Breakdown of triglycerides in heart muscle boosts cardiac function

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The heart relies heavily on oxidation of fatty acids for energy production. However, excess storage of fatty acids as triglycerides, within heart muscle cells, frequently observed in patients with obesity and diabetes, is often associated with cardiac dysfunction. The question remained: was this cause and effect? Now a team of investigators shows that baseline heart function "showed moderate, but significant improvement" in mouse models that overproduce an enzyme that breaks down these triglycerides, says principal investigator Jason Dyck, of the University of Alberta, Edmonton. The research is published in the February *Molecular and Cellular Biology.*

The investigators showed further that mice that overproduce the enzyme "were able to run 20% longer than the controls when subjected to a treadmill test," says first author Petra Kienesberger, of the University of Alberta.

Then, in experiments in which mouse models were surgically constructed to mimic hypertension, the researchers showed that "overproduction of the enzyme protects from the development of cardiac/contractile dysfunction under this pathological condition," says Kienesberger.

"Together, these data demonstrate for the first time that decreased myocardial triglyceride accumulation plays a role in regulating cardiac function at baseline as well as an important protective role in preventing cardiac dysfunction in response to a severe pressure overload, as

observed with hypertension," says Dyck.

"These findings are highly relevant to basic and clinical research," says Kienesberger. "They suggest that regulation of cardiac triglyceride content and breakdown plays a central role in mediating cardiac function, and that pharmacological modification of cardiac [enzymatic] activity [to break down triglyceride] could be used as therapy to improve contractile function of the diseased heart. However, it remains to be tested whether reducing triglycerides is also beneficial in obesity and diabetes. This concept… opens new avenues of research not previously identified."

The research was enabled only recently by new genetic tools that specifically target cardiac triglycerides and by a novel mouse model, in which triglyceride could be reduced by boosting the enzyme responsible for breaking it down, says Kienesberger.

More information: P.C. Kienesberger, T. Pulinilkunnil, M.M.Y. Sung, J. Nagendran, G. Haemmerle, E.E. Kershaw, M.E. Young, P.E. Light, G.Y. Oudit, R. Zechner, and J.R.B. Dyck, 2012. Myocardial ATGL overexpression decreases the reliance on fatty acid oxidation and protects against pressure overload-induced cardiac dysfunction. *Mol. Cell. Biol.* 32:740-750.

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