Blocking microRNA miR-25 halts progression of heart failure, improves cardiac function

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A team of cardiovascular researchers from Sanford-Burnham Medical Research Institute (Sanford-Burnham), the Cardiovascular Research Center at Icahn School of Medicine at Mount Sinai, and the University of California, San Diego have identified a small but powerful new player in the onset and progression of heart failure. Their findings, published in the journal Nature on March 12, also show how they successfully
blocked the newly discovered culprit to halt the debilitating and chronic life-threatening condition in its tracks.

In the study, investigators identified a tiny piece of RNA called miR-25 that blocks a gene known as SERCA2a, which regulates the flow of calcium in and out of heart-muscle cells. Decreased SERCA2a activity is one of the main causes of poor contraction of the heart and enlargement of heart-muscle cells leading to heart failure.

Using a functional screening system developed by researchers at Sanford-Burnham, the research team discovered miR-25 acts pathologically in patients suffering from heart failure, delaying proper calcium uptake in heart-muscle cells.

"Before the availability of high-throughput functional screening, our chance of teasing apart complex biological processes involved in disease progression like heart failure was like finding a needle in a haystack," said study co-senior author Mark Mercola, Ph.D., professor in the Development, Aging, and Regeneration Program at Sanford-Burnham and professor of bioengineering at UC San Diego Jacobs School of Engineering. "The results of this study validate our approach to identifying microRNAs as potential therapeutic targets with significant clinical value."

Mercola's laboratory has pioneered the use of robotic high-throughput methods of drug discovery to identify new targets for heart failure. According to co-lead study authors Christine Wahlquist and Agustin Rojas Muñoz, Ph.D., developers of the approach and researchers in Mercola's lab at Sanford-Burnham, they used high-throughput robotics to sift through the entire genome for microRNAs involved in heart-muscle dysfunction.

Subsequently, the researchers at the Cardiovascular Research Center at
Icahn School of Medicine at Mount Sinai found that injecting a small piece of RNA to inhibit the effects of miR-25 dramatically halted heart-failure progression in mice. In addition, it also improved their cardiac function and survival.

"In this study, we have not only identified one of the key cellular processes leading to heart failure, but have also demonstrated the therapeutic potential of blocking this process," said co-lead study author Dongtak Jeong, Ph.D., a post-doctoral fellow at the Cardiovascular Research Center at Icahn School of Medicine at Mount Sinai in the laboratory of the study's co-senior author Roger J. Hajjar, M.D.

Nearly six million Americans suffer from heart failure, which is when the heart becomes weak and cannot pump enough blood and oxygen throughout the body. Heart failure is a leading cause of hospitalization in the elderly. Often, a variety of medications are used to provide heart-failure patients temporary relief of their debilitating symptoms. However, these medications do not improve cardiac function or halt the progression of the disease.

"Currently, heart-failure medications do not effectively address the underlying mechanisms that weaken contractile function and lead to the enlargement of heart-muscle cells," said co-senior study author Roger J. Hajjar, M.D. "Our study provides us with the key evidence we need to begin developing miR-25 as an important new therapeutic target, while adding our successful technique to block this microRNA to our growing arsenal of promising heart-failure therapies that we will further develop and test in future clinical trials."

Currently, Hajjar's laboratory is developing novel gene therapies for patients with heart failure. One therapy, currently in phase IIb/III human clinical trials, uses a modified viral vector to deliver a gene that produces SERCA2a, an enzyme found in healthy heart-muscle cells. Another
therapy in preclinical development uses a disabled virus to deliver a gene called SUMO-1, which shrinks enlarged heart-muscle cells and improves cardiac function.

More information: Nature paper: dx.doi.org/10.1038/nature13073

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