From a single adult cell, flatworm crafts a new body

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A single adult cell from one of the most impressive masters of regeneration in the animal kingdom – the planarian – is all it takes to build a completely functional new worm, researchers have learned. The study provides the first hard evidence that adult planarians harbor pluripotent stem cells – cells capable of producing the diverse range of tissue types necessary to build a complete animal.

Distributed throughout the worm body, the newfound cells appear to have the same all-purpose qualities as embryonic stem cells. Such cells are essential for supplying the rapidly diversifying cells in a developing embryo, but usually disappear after the earliest stages of development. This is the first time pluripotent stem cells have been identified in an adult animal, according to Peter Reddien, the Howard Hughes Medical Institute early career scientist who led the study.

The cells' regenerative abilities are described in the May 13, 2011, issue of the journal *Science*. "The feats of the individual cells are amazing," Reddien said.

Scientists have long known about planarians' remarkable capacity for regeneration. A new flatworm, complete with skin, nervous system, primitive eyes, gut, muscle, and internal organs, can emerge from a body fragment hundreds of times smaller than the match-head sized original. But precisely how the worms rebuild themselves cell-by-cell has been elusive. "The central question," explained Reddien, "is where does all this material come from? Providing a cellular explanation for

regeneration is one of the great problems the community has faced."

Many animals, including people, continue to produce stem cells as adults. Unlike embryonic stem cells, however, adult stem cells in most animals have the capacity to become only a limited number of cell types. Hematopoietic stem cells in the bone marrow, for example, repopulate the various types of cells that make up the blood, whereas stem cells in the skin give rise to both skin and hair. Reddien says scientists were unsure whether planarian regeneration was spurred by one all-purpose stem cell or by several types of lineage-specific or tissue-specific adult stem cells working together.

To address the question, MIT colleagues Daniel Wagner, Irving Wang, and Reddien conducted a study in which they exposed worms to ionizing radiation, destroying cells' ability to divide. Because regeneration was thought to depend on neoblasts, dividing cells that migrate to and proliferate at wounds and other sites in need of repair, the research team used a dose of radiation low enough to let some of these survive. They then sorted through the cells to find neoblasts still capable of dividing.

When they let surviving neoblasts divide and grow into colonies of cells, they found that some of the individual cells seemed to possess all the qualities of a stem cell: "Did it make neurons? Did it make skin?" the team asked. Some neoblasts, termed clonogenic neoblasts, seemed capable of making it all. The HHMI team then put the clonogenic neoblasts to the ultimate test: they transplanted a single neoblast into a lethally irradiated worm lacking any other dividing cell.

What they observed, Reddien said, was "almost the type of event one might expect in a sci-fi movie." When a single neoblast is introduced into a planarian that cannot regenerate its own tissues, "eventually, it completely repopulates the animal with proliferating cells," Reddien explained. "Tissues of the host were slowly but surely replaced with

descendant cells from the transplanted, donor cell. All the various parts of the body – kidney, gut, eyes, brain, skin, muscle –were regenerated. It all came from one original starting cell."

By the time the process is complete, every cell in the worm has assumed the genetic identity of the donor cell. The rescued worms appear normal in every way: "It can eat and grow. It can even reproduce through the asexual mode of reproduction," Reddien said.

The discovery that an adult pluripotent stem cell is responsible for regeneration in planarians could lead to new insights useful in the budding field of human regenerative medicine. "Most of the genes in the planarian genome have human counterparts," Reddien noted. "Study of these cells should identify molecular mechanisms that can promote pluripotency, self-renewal, and deployment for regeneration of stem cells."

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