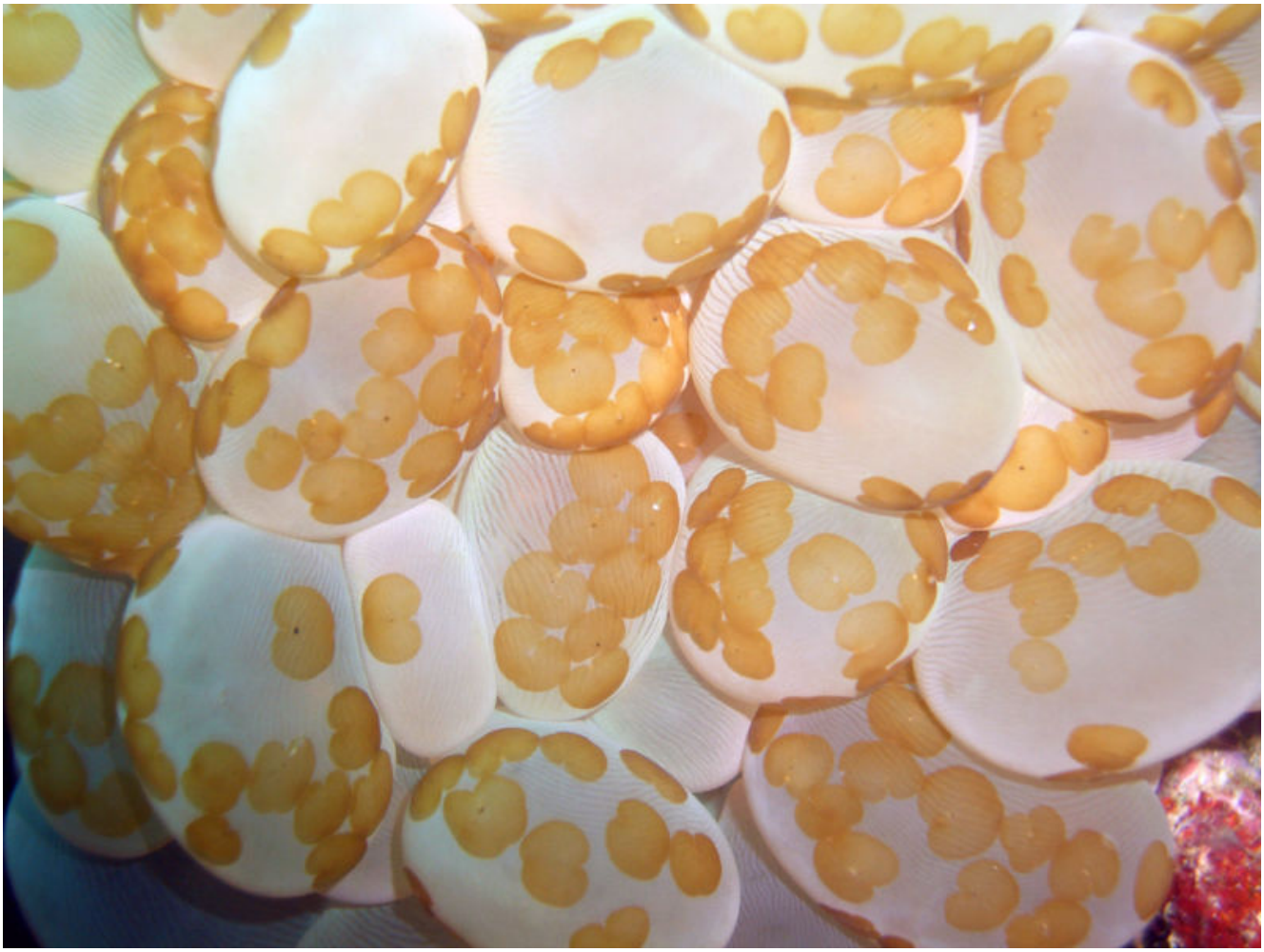
Figuring out how an odd, gutless worm regrows its head (or tail)



Enlarge / Some of the gutless worms (orange) cover a coral.

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In the movies, regeneration is the stuff of superheroes like Deadpool, who regrew the lower half of his body through some seriously awkward transitional scenes. Here in reality, regeneration is run of the mill, with lizards and amphibians regrowing limbs and tails while various worms are able to

regrow half their entire body. How they manage this has been the subject of extensive study, and we have a fair idea of some of the genes and processes involved. But it’s fair to say we don’t have a strong idea of how the whole process is coordinated and directed to form all of the needed tissues.

A step in that direction comes from a recent study that takes a strange angle on regeneration. To understand the process, the authors sequenced the genome of a worm that can regenerate into two full organisms after being cut in half. But the worm also happens to be part of a group that contains the closest living relatives of bilateral animals—those with a left and right side. As such, it could provide a fascinating perspective on our own evolution, but it’s something the researchers choose to ignore in this paper.

Xena coelo what a?

Most of the animals we’re familiar with are bilaterals, which have a left and right side. That includes some creatures (like sea urchins) where the two sides aren’t all that obvious. These bilateral animals also start out early in their development as three layers of cells: an outer layer that forms the skin and neural tissue; a central one that forms internal structures like muscles and bone; and an inner layer that goes on to form the lining of the gut.

But that’s not the only body plan around. Cnidarians like jellyfish appear to have complicated structures that don’t line up neatly with the organization we see in bilateral animals. But certain ocean worms form a group called *Xenacoelomorpha* that seems to be closer to bilateral animals. A *Xenacoelomorph* clearly has cells that form an exterior layer, and it also has loosely packed cells in its interior that resemble those that form muscles and bones in animals like us. But it seems to lack a distinct gut; its mouth simply allows access to the cavity the loosely packed cells occupy.

These surround each bit of incoming food and digest it.

Researchers have proposed this structure indicates that *Xenacoelomorphs* are likely to be the closest surviving relatives of bilateral animals. And the genome of one of those worms, *Hofstenia miamia*, as described in the recent paper, seems to confirm that. *Hofstenia's* genome indicates it's more closely related to us than it is to jellyfish, and it is most closely related to the least-complex bilaterian groups. Which means a careful analysis of its genome tells us things about the origins of bilateral life.

But that analysis isn't in the new paper. Mansi Srivastava, who runs the lab where most of the team worked, told Ars that scientists had previously identified nearly all of the genes that Hofstenia transcribes into RNA. These show that Hofstenia gene content is fairly typical of other animals and roughly similar to that of both bilaterians and other groups of animals. So, Srivastava said, interest shifted to how those genes are used, which requires analyzing how genes are activated or silenced.

On with its head!

And what better way to focus on that than to give a careful look at gene activity related to *Hofstenia's* impressive regeneration abilities, which include regrowing two complete animals when an adult worm is cut in half. To study this, the researchers chopped the animals in half, waited a few hours (there were time points between three hours and two days), and then tagged active sites in its genome.

To do the tagging, the researchers used a mobile genetic element, which is technically called a transposon and sometimes nicknamed a "jumping gene." Under the right conditions, these jumping genes will move to new locations in the genome but only if those locations are accessible. Areas where genes aren't active tend to be tightly packaged and

won’t be targeted by the jumping gene. Areas where genes are active, by contrast, have a looser and more open structure, which makes for a great target for a jumping gene.

By tracking which areas of the genome get targeted, the researchers were able to track where the DNA was being opened up so that new genes could become active. They came up with 18,000 different sites, many of which were presumably becoming active in order to enable regeneration. Some of them were head-specific while others became active largely in the tail. Still others were active in both body halves.

EGR

By computer, the team then looked for proteins that could stick to the DNA at these sites. One of the proteins, called EGR, is already known to be involved in wound healing in other organisms, and it appeared to stick to the earliest sites that become active. This suggests EGR acts as a “pioneer” that helps open up the DNA’s structure at sites near critical genes and allows them to take part in regeneration.

And it looks like EGR is part of an ancient pathway with deep roots in animals. Planarian worms, which are also famous for their regenerative ability, also have a version of EGR. It too appears to be one of the earliest acting genes during the regeneration process. Of course, humans have four proteins related to EGR, and we’re rather notable for having a limited capacity to regenerate. So figuring out how the activity of these proteins differs from the activity seen in distantly related animals might help explain why.

In the meantime, this new data provides a framework for future studies of the regeneration process. EGR’s pioneering function initiates a cascade of gene activity regulation—at least two of the genes it sticks to encode DNA-binding regulatory proteins themselves. So, over time, this may help provide a more complete picture of the regeneration process.

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