Our closest worm kin regrow body parts, raising hopes of regeneration in humans

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An intact, live acorn worm is pictured. The head is on the far left, and the worm will be cut in the middle. Credit: Shawn Luttrell/University of Washington

What if humans could regrow an amputated arm or leg, or completely restore nervous system function after a spinal cord injury?

A new study of one of our closest invertebrate relatives, the acorn worm, reveals that this feat might one day be possible. Acorn worms burrow in the sand around coral reefs, but their ancestral relationship to chordates means they have a genetic makeup and body plan surprisingly similar to ours.

A study led by the University of Washington and published in the December issue of the journal *Developmental Dynamics* has shown that acorn worms can regrow every major body part—including the head, nervous system and internal organs—from nothing after being sliced in half. If scientists can unlock the genetic network responsible for this feat, they might be able to regrow limbs in humans through manipulating our own similar genetic heritage.

"We share thousands of genes with these animals, and we have many, if not all, of the same genes they are using to regenerate their body structures," said lead author Shawn Luttrell, a UW biology doctoral student based at Friday Harbor Laboratories. "This could have implications for central nervous system regeneration in humans if we can figure out the mechanism the worms use to regenerate."

A close-up view of the cut site and tail end of the worm the day it was cut. Credit: Shawn Luttrell/University of Washington

The new study finds that when an acorn worm—one of the few living species of hemichordates—is cut in half, it regrows head or tail parts on each opposite end in perfect proportion to the existing half. Imagine if you cut a person in half at the waist, the bottom half would grow a new head and the top half would grow new legs.

After three or four days, the worms start growing a proboscis and mouth, and five to 10 days after being cut the heart and kidneys reappear. By day 15, the worms had regrown a completely new neural tube, the researchers showed. In humans, this corresponds to the spinal cord and brain.

After being cut, each half of the worm continues to thrive, and subsequent severings also produce vital, healthy worms once all of the body parts regrow.

"Regeneration gives animals or populations immortality," said senior author Billie Swalla, director of Friday Harbor Laboratories and a UW biology professor. "Not only are the tissues regrown, but they are regrown exactly the same way and with the same proportions so that at the end of the process, you can't tell a regenerated animal from one that has never been cut."

A head and neural tube have formed at the cut site. The worm's nervous system and organ functions are restored. Credit: Shawn Luttrell/University of Washington

The researchers also analyzed the gene expression patterns of acorn worms as they regrew body parts, which is an important first step in understanding the mechanisms driving regeneration. They suspect that a "master control" gene or set of genes is responsible for activating a pattern of genetic activity that promotes regrowth, because once regeneration begins, the same pattern unfolds in every worm. It's as if the cells are independently reading road signs that tell them how far the mouth should be from the gill slits, and in what proportion to other body parts and the original worm's size.

When these gene patterns are known, eventually tissue from a person with an amputation could be collected and the genes in those cells activated to go down a regeneration pathway. Then, a tissue graft could be placed on the end of a severed limb and the arm or leg could regrow to the right size, Swalla explained.

"I really think we as humans have the potential to regenerate, but something isn't allowing that to happen," Swalla said. "I believe humans have these same genes, and if we can figure out how to turn on these genes, we can regenerate."

Regeneration is common in many animal lineages, though among the vertebrates (which includes humans) it is most robust in amphibians and fish. Humans can regrow parts of organs and skin cells to some degree, but we have lost the ability to regenerate complete body parts.

The tail end of the worm after being cut. The boxed area indicates where the worm will grow a new head. Credit: Shawn Luttrell/University of Washington

Scientists suspect several reasons for this: Our immune systems—in a frenzy to staunch bleeding or prevent infection—might inhibit regeneration by creating impenetrable scar tissue over wounds, or perhaps our relatively large size compared with other animals might make regeneration too energy intensive. Replacing a limb might not be cost-effective, from an energy perspective, if we can adapt to using nine fingers instead of 10 or one arm instead of two.

The researchers are now trying to decipher which type of cells the worms are using to regenerate. They might be using stem cells to promote regrowth, or they could be reassigning cells to take on the task of regrowing tissue. They also hope to activate genes to stimulate complete regeneration in animals that currently aren't able to regrow all tissues, such as zebrafish.

More information: Shawn M. Luttrell et al, Head regeneration in hemichordates is not a strict recapitulation of development, *Developmental Dynamics* (2016). DOI: 10.1002/dvdy.24457

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