Stem cells not the only way to fix a broken heart

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Researchers appear to have a new way to fix a broken heart. They have devised a method to coax heart muscle cells into reentering the cell cycle, allowing the differentiated adult cells to divide and regenerate healthy heart tissue after a heart attack, according to studies in mice and rats reported in the July 24th issue of the journal *Cell*, a Cell Press publication. The key ingredient is a growth factor known as neuregulin1 (NRG1 for short), and the researchers suggest that the factor might one day be used to treat failing human hearts.

"To my knowledge, this is the first regenerative therapy that may be applicable in a systemic way," said Bernhard Kühn of Children's Hospital Boston and Harvard Medical School. For instance, he added, people might one day go to the clinic for daily infusions of NRG1 over a period of weeks. "In principle, there is nothing to preclude this going into the clinic. Based on the all the information we have, this is a promising candidate." He emphasized, however, that further studies would be required to demonstrate safety before such treatment could be tested in human patients.

The heart had long been considered an organ largely incapable of repairing itself. Heart muscle cells, also known as cardiomyocytes, do proliferate during prenatal development. Soon after birth, however, the cells become binucleated, meaning that they have two nuclei, and withdraw from the cell cycle, giving rise to the notion that adult cardiomyocytes are terminally differentiated and incapable of further proliferation.

However, recent evidence has shown that adult heart muscle cells can replace themselves at some low level, with perhaps half of the cells in the heart turning over in the course of a lifetime, Kühn said. The new study provides multiple lines of evidence for this turnover ability - including video of the cells in action - and shows that neuregulin1 can ramp up the process.

In the current study, the researchers first tested the ability of various molecules to spur cell division in cultured cardiomyocytes. If cardiomyocytes are to reenter the cell cycle along the border zone of injury, the researchers surmised that there must be an extracellular signal that triggers the response, Kühn explained.

They looked to several factors known to drive cardiomyocyte proliferation during prenatal development. Of those, NRG1 had the most significant effect, inducing the division of those cardiomyocytes with one nucleus instead of two.

By manipulating the NRG1 receptor up or down, the researchers showed they could increase or decrease cardiomyocyte proliferation in living animals. Moreover, injecting NRG1 in adult mice sparked cardiomyocyte cell-cycle activity and promoted the regeneration of heart muscle, leading to improved function after the animals suffered a heart attack. That regeneration could not be traced to undifferentiated progenitor cells, they report.

The researchers say they aren't sure whether NRG1 is responsible for the natural repair process, but their findings show that it clearly can enhance it. They also note that the NRG1 receptor and NRG1 itself are always present in the adult heart, though it is not clear if they are in the right place or in sufficient quantities.

"Collectively, we have identified the major elements of a new approach

to promote myocardial regeneration," the researchers wrote." Many efforts and important advances have been made toward the goal of developing stem-cell based strategies to regenerate damaged tissues in the heart as well as in other organs. The work presented here suggests that stimulating differentiated cardiomyocytes to proliferate may be a viable alternative that could be developed into a simple strategy to promote myocardial regeneration in mammals."

Before making the leap to the clinic, Kühn's group intends to further explore how the treatment works at the fundamental level. They will also characterize the regenerative response in pigs, which have more in common with humans than rodents do, before testing the approach in human patients. Ultimately, such a treatment might serve as a useful alternative or complement to treatments designed to seed damaged hearts with regenerative stem cells, Kühn said.

Source: Cell Press (news : web)