Research Offers Clue Into How Hearts Can Regenerate in Some Species

By NICHOLAS WADE
Published: March 24, 2010

Doctors who have treated heart attack patients with injections of stem cells have had little success so far in making the heart regenerate its stricken tissues. Researchers have now discovered that in nature, hearts are regenerated in a quite different way, one that does not depend on stem cells.

The finding may explain the lack of clinical success with the stem cells, as well as suggest new approaches.

Humans can regenerate the liver but cannot replace limbs and other organs. But fish and amphibians can grow new fins or limbs, and the zebra fish, which has been adopted by researchers as a laboratory organism, can even regenerate its heart after the bottom fifth has been lopped off. The fish are sluggish for a while but regrow the missing part of their heart in a month.

The human heart does have a very limited capacity to generate new heart muscle cells — about half the cells are replaced over the course of a person’s lifetime. But this regenerative capacity does not accelerate in response to a heart attack. Instead, the damaged cells are replaced by scar tissue, which does not contract.

Researchers assumed that the situation is different in the zebra fish because of stem cells that could generate more heart muscle cells after injury. A report in 2006 by Kenneth D. Poss and colleagues at Duke University offered confirmation that stem cells are the source of the repair process. Stem cells are general purpose cells that generate the mature, functional cells of the body.

But two independent reports in the journal Nature on Thursday contradict the stem cell idea, reporting that the mature heart muscle cells are the principal source for regenerating the zebra fish heart.

One of the reports is by Dr. Poss, who has revised his earlier findings. The second study effectively rules out stem cells, saying their contribution could be only marginal at best. The report is from a team led by Chris Jopling and Juan Carlos Izpisúa Belmonte of the Center for Regenerative Medicine in Barcelona, Spain.

The Barcelona team genetically engineered the zebra fish’s heart muscle cells so that when they proliferated they would synthesize a fluorescent green protein. After cutting off the bottom of the heart and letting it regenerate, they found that all the cells in the new part of the heart glowed green, proving that existing heart muscle cells were the principal or only source of the new tissue.

Nature's recipe for regeneration, at least in this case, is evidently to take the mature cells and walk them back in development to a stemlike state. The second step is for these stemlike heart muscle cells to grow and divide, generating replacement tissue. This contrasts with the assumption that tissues would be generated from stem cells that differentiate, or mature, into adult cells.

"If you look at how mother nature does it, the muscle cells don't go back to the embryonic state, they just dedifferentiate a little," Dr. Izpisúa Belmonte said. "So we should look at how animals do it and try to imitate them."

Zebra fish and mammals are separated by a long evolutionary distance and yet, surprisingly, the first step in the regeneration process, the dedifferentiation of heart muscle cells, occurs in mammals as well. In zebra fish the structure of the muscle fiber disintegrates as the cells dedifferentiate. The same process can be seen after injury in the hearts of mice, rats and dogs, Dr. Izpisúa Belmonte said, but the cells get stuck in the second process, that of proliferating to form new tissue.

"This opens a new vista," he said, "because all we need do is to induce the proliferation of these cells in mammals."

Charles Murry, an expert on heart cell biology at the University of Washington in Seattle, said the two reports raised the tantalizing question of why human hearts could not complete the regeneration process. In human hearts, too, Dr. Murry said, the muscle cells dedifferentiate after injury and double up their DNA, a necessary precursor to cell division. But they do not finish the process, for reasons that are so far unknown.

Learning how to overcome that block may not be so easy, in Dr. Murry's view. "It's tempting to say 'Let's do it how nature does it,' " he said, "but we don't know how nature does it. Some of the best molecular biologists in the world have been working on this for a couple of decades and it hasn't cracked yet."

Many heart patients have received injections of stem cells, often ones taken from their own bone marrow. But the beneficial effects have generally been unremarkable. "Many of the cell-based treatment protocols have proven modestly effective at best," Stefan Janssens of the University of Leuven in Belgium concludes in the current Annual Review of Medicine.

Dr. Murry agreed that results had been disappointing, but said both approaches, using stem cell treatments and trying to understand nature's favored recipe for regeneration, should be pursued in parallel.

A version of this article appeared in print on March 25, 2010, on page A20 of the New York edition.