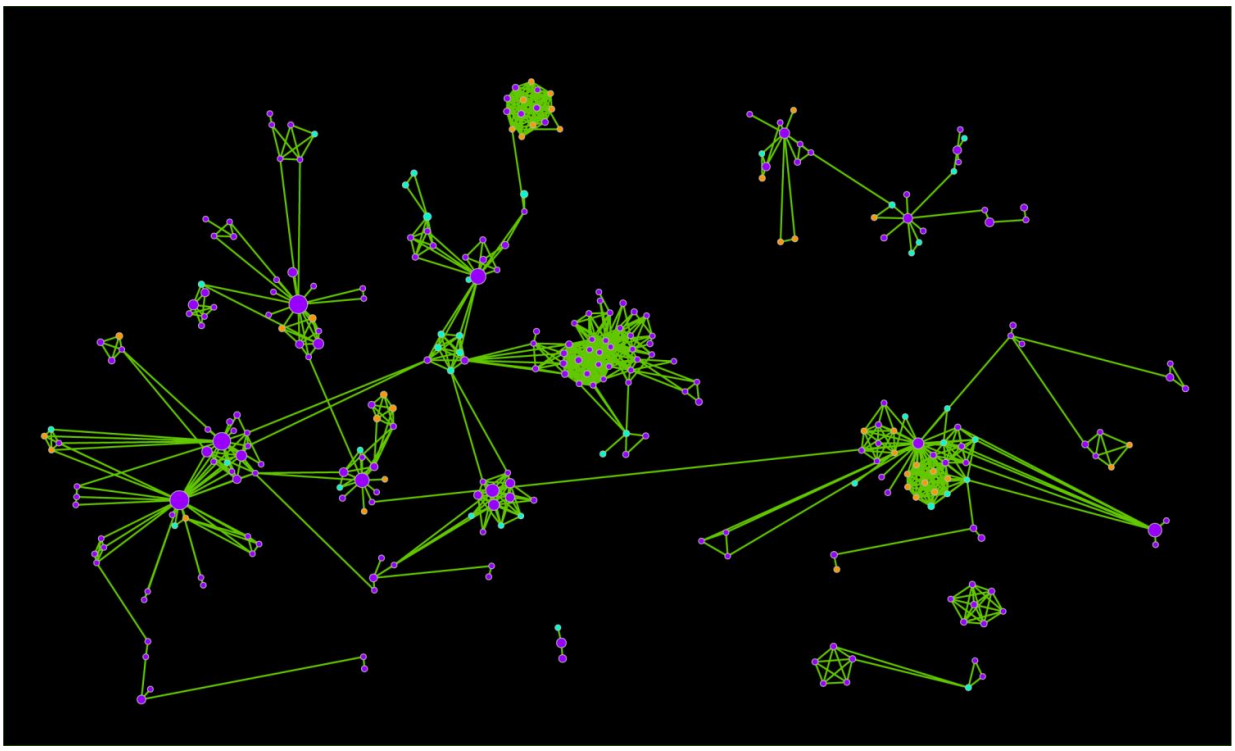
Heart signaling map sheds light on the molecular culprits behind cardiovascular disease

October 10 2016



Map of protein signaling pathways that went off course in DCM hearts. Credit: Uros Kuzmanov

Having a big heart is not always a virtue and, from a physiologist's point of view, it can be deadly. An enlarged heart is a hallmark of dilated

cardiomyopathy (DCM) and, despite being the most common inherited disease of the heart muscle, doctors don't really know why it occurs. But that could now change as a new University of Toronto study begins to shine light on the molecular causes behind DCM.

Published this week in the *Proceedings of the National Academy of Sciences*, the study reveals widespread differences in protein biochemistry between healthy and diseased hearts. This expands our understanding of heart physiology and opens the door for future research that could improve detection and treatment of DCM.

Affecting all ages, the disease begins usually in adolescence and strikes one in five Canadians, with huge healthcare, economic and social costs. It occurs when a normal-looking heart begins to dilate, or stretch, for no apparent reason. This enlarged heart can no longer maintain the normal rhythm and pump the blood around the body, which leads to heart failure . Although we know that DCM is rooted in genetics, its molecular culprits remain poorly understood.

Led by Professors Andrew Emili and Anthony Gramolini, the researchers mapped changes in protein signalling pathways in heart cells that lead to DCM. Emili is member of U of T's Donnelly Centre for Cellular and Biomolecular Research and a Professor of Molecular Genetics, while Gramolini is part of the Ted Rogers Centre for Heart Research, an Associate Professor in Physiology and a Scientist at the University Health Network.

The Emili and Gramolini teams combined strengths to dig deep into the heart muscle and compare changes in protein signalling networks that are active in healthy and DCM hearts. Proteins are the end products of genes, and they do most of the work in cells - for example, heart growth during development is controlled by complex signalling networks between thousands of different proteins. Their activity is often regulated

by phosphorylation - a biochemical reaction where a phosphate group is added onto a protein to make it more, or less, active, or to change its position in the cell, or to mark it for destruction. By scanning the patterns of protein phosphorylation, they were able to study how sick hearts ramp up, or dampen, entire protein signalling pathways - thus becoming vulnerable to heart failure.

"We decided to measure global protein phosphorylation in heart tissue to get a sense for how signalling pathways differ between DCM and normal hearts," said Dr. Uros Kuzmanov, who spearheaded the project as a postdoctoral research fellow in both Emili and Gramolini labs. No such study had been attempted on such a scale in the past.

As a stand in for the human disease, Kuzmanov used mice that carry a mutation, akin to one found in human patients, that makes them develop all signs of DCM. To get a better understanding of how the disease begins, the teams collected heart samples from young adult healthy and mutant mice, at a time when their heart muscles just began to stretch, for a side-by-side analysis. The researchers then ground the heart tissue to remove the proteins, which were fed into a mass spectrometer to be counted.

Based on the changes in the levels of thousands of phosphorylated proteins, the researchers uncovered hundreds of signalling pathways that went off course in DCM hearts. This is the first comprehensive map of molecular signaling events - including those unexpected - that go awry in heart failure.

Next, the teams will carry out similar analysis in human tissue. If, as expected, they can detect similarly robust changes in the same signalling pathways in patients' hearts, then the human map could help scientists nail down promising new drug targets or biomarkers for early detection.

"We expect to be able to detect specific changes in signalling pathways in different cardiac patients," said Kuzmanov. "And our approach is not limited to the DCM—it could be applied to all heart disease."

More information: *Proceedings of the National Academy of Sciences*, DOI: 10.1073/pnas.1606444113

Provided by University of Toronto