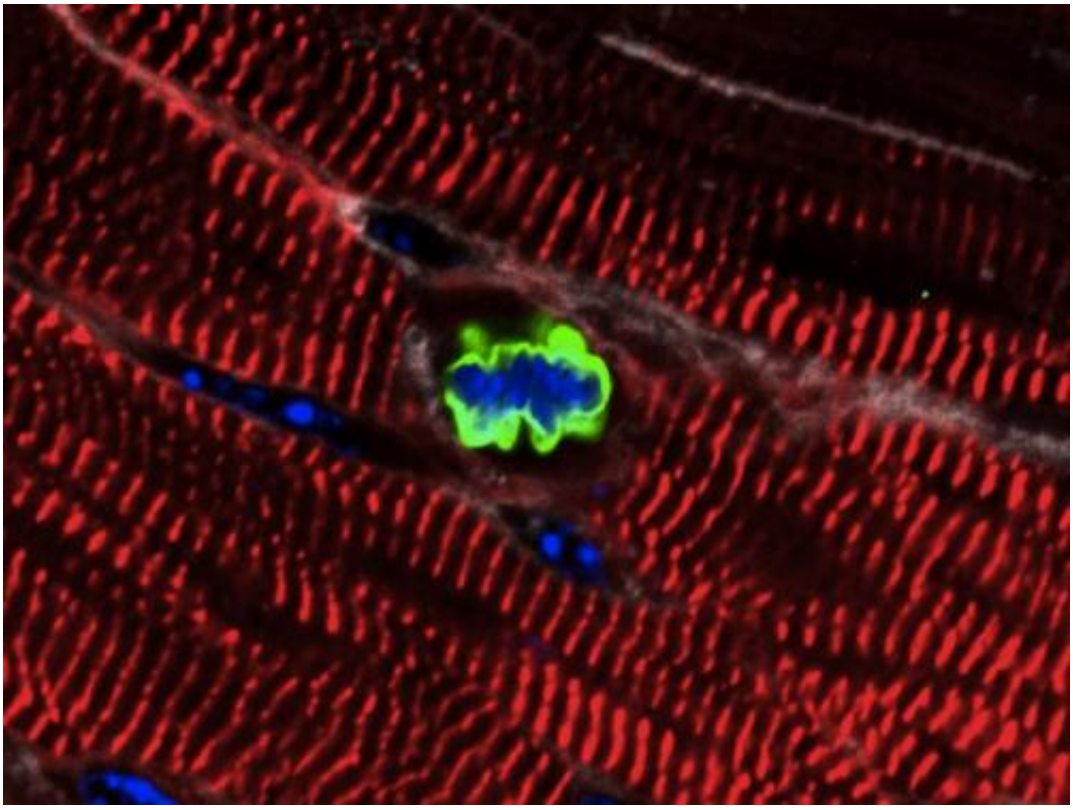
Researchers describe new approach to promote regeneration of heart tissue

March 18 2015



Adult cardiomyocyte that has re-entered the cell cycle after expression of miR302-367. Credit: Lab of Ed Morrisey, PhD, Perelman School of Medicine, University of Pennsylvania

The heart tissue of mammals has limited capacity to regenerate after an injury such as a heart attack, in part due to the inability to reactivate a cardiac muscle cell and proliferation program. Recent studies have

indicated a low level of cardiac muscle cell (cardiomyocytes) proliferation in adult mammals, but it is insufficient to repair damaged hearts.

A team led by Ed Morrisey, PhD, a professor of Medicine and Cell and Developmental Biology and the scientific director of the Institute for Regenerative Medicine in the Perelman School of Medicine at the University of Pennsylvania, has now shown that a subset of RNA molecules, called microRNAs, is important for cardiomyocyte cell proliferation during development and is sufficient to induce proliferation in cardiomyocytes in the adult heart. MicroRNAs, which do not generate proteins, repress gene expression by binding messenger RNAs, which do generate proteins, and promote their degradation. The findings appear this week in *Science Translational Medicine*.

The team found that the loss of the microRNA cluster miR302-367 in mice led to decreased cardiomyocyte cell proliferation during development. In contrast, increased expression of the microRNA cluster in adult hearts led to a reactivation of proliferation in the normally non-reproducing adult cardiomyocytes.

This reactivation occurred, in part, through repression of a pathway called Hippo that governs cell proliferation and organ size. "The Hippo pathway normally represses cell proliferation when it is turned on. The cluster miR302-367 targets three of the major kinase components in the Hippo pathway, reducing pathway activity, which allows cardiomyocytes to re-enter the cell cycle and begin to regrow heart muscle," explains Morrisey. "This is a case of repressing a repressor."

In adult mice, re-expression of the microRNA cluster reactivated the cell cycle in cardiomyocytes, resulting in reduced scar formation after an experimental myocardial infarction injury was induced in the mice. There was also an increase in the number of heart muscle cells in these

same mice.

However, long-term expression of more than several months of the microRNA cluster caused heart muscle cells to de-differentiation and become less functional. "This suggested to us that persistent reactivation of the cell cycle in adult cardiomyocytes could be harmful and causes the heart to fail," says Morrisey. The investigators surmised that cardiomyocytes likely need to de-differentiate to divide, but they may lose their ability to contract over time.

"We overcame this limitation by injecting synthetic microRNAs with a short half-life called mimics into the mice," says Morrisey. Mimic treatment for seven days after cardiac infarction led to the desired increase in cardiomyocyte proliferation and regrowth of new heart muscle, which resulted in decreased fibrosis and improved heart function after injury.

Importantly, the team found that the transient seven-day treatment did not lead to the progressive loss of cardiac function as seen in the genetic models of increased microRNA expression. Overall, these results suggested that any treatment that promotes cardiomyocyte proliferation to improve cardiac regeneration will likely need to be transient to avoid the deleterious effects of maintaining a high level of proliferation and de-differentiation in a tissue that is normally non-proliferative.

"The next stage in this study is to determine whether miRNA mimics will work in a larger animal model and to collaborate with bioengineers to create a local delivery system for the heart, rather than giving it systemically," notes Morrisey.

More information: A microRNA-Hippo pathway that promotes cardiomyocyte proliferation and cardiac regeneration in mice, *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ …

scitranslmed.aaa7538

Provided by University of Pennsylvania School of Medicine