Team identifies new approach to tackling heart disease in people with Type 2 diabetes

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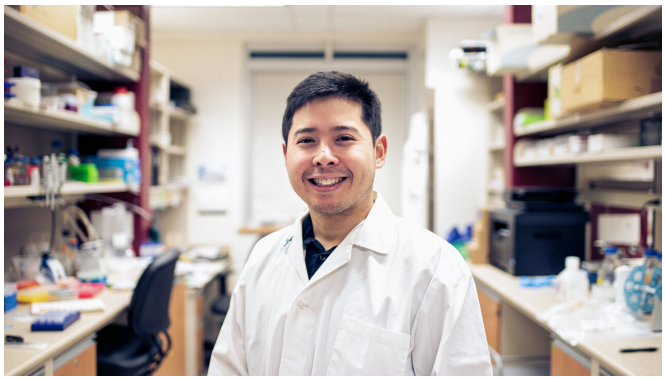

Pharmacy researcher John Ussher led new research identifying a protein that could be key to developing treatments to prevent a type of heart failure that is common but often hidden in people with Type 2 diabetes. Credit: Julia Brown Photography

A University of Alberta laboratory has uncovered a new approach to preventing heart failure in people with Type 2 diabetes, according to research findings published today in the journal *Cell Reports*.

"We know people with diabetes take drugs for years to control their blood sugars, but the drugs don't cure their diabetes," said lead author John Ussher, associate professor in the Faculty of Pharmacy and Pharmaceutical Sciences. "The majority eventually die not from high blood sugar, but from heart disease."

People with Type 2 diabetes have a defect in their hearts' ability to burn carbohydrates as a fuel source, Ussher explained, which can eventually lead to diastolic heart failure, in which the heart contracts normally but does not relax properly between pumps.

Ussher's lab used a combination of genetic alterations and drug treatments in animal models to show this process can be halted by blocking the action of a key protein called FoxO1.

"Our research demonstrated that if you can fix the heart's ability to burn sugar for fuel, then the heart can relax better and not get this form of heart failure in the presence of diabetes," said Ussher, who is Canada Research Chair (Tier 2) in Pharmacotherapy of Energy Metabolism in Obesity and a member of both the Alberta Diabetes Institute and the U of A's Cardiovascular Research Centre.

Narrowing in on the target

Ussher noted that Type 2 diabetes affects nearly 400 million people around the world. While many will experience systolic heart failure or problems with the way their heart pumps, studies show just as many will have diastolic or relaxation problems, but they often have no symptoms. Ussher urged earlier screening for diastolic heart disease among people diagnosed with diabetes and pre-diabetes.

"This is devastating for the individuals and a major burden on the health-care system," Ussher said. "There are no approved therapies that can reverse this type of heart failure, which is why it's very important to try to develop treatments."

Ussher's next step will be to try to better understand the mechanism of the experimental drug they used to inhibit the FoxO1 protein, and then improve upon it, as it has not been tested in humans and may have unknown side-effects.

"Another problem is FoxO1 is a protein that controls the expression of hundreds or thousands of genes," he explained. "There's one gene that we want to modify to benefit the heart failure, but what are the other 99 or 999 genes being affected by modifying this protein? How might these genes impact the body?"

A better approach, Ussher said, would be to modify

the individual protein that interferes with sugar metabolism, whose gene expression is controlled by FoxO1.

"We believe that would be a more specific and better target that would have less potential for adverse effects, so the long-term goal for us is to focus on using chemistry and other approaches to make new compounds that could target that specific protein," he said.

More information: Keshav Gopal et al. FoxO1 inhibition alleviates type 2 diabetes-related diastolic dysfunction by increasing myocardial pyruvate dehydrogenase activity, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.108935

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