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RESEARCH NEWS

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Restarting Regeneration One Step at a Time

Image Title: Hedgehog signaling in planarians regulates regeneration polarity in planarians. Loss of this signaling pathway prevents tail regeneration (Low), while an increase in signaling results in the regeneration of tails at both anterior and posterior end (High). Green: digestive system. Red: Central nervous system. Blue: brain. - Rink, Gurley, Elliot Sánchez Alvarado

Planarians may be lowly flatworms, but the tiny crawlers possess powers that even superheroes would envy. Cut off the worm’s head or tail, and a new one sprouts to replace it. In the flatworm’s body, nerves, muscles, connective tissues, and whole organs regenerate when damaged or removed.

“These animals can regrow virtually everything lost to amputation,” says Alejandro Sánchez Alvarado, a Howard Hughes Medical Institute investigator at the University of Utah.

Every day, the human body replaces an estimated 10 billion cells lost to injury or ordinary cellular housekeeping. More dramatically, salamanders, flatworms, and hydra, among other organisms, grow entirely new body parts when these are lost to injury or amputation. Scientists have marveled at such regenerative skills for centuries, but lack of good model organisms and effective techniques has managed to keep regeneration a biological mystery.

"We found that this pathway is very important in modulating the cell-cell communication that takes place during regeneration."
- Alejandro Sánchez Alvarado

Sánchez Alvarado has helped to establish the planarian, *Schmidtea mediterranea,* as a powerful model system, which he is using to learn how the flatworms accomplish their amazing regenerative feats. To that end, he is investigating basic cellular signaling pathways – molecular circuits with such deep evolutionary roots that flatworms, fruit flies, fish, and people all possess them. Sánchez Alvarado says that there are at least seven major pathways of this kind – all of which are involved in determining how embryos form during development. Since regeneration, like embryonic development, requires that an organism build new body parts and position them correctly within an existing organism, Sánchez Alvarado reasoned that these signaling pathways would be a good place to begin looking for the molecular tools used in regeneration.

Last year, he and his team discovered that one of these molecular circuits, called the WNT pathway, is a key player in planarian regeneration. Now, he's deduced an important regenerative role for another important circuit, the Hedgehog signaling pathway. The new findings were published October 22, 2009 in *Science Express*.

"We found that this pathway is very important in modulating the cell-cell communication that takes place during regeneration," says Sánchez Alvarado.

Previous research by many other scientists had shown that the Hedgehog pathway is vital for normal development of animals ranging from fruit flies to humans. In particular, elements of the pathway ensure that all the major body parts end up in the right place. When Hedgehog signaling goes awry, however, proper development can be disrupted, leading to severe and often fatal birth defects.

To study Hedgehog in planarians, Sánchez Alvarado and his team first had to find out if the many Hedgehog-related genes exist in the worms. A search of the planarian genome found that most of the Hedgehog elements from mammals also exist in planarians. This work confirmed the deep evolutionary origin of Hedgehog, as mammals and planarians are separated by hundreds of millions of years of evolution.

Next, Sánchez Alvarado and his colleagues, postdoctoral scientists Jochen C. Rink and Kyle A. Gurley and graduate student Sarah A. Elliot, manipulated different parts of the Hedgehog pathway to gauge their impact on regeneration. Using RNAi technology – a technique to selectively turn genes on or off – Sánchez Alvarado squelched the Hedgehog pathway, then amputated different parts of the planarians. The results were surprising. Worms with impaired Hedgehog signaling could regrow their heads as usual. But *sans* Hedgehog, planarians were unable to regenerate their tails.

The team then turned up the amount of Hedgehog signaling in the planarians. When Sánchez Alvarado and his colleagues amputated a planarian's head under these conditions, the animal grew a second tail where the new head should have appeared. He and his team observed that too much Hedgehog leads to two-tailed flatworms without heads.

The researchers concluded that Hedgehog signaling is vital for orienting regeneration along the head-to-tail axis. This regenerative role fits with the role of Hedgehog in embryonic development, where it drives the early body pattern and, in essence, tells an embryo to grow its feet at the bottom and its head at the top.

Further, Sánchez Alvarado found that Hedgehog signaling accomplishes its work by acting on the WNT pathway, the signaling pathway he had investigated in earlier studies. "The way Hedgehog seems to be working in regeneration in planarians is by modulating the expression and activity of the WNT pathway. It does this by turning on specific WNTs, which are the ligands -- the actors -- of the WNT pathway," says Sánchez Alvarado. "By doing so, tissues and cells responding to amputation determine whether a posterior or anterior end is to be regenerated."

The experiments also show the temporal relationship between the two signaling pathways, and places Hedgehog at the front of the line, where it drives changes in the second pathway, the WNT pathway. "The actual hierarchy and interactions of these pathways in regeneration was not known before," Sánchez Alvarado says.

The findings edge Sánchez Alvarado closer to his ultimate goal: Understanding the precise sequence of molecular events that occur during regeneration. Once this molecular flowchart is worked out, Sánchez Alvarado envisions trying to trigger regeneration in animals – such as mammals - that show very little ability to regrow damaged parts. "You can imagine a situation where you can coax tissues to deploy those and other pathways in time and space in a fashion that leads to regeneration," says Sánchez Alvarado.

Humans appear to possess all of the genetic and molecular tools needed for regeneration that have been identified so far, and Sánchez Alvarado thinks that one day, medicine might provide a way to jump-start a deep, latent regeneration ability.

“There’s a reason these particular regeneration pathways aren’t activated in mammals,” says Sánchez Alvarado. “Each step we take is a step closer to understanding that reason, and possibly overcoming it.”