**Inside a Champion of Regeneration**

*What enables some organisms to regrow lost body parts? Carolyn Adler casts light on pluripotent stem cells and the molecules that regulate them.*

by Alan Dove

If a salamander loses a limb, it simply grows a new one. Many arthropods can do the same trick. The champions of regeneration, though, are planarians, a large family of flatworms found in water worldwide. Cut off a planarian’s tail, and not only does the organism generate a new tail, the tail generates a whole new body and head of its own. It’s one of the most spectacular and bizarre phenomena in nature, and researchers still don’t really understand how it works.

“The biology is amazing,” says Carolyn E. Adler, Molecular Medicine. “People have noted for over 200 years that these animals are capable of regenerating entire animals from tiny pieces, but only in the last 20 years or so have we begun to understand the molecular and cellular regulators responsible for it.” Since joining the Cornell faculty in 2015, Adler has been pushing the field forward, often by revisiting classical experiments with modern techniques.

Much of her work focuses on planarian stem cells, populations of cells capable of reproducing themselves and differentiating into various types of tissues. Adult humans have small populations of relatively specialized stem cells, such as those that generate a continuous supply of new skin or replace different types of blood cells. In planarians, though, stem cells are much more numerous and flexible; about 20 percent of a typical planarian’s body consists of stem cells, a vast reserve that enables the organism to replace any tissue or organ.

**Unexpected Tenacity**

While these stem cells drive planarians’ amazing regeneration after physical wounding, they have a weakness: radiation. “When you expose them to radiation, most stem cells are lost; we used radiation initially to reduce the number of stem cells, so that we could see what happened to these cells after injury,” Adler says. The idea was that it would be easier to track the smaller population of stem cells to figure out what they were doing.

Serendipitously, researchers found that an injury can offset some of the effects of radiation. “My student discovered that there was a critical window of time adjacent to radiation, when injury had a very robust effect on stem cell survival,” Adler says. An injury shortly before or shortly after the radiation dose preserves the stem cells around the injury. Only stem cells close to the injury survived, indicating that the process operated locally.

Adler’s team subsequently determined that a protein that regulates the cells’ response to DNA damage also drives their vulnerability to radiation. Suppressing that protein’s production made all of the stem cells resistant to radiation. “In contrast to our previous work, where we found that we could get the stem cells to survive locally, now we have a way of getting them to survive globally throughout the organism,” Adler says.

The results bear a striking resemblance to some aspects of human cancer, which also involves populations of actively replicating, often radiation-sensitive cells. Mutations in genes that respond to DNA damage can make tumors more aggressive and resistant to radiation. “This is one of the really interesting things about planarians. You would think because they have such abundant and hyperactive stem cells that they would also be prone to getting some sort of planarian tumor, but we don’t know what that looks like because it doesn’t happen; they have some intrinsic control to stop regeneration at the right time,” Adler says.

**Knowing Where to Stop**

Besides rigorous control over when they start and stop reproducing, planarian stem cells have the uncanny ability to detect which structures need replacement. A drastic injury such as decapitation prompts each of the two pieces of the organism to grow a whole new head or body, but planarians with a single organ removed will regenerate only that organ. How do the stem cells determine what structures to make?

To answer that question, Adler developed a technique she calls chemical amputation. A planarian feeds by extending its throat, or pharynx, from the middle of its body like the hose of a vacuum cleaner. Exposing the organism to a solution of sodium azide removes its pharynx without affecting any other structures. “We think that this kind of selective and targeted amputation is a way of understanding how the stem cells are sensing what needs to be made,” Adler says.

In typical planarian fashion, the chemical amputees promptly regrow new pharynxes. By inactivating gene products in the planarian individually, Adler’s lab has identified a single gene that is required for regeneration of the pharynx but apparently no other organ. The researchers are now searching for the genes that detect other structural losses, and the regulatory system that must exist to orchestrate their activities.

**A Small Research Community**

Despite their evident potential as a model organism, planarians weren’t widely studied when Adler started working on them. Compared to fruit flies, round worms, and mouse models, Adler says planarians are “a less established system, so there are fewer existing resources. You have to build everything yourself. You have to create the research community yourself. It’s a completely DIY experience.”

Those challenges are part of what drew her to the field. “Even though it’s still very frustrating that we have to do everything ourselves, I really wanted that aspect of being part of a community of builders and helping to nurture that research community, which I am very much involved in,” Adler says.

The COVID-19 pandemic made that a lot harder. “It was horrible,” Adler says, adding that “as a young, untenured professor, this time was really difficult [and] the pandemic affected us for so long, in terms of training, recruitment, and sustainability of the lab. It has been really challenging.” She credits Cornell with allowing her team to return to the lab as soon as they could do so safely, in the fall of 2020.

“One of the things that has always been a critical aspect of working in the lab is the people, and being there to engage with those people on a daily basis,” Adler says. With the return of in-person work and seminars, she’s optimistic that her lab, and the burgeoning community of planarian researchers around the world, will fully regenerate its momentum.