Compound improves cardiac function in mice with genetic heart defect

20 February 2014

Congenital heart disease is the most common form of birth defect, affecting one out of every 125 babies, according to the National Institutes of Health. Researchers from the University of Missouri recently found success using a drug to treat laboratory mice with one form of congenital heart disease, hypertrophic cardiomyopathy—a weakening of the heart caused by abnormally thick muscle. By suppressing a faulty protein, the researchers reduced the thickness of the mice's heart muscles and improved their cardiac functioning.

Maike Krenz, M.D., has been studying hypertrophic cardiomyopathy for more than 10 years, soon after a gene was discovered in 2001 that linked the disease to the genetic conditions Noonan syndrome and LEOPARD syndrome. In Noonan and LEOPARD syndromes, the thickened heart muscle of hypertrophic cardiomyopathy is caused by a defective Shp2 protein, created by a mutation in the gene PTPN11.

"Previously, not much has been known about the biochemistry behind Shp2 and hypertrophic cardiomyopathy," said Krenz, an assistant professor of medical pharmacology and physiology at the MU School of Medicine, and a researcher at MU's Dalton Cardiovascular Research Center. "We know the thickened heart muscle is sick and doesn't work properly, and we know a defective Shp2 protein can cause heart muscle to thicken. However, to create an effective treatment, we need to know what Shp2 is doing inside the heart to cause the defect."

To test whether they could interrupt the heart's hypersensitivity to growth signals, the researchers gave a chemical compound, PHPS1, to mice with a mutated gene that produces the defective Shp2 protein.

"Not only did the compound reduce the thickness of the heart muscle to the size of normal heart muscle, but it also improved the cardiac pumping of the heart," Krenz said. "That's important because people with hypertrophic cardiomyopathy have an increased risk of sudden cardiac death. If we could develop an effective treatment for the disease and improve patients' heart function, we would be able to improve health outcomes for these patients."

Because of the role Shp2 plays in signaling heart growth, Krenz believes the research could be translated in the future into improved treatments for other types of heart disease, such as damage caused by heart attack.

More information: Krenz presented the research findings, "Inhibition of Shp2's Phosphatase Activity Ameliorates Cardiac Hypertrophy in LEOPARD Syndrome Models," at the American Heart Association's Scientific Sessions conference in November 2013, where it received the Outstanding Research Award in Pediatric Cardiology.

Provided by University of Missouri-Columbia