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Contact: Richard Merritt
Merri006@mc.duke.edu
919-684-4148
Duke University Medical Center

Key to zebrafish heart regeneration uncovered

DURHAM, N.C. -- When a portion of a zebrafish's heart is removed, the dynamic interplay between a mass of stem cells that forms in the wound and the protective cell layer that covers the wound spurs the regeneration of functional new heart tissue, Duke University Medical Center scientists have found.

The scientists further discovered that key growth factors facilitate the interaction between the cell mass and the protective covering, encouraging the formation of new heart muscle.

Many cell biologists believe the ability to regenerate damaged heart tissue may be present in all vertebrate species, but that for unknown reasons, mammals have "turned off" this ability over the course of evolution. Zebrafish could provide a model to help researchers find the key to unlocking this dormant regenerative capacity in mammals, and such an advance could lead to potential treatments for human hearts damaged by disease, the Duke scientists said.

"If you look in nature, there are many examples of different types of organisms, such as axolotls, newts and zebrafish, that have an elevated ability to regenerate lost or damaged tissue," said Kenneth Poss, Ph.D., senior researcher for the team, which published the findings on Nov. 3, 2006, in the journal Cell. First authors of the paper were Alexandra Lepilina, M.D., and Ashley Coon.

"Interestingly, some species have the ability to regenerate appendages, while even fairly closely related species do not," Poss added. "This leads us to believe that during the course of evolution, regeneration is something that has been lost by some species, rather than an ability that has been gained by other species. The key is to find a way to 'turn on' this regenerative ability."

The research was supported by the National Institutes of Health, the American Heart Association, the March of Dimes and the Whitehead Foundation.

Scientists previously had suspected that zebrafish regenerated their heart tissue by the direct division of existing cardiac muscle cells adjacent to the injury, Poss said.

However, Poss and colleagues found that the process more closely resembles what happens when a salamander regenerates a lost limb. In the salamander, the site of injury becomes the gathering point for a mass of undifferentiated stem, or progenitor, cells, which are immature cells with the potential to be transformed into other cell types. This mass of undifferentiated cells is known as a blastema. As the progenitor cells receive the correct biochemical cue, they turn into distinct cell types, such as bone, muscle and cartilage, to form the new limb.

Poss believes that when a portion of the heart tissue is removed from zebrafish, a blastema forms at the site of injury. However, the progenitor cells will not achieve their full regenerative potential without interactions with the layer of "epicardial" cells that forms over the blastema. The entire heart is wrapped in a membrane known as the epicardium.

By the third day after injury, the epicardial cells begin to cover the injury site, a process that takes approximately two weeks. The precursor cells within the blastema begin to differentiate into cardiac muscle cells and proliferate within the first three to four days after injury, the researchers found in their experiments.

"Within days of the injury, we find a significant increase in the expression of certain genes in the epicardial cover," Poss said. "These genes are typically expressed only during embryonic development of the cardiovascular system. The epicardial cells mobilize to cover the wound and blastema, and help provide new blood vessels, creating a protective niche where the new heart muscle can grow."

The researchers found that biochemical signaling between the blastema and the epicardium is controlled in part by proteins called fibroblast growth factors, which are involved in wound healing and embryonic development.

"When we blocked signaling by fibroblast growth factors in our zebrafish model, we found that the regeneration gets to a certain point and then stops," Poss said. "The new blood vessels show poor invasion of the newly regenerating cells, halting the formation of new heart muscle."

Poss said that a continued understanding of the processes involved in regeneration of the zebrafish heart could lead to therapies to repair human heart muscle damaged by disease or heart attack.

"Multiple types of progenitor cells have been identified within the mammalian heart, yet it displays little or no regeneration when damaged," Poss said. "By contrast, zebrafish mount a vigorous regenerative response after cardiac injury. Future studies in zebrafish could help us discover why this regenerative ability is lacking in mammals and potential ways to stimulate it."

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Other researchers involved in the study included Kazu Kikuchi, Jennifer Holdway and Richard Roberts of Duke, and C. Geoffrey Burns of Massachusetts General Hospital.
