MicroRNAs help zebrafish regenerate fins

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Biologists have discovered a molecular circuit breaker that controls a zebrafish's remarkable ability to regrow missing fins, according to a new study from Duke University Medical Center.

Tiny wonders of the aquarium world, zebrafish can regenerate organs and tissues, including hearts, eye parts and fins. When a fin is lost, the fish regenerates a perfect copy in two weeks by orchestrating the growth of many tissue types, including bone, nerves, blood vessels, connective tissue and skin.

Scientists hope that understanding how zebrafish repair themselves will lead to new treatments for human conditions caused by damaged tissue, such as heart failure, diabetes and spinal cord injuries.

The regeneration regulator is one of a group of recently discovered molecules called microRNAs: small pieces of ribonucleic acid (RNA) that each can potentially control the activity of dozens of different genes. In humans, microRNAs play important roles in cell growth and death, among other functions. There are hundreds of kinds of microRNAs, and scientists are constantly discovering new roles they play.

In zebrafish, one or more microRNAs appear to be important to keep regeneration on hold until the fish needs new tissue, the Duke researchers say. In response to an injury, the fish then damp down levels of these microRNAs to aid regrowth. The team discovered that the ability of zebrafish to replace amputated fins is particularly sensitive to levels of a particular microRNA called miR-133.

The discovery makes sense because any animal that can rapidly grow new tissue needs to keep the system in check, said senior author Kenneth Poss, Ph.D., assistant professor of cell biology. "They probably need to have mechanisms to reduce the potential for unwelcome growth. The implication is that in order to make human tissue regenerate more effectively, we might want to look at some of these microRNAs as potential targets."

The results appear in the March 15, 2008 issue of the journal *Genes & Development*. Postdoctoral scholar Viravuth Yin, Ph.D., a member of Poss' lab, is first author on the study. Funding was provided by the National Institutes of Health, the American Heart Association, the Whitehead Foundation and Pew Charitable Trusts.

Poss and many other cell biologists believe that mammals may have the same tissue regeneration capability as zebrafish, salamanders and newts, but that it is locked away somewhere in our genome, silenced in the course of evolution. "The key is finding a way to turn on this regenerative ability in humans," Poss said.

The Duke researchers began their study by ferreting out any microRNAs present in fins at different stages of regrowth, then measuring whether there was a lot or a little of each molecule.

Dr. Poss' team eventually zeroed in on some of the most important microRNAs for regrowth by studying genetically modified zebrafish. The modification allows a critical signaling pathway to be shut down during regeneration. The pathway sends biochemical cues called growth factors that stimulate cell division and organ growth.

Levels of one microRNA in particular, miR-133, dropped during normal regeneration. But when the scientists blocked the signaling pathway briefly during regeneration, the amount of miR-133 jumped back up to

the level found in uninjured fins. Further experiments showed that tweaking the concentration of miR-133 affected fin growth. When levels were raised, fin regrowth slowed; when they were dropped, regeneration sped up.

"Our work shows microRNAs appear to have an important role in regenerating complex tissues. Further studies could help us discover potential ways to stimulate this ability in mammals," Poss said.

Source: Duke University