Embryonic microRNA fuels heart cell regeneration, researchers show

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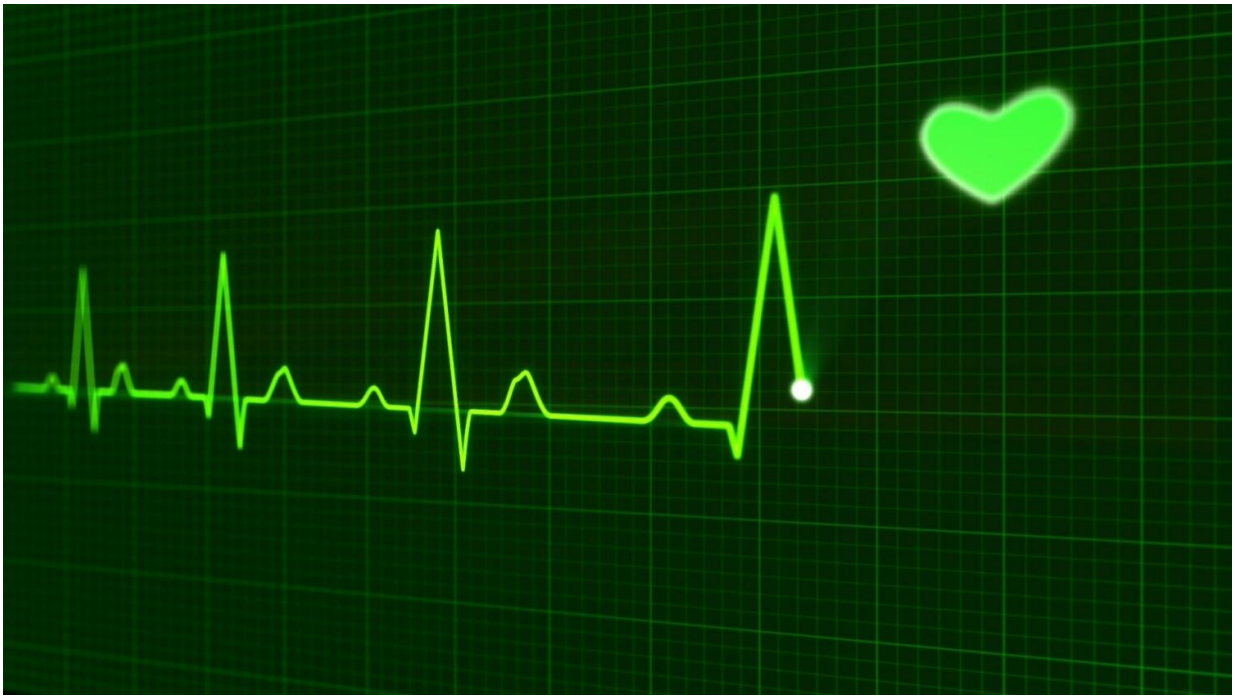

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By adulthood, the heart is no longer able to replenish injured or diseased cells. As a result, heart disease or an event like a heart attack can be disastrous, leading to massive cell death and permanent declines in function. A new study by scientists at the Lewis Katz School of Medicine at Temple University (LKSOM), however, shows that it may be possible to reverse this damage and restore heart function, even after

a severe heart attack.

The study, published June 21 in the print edition of the journal *Circulation Research*, is the first to show that a very small RNA molecule known as miR-294, when introduced into heart cells, can reactivate heart cell proliferation and improve heart function in mice that have suffered the equivalent of a heart attack in humans.

"In previous work, we discovered that miR-294 actively regulates the cell cycle in the developing heart," said Mohsin Khan, Ph.D., Assistant Professor of Physiology at the Center for Metabolic Disease Research at LKSOM. "But shortly after birth miR-294 is no longer expressed."

Dr. Khan and colleague Raj Kishore, Ph.D., Professor of Pharmacology and Medicine and Director of the Stem Cell Therapy Program in the Center for Translational Medicine at LKSOM, both senior investigators on the new study, wondered whether miR-294 could serve as a sort of fountain of youth for heart cells.

"The heart is very proliferative when miR-294 is expressed in early life," Dr. Kishore explained. "We wanted to see if reintroducing it into adult heart cells would turn them back to an embryonic-like state, allowing them to make new heart cells."

The researchers tested their idea in mice that had myocardial infarction (heart attack). Mice were treated with miR-294 continuously for two weeks after sustaining myocardial injury. Two months following treatment, the researchers observed noticeable improvements in heart function and a decrease in the area of damaged tissue. Examination of treated heart cells revealed evidence of cell cycle reentry, indicating that the cells had been reactivated, regaining the ability to produce new cells.

"The miR-294 treatment reawakened an embryonic signaling program in

the adult heart cells," said Dr. Khan. "Because of this, the old heart cells were no longer quite like adult cells, but neither were they fully embryonic. In this in-between state, however, they had the ability to make new cells."

The researchers were able to control miR-294 expression, turning it on or off and thereby dictating the amount of proliferative activity in the heart.

Drs. Khan and Kishore plan next to replicate the study in a large animal model. They also want to gain a deeper understanding of what miR-294 is doing in the heart. "There is evidence that it does more than control the cell cycle," Dr. Khan said. "If it has multiple targets, we need to find them."

More information: Austin Borden et al, Transient Introduction of miR-294 in the Heart Promotes Cardiomyocyte Cell Cycle Reentry After Injury, *Circulation Research* (2019). DOI: 10.1161/CIRCRESAHA.118.314223

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