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May 28, 2019

Researchers Gain Insight into How Heart Failure Develops in People with Chronic Kidney Disease

Understanding the mechanism behind heart failure with preserved ejection fraction has moved closer to reality with a new study from investigators at the Interdisciplinary Stem Cell Institute (ISCI) at the University of Miami Miller School of Medicine.

From left, Guerline Lambert, M.S., Lauro Takeuchi, D.M.D., Camila Irion, Ph.D., Lina Shehadeh, Ph.D., Keyvan Yousefi, Pharm.D., Joshua M. Hare, M.D., Keith Webster, Ph.D., and Trevor Eisenberg.

The study results were published in the *Journal of the American College of Cardiology*, one of the highest-ranking journals in the field of cardiovascular research.

The story so far involves a “bad” protein, a “good” enzyme and an unexpected finding when comparing animals and humans.

In contrast with heart failure with reduced ejection fraction – where the heart tends to pump blood less effectively over time – heart failure with preserved ejection fraction (HFpEF) is more

common among people over age 65. In addition, treating patients with HFpEF can be complex, as they often present with other conditions at the same time, including hypertension, obesity, diabetes and kidney disease.

“In fact, people with chronic kidney disease and HFpEF do constitute a distinct, high-risk subgroup,” said Lina A. Shehadeh, Ph.D., senior author of the study and associate professor in the Department of Medicine’s Division of Cardiology and the ISCI.

Dr. Shehadeh, lead author Keyvan Yousefi, Pharm.D., and colleagues across the Miller campus collaborated on a study looking at HFpEF in a mouse model of Alport Syndrome, a rare kidney disease.

The current work builds on previous research that identified, for the first time, the role of the protein osteopontin in Alport Syndrome. The new results suggest that reducing high levels of osteopontin could reduce the severity of heart failure with preserved ejection fraction.

The new research further indicts osteopontin as a “bad player.” It also expands Dr. Shehadeh’s work beyond the mouse model, examining human heart tissue from heart failure patients with reduced or preserved ejection fraction, as well as cardiac cells grown in the lab using induced pluripotent stem cells.

The investigation also supports a “good actor” role for an enzyme called 2-Oxoglutarate Dehydrogenase-Like or OGDHL. In the presence of elevated levels of osteopontin, however, OGDHL becomes dysregulated, the study shows.

But that’s where the unexpected result emerged.

“We were surprised to see that validation of OGDHL expression in human cardiac biopsies showed opposite results than those in the mouse,” Dr. Shehadeh said. This means that instead of OGDHL levels being low as in the sick mice, they were high in the patients.

“This could be attributed to the fact that the cardiac patients were obese and diabetic, unlike our mouse model,” she added. “However, the bottom line is that OGDHL is dysregulated in the human HFpEF hearts, and this was found based on our mouse studies.”

The HFpEF preclinical research also shows that these mice develop diastolic heart dysfunction, cardiac hypertrophy (thickening of the heart muscle) and fibrosis (formation of excess tissue). The researchers further demonstrated that lowering the levels of osteopontin improved these outcomes.

The findings suggest therapeutic targets to help people living with chronic kidney disease and HFpEF. Specifically, future treatment could include a blocker to reduce levels of the osteopontin protein or substances to maintain regulation of OGHDL.

Miller School investigators are leaders regarding this high-risk form of heart failure.

“UM doctors and researchers are aware how disadvantaged HFpEF patients are, and how there is a pressing unmet need for understanding the mechanisms of the disease, and finding novel

therapies," Dr. Shehadeh said.

Dr. Shehadeh is grateful to the Miami Heart Research Institute, NIH and AHA for funding this research program.

"One of the next investigations is an NIH-funded study to validate the findings in a pig model of renal-induced HFpEF," she added.

"This is a really nice multidisciplinary project, since it employs the expertise and intellectual contribution from several experts in the field from basic, translational, and clinical cardiology," said Dr. Yousefi, a Ph.D. candidate in the Department of Molecular and Cellular Pharmacology who received a Pre-doctoral Fellowship Award from the American Heart Association in 2018 to pursue this project. "I am proud to be part of an esteemed team of researchers, including Drs. Joshua Hare and Keith Webster from the Miller School, Dr. David Kass from the Johns Hopkins University, and Dr. Henk Granzier from the University of Arizona."

Authors on this paper also included Dr. Camila Irion, co-first author and postdoctoral researcher in the Shehadeh lab, Drs. Konstantinos Hatzistergos and Lauro Takeuchi from ISCI, Dr. Wen Ding, former Ph.D. student in the Shehadeh lab and now a postdoctoral fellow at Yale School of Medicine, Guerline Lambert, research associate in the Shehadeh lab, Drs. Dong I. Lee and Virginia Hahn from Johns Hopkins, and Trevor Eisenberg and Sarah Sukkar, UM medical students.