

Study shows key enzyme in fetal heart development also involved in adult heart disease

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Scientists at the Stanford University School of Medicine have identified for the first time an enzyme that plays vital roles in both fetal heart development and in causing cardiac hypertrophy — an enlargement of the heart — in adults. The discovery could be used in the future to try to develop new treatments for heart disease.

The study, which is to be published July 1 in *Nature*, was conducted by Ching-Pin Chang, MD, PhD, assistant professor of cardiovascular medicine, and his laboratory, which studies mechanisms of heart development and has spent several years investigating the epigenetic underpinnings of embryonic heart development and adult heart diseases. (In biology, and specifically genetics, epigenetics is the study of inherited changes in [gene expression](#) caused by mechanisms other than changes in the underlying DNA sequence.)

Hypertrophic cell growth, accompanied by [heart muscle](#) fibrosis or scarring, occurs when the adult heart is stressed by various insults such as high blood pressure. This can eventually cause failure of the heart. Chang and his colleagues found that the enzyme Brg1 of a protein complex called BAF plays a key epigenetic role in triggering this process. The Brg1/BAF protein complex alters the way DNA is wrapped around proteins called histones and thus influences how the cell develops.

In its research on the fetal hearts of mice, the Chang lab found that Brg1 regulates fetal heart muscle [cell proliferation](#) and differentiation and maintains the fetal heart muscle in an "embryonic" state. In the absence of Brg1, the fetal heart muscle cell loses its embryonic features and takes on an "adult" cell identity.

"We found that Brg1 plays important roles in mouse embryonic heart development by turning specific muscle genes on/off," said Calvin Hang, a graduate student in Chang's lab and the study's first author. "Because the diseased adult hearts often turn on fetal genes that otherwise should be off, we wanted to know if Brg1 also played a role in adult heart disease."

"Unlike in embryos, the Brg1 gene is turned off in normal adult myocardium (heart muscle)," said Chang, the study's senior author. The enzyme naturally disappears when the heart matures. "But it gets reactivated by cardiac stress."

The scientists showed that reactivation of Brg1 in the stressed adult heart triggers a cellular process that turns on those fetal genes that are normally silent in the adult heart. And this leads to disease.

So the researchers checked whether the disease process — the hypertrophy of the adult heart — would occur if the Brg1 enzyme was knocked out.

Like in the experiments on the fetal hearts of mice, scientists used tissue-specific and time-controlled gene knockout technology to eliminate the Brg1 gene in adult hearts of mice, then physically stressed those hearts to see if disease occurs. They found that the amount of heart hypertrophy decreased dramatically.

"When the Brg1 gene is deleted, the stressed adult mouse heart has only

minimal pathological changes," Chang said. "It does not have significant hypertrophy. There's no fibrosis or scarring."

When activated by cardiac stress in adult hearts in mice, Brg1/BAF assembles a large protein complex with two other epigenetic factors, HDAC and PARP, to control heart muscle growth and differentiation as they normally do in the fetal heart except that this fetal complex now functions in the adult cell. This results in heart hypertrophy and fibrosis in the mice.

Chang and his colleagues went one step further to examine Brg1 gene activation, on a small scale, in human heart tissues stored in freezers in the Stanford Cardiovascular Genomics and Proteomics Tissue Bank. Heart tissues from four patients with hypertrophic cardiomyopathy of unknown causes were used in the experiments along with six healthy heart samples taken from transplant donor hearts. They found that Brg1, as observed in stressed adult mouse hearts, was activated in the hearts of patients with hypertrophic cardiomyopathy. The level of Brg1 activation in these patients correlated strongly with the severity of the disease.

"It was a pioneering study, but the results were encouraging," Chang said.

These observations suggest that Brg1 activation may contribute to the development of certain human hypertrophic [heart](#) disease. "We hope to develop a chemical inhibitor that can target Brg1 activity in hypertrophic hearts and treat this disease," Chang said.

Provided by Stanford University Medical Center

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