stem cell bank here and begin making these mouse-derived tissue constructs," Elson says. The mouse constructs are more useful because of the molecular genetic tools available for mice.

Staggering investments of time and money have failed to produce new drugs for heart failure. The scientists hope that the artificial tissues will allow many more drugs to be tested under conditions closer to those within the human body. Their hope is that drug candidates that get as far as animal testing and clinical trials will then be more likely to be safe and effective.

Provided by Washington University in St. Louis