Salamanders, regenerative wonders, heal like mammals, people

July 1 2009

Pacific Giant Salamander (Dicamptodon tenebrosus). Via Wikipedia

The salamander is a superhero of regeneration, able to replace lost limbs, damaged lungs, sliced spinal cord -- even bits of lopped-off brain. But it turns out that remarkable ability isn't so mysterious after all -- suggesting that researchers could learn how to replicate it in people.

Scientists had long credited the diminutive amphibious creature's outsized capabilities to "pluripotent" cells that, like human embryonic stem cells, have the uncanny ability to morph into whatever appendage, organ or tissue happens to be needed or due for a replacement.

But in a paper set to appear Thursday in the journal *Nature,* a team of seven researchers, including a University of Florida zoologist, debunks that notion. Based on experiments on genetically modified axolotl salamanders, the researchers show that cells from the salamander's different tissues retain the "memory" of those tissues when they

regenerate, contributing with few exceptions only to the same type of tissue from whence they came.

Standard mammal stem cells operate the same way, albeit with far less dramatic results -- they can heal wounds or knit bone together, but not regenerate a limb or rebuild a spinal cord. What's exciting about the new findings is they suggest that harnessing the salamander's regenerative wonders is at least within the realm of possibility for human medical science.

"I think it's more mammal-like than was ever expected," said Malcolm Maden, a professor of biology, member of the UF Genetics Institute, and author of the paper. "It gives you more hope for being able to someday regenerate individual tissues in people."

Also, the salamanders heal perfectly, without any scars whatsoever, another ability people would like to learn how to mimic, Maden said.

Axolotl salamanders, originally native to only one lake in central Mexico, are evolutionary oddities that become sexually reproducing adults while still in their larval stage. They are useful scientific models for studying regeneration because, unlike other salamanders, they can be bred in captivity and have large embryos that are easy to work on.

When an axolotl loses, for example, a leg, a small bump forms over the injury called a blastema. It takes only about three weeks for this blastema to transform into a new, fully functioning replacement leg -- not long considering the animals can live 12 or more years.

The cells within the blastema appear embryonic-like and originate from all tissues around the injury, including the cartilage, skin and muscle. As a result, scientists had long believed these cells were pluripotential -- meaning they came from a variety of sites and could make a variety of

things once functioning in their regenerative mode.

Maden and his colleagues at two German institutions tested that assumption using a tool from the transgenic kit: the GFP protein. When produced by genetically modified cells, GFP proteins have the useful quality of glowing livid green under ultraviolet light. This allows researchers to follow the origin, movement and destination of the genetically modified cells.

The researchers experimented on both adult and embryonic salamanders.

With the embryos, the scientists grafted transgenic tissue onto sites already known to develop into certain body parts, then observed how and where the cells organized themselves as the embryo developed. This approach allowed them to see, literally, what tissues the transgenic tissue made. In perhaps the most vivid result, the researchers grafted GFP-modified nerve cells onto the part of the embryo known to develop into the nervous system. Once the creatures developed, ultraviolet light exams of the adults revealed the GFP cells stretched only along nerve pathways -- like glowing green strings throughout the body

With the adults, they took tissue from specific parts or organs from transgenic GFP-producing axolotls, grafted it onto normal axolotls, then cut away a chunk of the grafted tissue to allow regeneration. They could then determine the fate of the grafted green cells in the emerging blastema and replacement tissue.

The researchers' main conclusion: Only 'old' muscle cells make 'new' muscle cells, only old skin cells make new skin cells, only old nerve cells make new nerve cells, and so on. The only hint that the axolotl cells could revamp their function came with skin and cartilage cells, which in some circumstances seemed to swap roles, Maden said.

Maden said the findings will help researchers zero in on why salamander cells are capable of such remarkable regeneration. "If you can understand how they regenerate, then you ought to be able to understand why mammals don't regenerate," he said.

Maden said UF researchers will soon begin raising and experimenting on transgenic axolotls at UF as part of the The Regeneration Project, an effort to treat human brain and other diseases by examining regeneration in salamanders, newts, starfish and flatworms.

Source: University of Florida (news : web)