Promising target in treating and preventing the progression of heart failure identified

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Researchers at Mount Sinai School of Medicine have identified a new drug target that may treat and/or prevent heart failure. The team evaluated failing human and pig hearts and discovered that SUMO1, a so-called "chaperone" protein that regulates the activity of key transporter genes, was decreased in failing hearts. When the researchers injected SUMO1 into these hearts via gene therapy, cardiac function was significantly improved. This research indicates that SUMO1 may play a critical role in the pathogenesis of heart failure. The data are published online in *Nature*.

Led by Roger J. Hajjar, MD, Director of Mount Sinai's Wiener Family Cardiovascular Research Laboratories, and the Arthur and Janet C. Ross Professor of Medicine, Mount Sinai School of Medicine, the team has been evaluating the transporter gene SERCA2a in patients with severe heart failure as part of the CUPID (Calcium Up-regulation by Percutaneous administration of gene therapy In cardiac Disease) trial. When delivered via an adeno-associated virus vector—an inactive virus that acts as a medication transporter—into cardiac cells, SERCA2a demonstrated improvement or stabilization with minimal side effects. However, they found that while injection with SERCA2a restored cardiac function, over time the new SERCA2a became dysfunctional. This indicated that something else upstream from SERCA2a was causing the dysfunction in the heart.

Changwon Kho, PhD and Ah Young Lee, PhD, two postdoctorate students in the study of cardiac proteins at Mount Sinai School of

Medicine, identified SUMO1 as the regulator of SERCA2a, showing that it enhanced its function and improved its stability and enzyme activity. Dr. Hajjar and his team studied human and animal models and found that when SUMO1 was decreased, SERCA2a became dysfunctional, showing that SUMO1 plays a protective role. When the team injected SUMO1 as a gene therapy, they found that it protected SERCA2a from the oxidative stresses and dysfunction that are prevalent in heart failure.

"Our experiments over the last four years beginning with the discovery of SUMO1 as an interacting protein of SERCA2a have shown that it plays a critical role in the development of heart failure," said Dr. Hajjar. "In fact, SUMO1 may be a therapeutic target at the earliest signs of development, and may be beneficial in preventing its progression, a much-needed advance for the millions suffering from this disease."

Led by Dr. Hajjar, the Mount Sinai team discovered the landmark potential of SERCA2a in 1999, and has been pursuing its potential as a treatment delivered via gene therapy in state-of-the-art custom built laboratories at Mount Sinai School of Medicine. Furthering their efforts to bringing critical therapeutics from bench to bedside, Dr. Hajjar's team will test the effects of SUMO1 in a preclinical model of heart failure in pigs. Similar to their efforts in the CUPID, they will explore the delivery of SUMO1 via gene therapy. Additionally, the research team has developed a cellular test to screen for compounds that may increase the interaction of SERCA2a with SUMO1, evaluating SUMO1 as an adjunctive therapy to SERCA2a.

"Dr. Hajjar and his team at the Cardiovascular Research Institute at Mount Sinai are fundamentally changing how we think about and treat heart disease," said Valentin Fuster, MD, Director of Mount Sinai Heart, the Zena and Michael A. Wiener Cardiovascular Institute and the Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, The Mount

Sinai Medical Center. "Mount Sinai has led the charge in cardiovascular translational research, and this breakthrough exemplifies that commitment to bringing research breakthroughs from discovery to therapy."

According to the U.S. Centers for Disease Control and Prevention, about 5.8 million Americans suffer from heart failure, and 670,000 new cases are diagnosed each year. One in five people who have heart failure die within one year of diagnosis. Heart failure is most often treated with aggressive medical and device therapy, but has no cure. The most common symptoms of heart failure are shortness of breath, feeling tired, and swelling in the ankles, feet, legs, and sometimes the abdomen.

Provided by The Mount Sinai Hospital