Planarian genes that control stem cell biology identified

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Despite their unassuming appearance, the planarian flatworms in Whitehead Institute Member Peter Reddien's lab are revealing powerful new insights into the biology of stem cells—insights that may eventually help such cells deliver on a promising role in regenerative medicine.

In this week's issue of the journal *Cell Stem Cell*, Reddien and scientists in his lab report on their development of a novel approach to identify and study the genes that control stem cell behavior in planarians. Intriguingly, at least one class of these genes has a counterpart in human embryonic stem cells.

"This is a huge step forward in establishing planarians as an in vivo system for which the roles of stem cell regulators can be dissected," says Reddien, who is also an associate professor of biology at MIT and a Howard Hughes Medical Institute (HHMI) Early Career Scientist. "In the grand scheme of things for understanding stem cell biology, I think this is a beginning foray into seeking general principles that all animals utilize. I'd say we're at the beginning of that process."

Planarians (*Schmidtea mediterranea*) are tiny freshwater flatworms with the ability to reproduce through fission. After literally tearing themselves in half, the worms use stem cells, called cNeoblasts, to regrow any missing tissues and organs, ultimately forming two complete planarians in about a week.

Unlike muscle, nerve, or skin cells that are fully differentiated, certain

stem cells, such as cNeoblasts and embryonic stem cells are pluripotent, having the ability to become almost cell type in the body. Researchers have long been interested in harnessing this capability to regrow damaged, diseased, or missing tissues in humans, such as insulin-producing cells for diabetics or nerve cells for patients with spinal cord injuries.

Several problems currently confound the therapeutic use of stem cells, including getting the stem cells to differentiate into the desired cell type in the appropriate location and having such cells successfully integrate with surrounding tissues, all without forming tumors. To solve these issues, researchers need a better understanding of how stem cells tick at the molecular level, particularly within the environment of a living organism. To date, a considerable amount of embryonic stem cell research has been conducted in the highly artificial environment of the Petri dish.

With its renowned powers of regeneration and more than half of its genes having human homologs, the planarian seems like a logical choice for this line of research. Yet, until now, scientists have been unable to efficiently find the genes that regulate the planarian stem cell system.

Postdoctoral researcher Dan Wagner, first author of the *Cell Stem Cell* paper, and Reddien devised a clever method to identify potential genetic regulators and then determine if those genes affect the two main functions of stem cells: differentiation and renewal of the stem cell population.

After identifying genes active in cNeoblasts, Wagner irradiated the planarians, leaving a single surviving cNeoblast in each planarian. Left alone, each cNeoblast can form colonies of new cells at very specific rates of differentiation and stem cell renewal.

The researchers knocked down each of the active genes, one per planarian, and observed how the surviving cNeoblasts responded. By comparing the rate of differentiation and stem cell renewal to that of normal cNeoblasts, they could determine the role of each gene. Thus, if a colony containing a certain knocked down gene were observed to have fewer stem cells than the controls, it could be concluded that gene in question plays a role in the process of stem cell renewal. And if the colony had fewer differentiated cells than normal, the knocked down gene could be associated with differentiation.

"Because it's a quantitative method, we can now precisely measure the role of each gene in different aspects of stem cell function," says Wagner. "Being able to measure stem cell activity with a colony is a great improvement over methods that existed before, which were much more indirect."

In total, Wagner identified 10 genes impacting cNeoblast renewal, and two genes with roles in both renewal and differentiation. According to Wagner, three of the stem cell renewal genes are particularly intriguing because they code for proteins that are similar to components of Polycomb Repressive Complex 2 (PRC2), known to regulate stem cell biology in mammalian embryonic stem cells and in other stem cell systems.

"It's interesting because it suggests a parallel between how stem cells operate in planarians and in mammals. For example, there might be similarities between how cNeoblasts and embryonic stem cells function and maintain stemness at the molecular level," he says.

More information: "Genetic Regulators of a Pluripotent Adult Stem Cell System in Planarians Identified by RNAi and Clonal Analysis" *Cell Stem Cell*, March 2, 2012.

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