Researchers use microRNAs to induce regeneration of heart tissue

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(Medical Xpress)—A research team working at Italy's International Centre for Genetic Engineering and Biotechnology has succeeded in causing heart tissue to regenerate by introducing two microRNAs into damaged mice hearts. The necessary microRNAs were discovered, the team writes in their paper published in the journal *Nature*, after an exhaustive search.

Because heart tissue doesn't regenerate naturally – its cells stop proliferating shortly after birth, researchers have been searching for a means to cause them to do so artificially. Thus far, such efforts have not proven fruitful and thus people that suffer damage to their hearts as a result of disease or heart attack are left with scar tissue rather than the muscle needed to pump blood. This new research may change that.

MicroRNAs are short segments of RNA whose purpose is to cause genes to switch on and off. To find out which ones are responsible for causing heart cells to divide, the team studied 875 of them taken from a human heart and implanted into rodent muscle. In so doing they found 204 of them that reactivated cell proliferation and 40 and that did so strongly. They then chose the two strongest and injected them into the hearts of live mice that had been caused to suffer damage to their hearts, using a harmless virus as a carrier.

After two weeks, the mice that had been injected with the MicroRNAs showed less damage than prior to the treatment, indicating regeneration had occurred. After two months, the damaged tissue area had been

reduced by half. The team also noted that contraction strength improved as did other heart functions that were measured.

The research team concludes by suggesting that their method of using MicroRNAs to induce regeneration of damaged heart tissue might be used someday soon to treat heart attack victims, though they also point out that much more research must be conducted – therapies that cause cells to divide can sometimes lead to cancerous tumors, for example. Such research will start, they say by testing their procedure with much larger animals. There's also the problem of the delivery system – injecting a live virus into a person's heart simply isn't feasible.

More information: Functional screening identifies miRNAs inducing cardiac regeneration, *Nature* (2012) doi:10.1038/nature11739

Abstract
In mammals, enlargement of the heart during embryonic development is primarily dependent on the increase in cardiomyocyte numbers. Shortly after birth, however, cardiomyocytes stop proliferating and further growth of the myocardium occurs through hypertrophic enlargement of the existing myocytes. As a consequence of the minimal renewal of cardiomyocytes during adult life, repair of cardiac damage through myocardial regeneration is very limited. Here we show that the exogenous administration of selected microRNAs (miRNAs) markedly stimulates cardiomyocyte proliferation and promotes cardiac repair. We performed a high-content microscopy, high-throughput functional screening for human miRNAs that promoted neonatal cardiomyocyte proliferation using a whole-genome miRNA library. Forty miRNAs strongly increased both DNA synthesis and cytokinesis in neonatal mouse and rat cardiomyocytes. Two of these miRNAs (hsa-miR-590 and hsa-miR-199a) were further selected for testing and were shown to promote cell cycle re-entry of adult cardiomyocytes ex vivo and to promote cardiomyocyte proliferation in both neonatal and adult animals.

After myocardial infarction in mice, these miRNAs stimulated marked cardiac regeneration and almost complete recovery of cardiac functional parameters. The miRNAs identified hold great promise for the treatment of cardiac pathologies consequent to cardiomyocyte loss.