Possible key to regeneration found in planaria's origins

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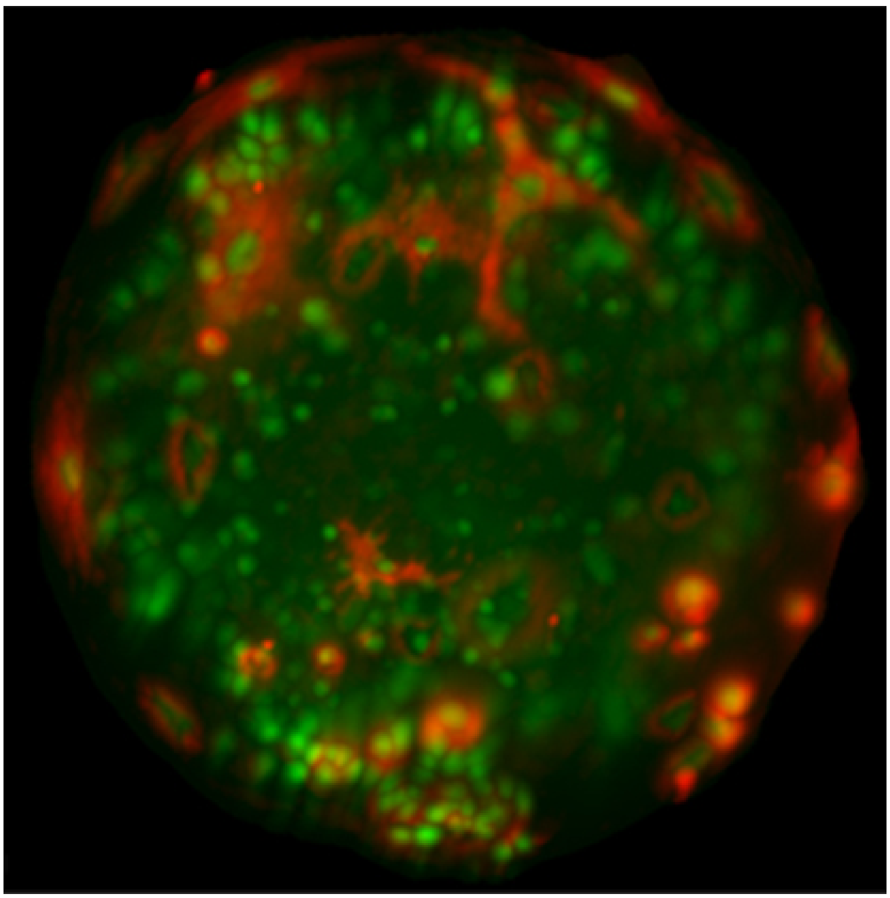

Three-dimensional reconstruction of a Stage 3 S. mediterranea embryo, stained with a pan-embryonic cell marker (red) and a nuclear dye (green). Credit: Image courtesy of Erin Davies, Ph.D., Amanda Kroesen, and Sean McKinney, Ph.D.

A new report from the Stowers Institute for Medical Research chronicles the embryonic origins of planaria, providing new insight into the animal's remarkable regenerative abilities.

The work, published online in *eLife*, is the first to discover that adult stem cells called neoblasts, key to planaria regeneration, arise during a specific stage of embryonic development. Ordinarily, embryonic cells do not persist beyond embryogenesis. However, neoblasts made in early planarian embryos persist beyond embryonic development and are present throughout the animal's lifetime. Neoblasts seemingly retain the ability to access embryonic developmental programs during adulthood to drive the regeneration of body parts lost to traumatic injury.

"While a large body of research focuses on regeneration in adult planaria, much less is known about planarian embryogenesis - the process of growing from a single fertilized egg into a properly formed organism," says Erin Davies, Ph.D., the study's first author and a postdoctoral research associate in the laboratory of Howard Hughes Medical Institute and Stowers Institute Investigator Alejandro Sánchez Alvarado, Ph.D.

Wanting to know more, Davies and colleagues generated a staging series, or a set of unique molecular fingerprints, for *Schmidtea mediterranea* embryos, as well as a gene expression atlas describing embryonic tissues and the formation of major organ systems during embryogenesis. These resources are available online at https://planosphere.stowers.org. Together, these tools lay the foundation for scientists to begin comparing the processes of embryogenesis and regeneration in planaria.

"In planaria, we have a really great system for studying regeneration during adulthood," Davies says. "It offers us the opportunity to start to compare and contrast what is similar and what is different about developmental processes during embryogenesis and regeneration in an adult animal."

Planaria have an ability to regenerate that is unparalleled among other organisms. If an adult worm is cut apart, nearly any piece can form a new, fully-functional animal complete with a brain and nervous system, eyes, kidneys, gut, muscle, and skin - within just two weeks. Adult stem cells called neoblasts power the planaria's extraordinary talent for regeneration. These cells both replace themselves and make every type of cell needed to create an adult worm. But their origin has been unclear.

"Because neoblasts have only been studied in adults, we did not know how they were made in the first place during embryonic development," says Sánchez Alvarado. "Our work has uncovered both the precise embryonic time when neoblasts are formed, and the gene expression profile that precedes their formation."

The researchers observed a large-scale shift in the types of genes being expressed at about one week into development, explains Davies.

"The genes that we think of as being required to make different types of tissues in the body - brain, muscle, gut, kidneys - all these genes start to turn on during this time window," she says.

The researchers found that when planarian embryonic cells start to form major organ systems, adult neoblasts arise as well. When transplanted into adult planaria depleted of stem cells, these embryonic cells took hold and proliferated. The embryonic cells replenished the adult planarian stem cell population and extended its life. However, transplanted embryonic cells from earlier time periods did not take, and the adult planarian hosts died.

During embryogenesis, neoblast offspring help build the worm. Once established, neoblasts are maintained throughout the worm's life, allowing the animal continued access to embryonic development programs during adulthood. Understanding this unique planarian flatworm attribute may provide further insight into their incredible regenerative abilities.

"Planarian embryogenesis has remained obscure for many decades, and the embryogenesis of Schmidtea mediterranea particularly so. It is to Erin Davies' great credit that this is no longer the case and that we, as a community interested in regeneration and stem cell biology, can now peer into a world of biological activity we could not access previously," adds Sánchez Alvarado.

The finding lays the foundation for future research on how stem cells are specified, maintained, and regulated, and will facilitate direct comparisons of gene function during embryogenesis and regeneration. Many of the genes required to build and maintain organs in planaria appear to work in both developmental contexts.

"I think that there are likely to be many similarities, but also critical differences," Davies adds. "We understand very little about how regeneration cues are transmitted to stem cells in the adult. In planaria, we'll have the opportunity to investigate embryonic and regenerative processes both at the level of single genes, and globally at the level of what happens to all genes expressed in a particular tissue over time."

Knowledge of the developmental pathways responsible for regeneration could also guide future therapeutic advances for patients suffering from degenerative diseases or traumatic injuries.

Other Stowers contributors include Kai Lei, Ph.D., Chris Seidel, Ph.D., Amanda Kroesen, Sean McKinney, Ph.D., Longhua Guo, Ph.D., Sofia Robb, Ph.D., Eric Ross and Kirsten Gotting.

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Lay summary of findings

Planarian flatworms have an ability to regenerate that is unparalleled among other organisms. If an adult worm is cut apart, almost any piece can form a new, fully-functional animal complete with a brain and nervous system, eyes, kidneys, gut, muscle, and skin - within just two weeks. That's why scientists consider them an ideal organism in which to study regeneration. But this phenomenon is still poorly understood.

A new report from researchers in the Sánchez Alvarado Lab at the Stowers Institute for Medical Research chronicles stage-by-stage how the planarian flatworm develops as an embryo and provides new insight into the animal's remarkable regenerative abilities. The work is the first to show that stem cells key to planarian regeneration, called neoblasts, form during a specific stage of embryonic development. Neoblasts are present throughout the worm's life, and can replenish themselves and make every type of cell in the body. This feature is unique to planarian flatworms, and may underlie their incredible regenerative abilities. The findings could guide future therapeutic advances for patients suffering from degenerative diseases or traumatic injuries.

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