DNA 'tattoos' link adult, daughter stem cells in planarians

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Unlike some parents, adult stem cells don't seem to mind when their daughters get a tattoo. In fact, they're willing to pass them along. Using the molecular equivalent of a tattoo on DNA that adult stem cells (ASC) pass to their "daughter" cells in combination with gene expression profiles, University of Utah researchers have identified two early steps in adult stem cell differentiation—the process that determines whether cells will form muscle, neurons, skin, etc., in people and animals.

The U of U researchers, led by Alejandro Sánchez Alvarado, Ph.D., professor of neurobiology and anatomy, identified 259 genes that help defined the earliest steps in the differentiation of adult stem cells in planarians—tiny flatworms that have the uncanny ability to regenerate cells and may have much to teach about human stem cell biology.

The findings, reported in the Sept. 11 issue of *Cell Stem Cell* establish planarians as an excellent model for studying adult stem cells in a live animal, rather than a laboratory culture dish.

"This allows us to study an entire stem cell population in its own environment," said Sánchez Alvarado, also an investigator with the Howard Hughes Medical Institute and the study's senior author. "It's likely that what we learned here can be applied to our own stem cell biology."

Planarians share similar biology with humans in many ways. They also, for reasons unknown, regenerate cells unlike any other animal—an

entirely new worm can form from just a fragment of another worm. Planarians constantly regenerate new cells to replace those that die naturally or from injury.

The process begins when adult stem cells divide into two new cells (daughter cells): one becomes like its mother (a stem cell), while the other will move on to give rise to the cells that will serve specific functions in planarian life. For example, some cells may form part of the worm's musculature, while others will form part of the brain.

Because daughters and mother cells are indistinguishable from each other in appearance, the researchers devised methods to detect specific differences in gene expression in the BrdU-labeled cells. The researchers identified 259 genes associated with the stem cells and their daughters. When the U team disabled some of these genes, they found that in some cases no defects were observed, while in others deficiencies were detected in the way the cells were patterned in regenerating planarians.

Sánchez Alvarado and two colleagues then marked adult stem cells in the worms by injecting BrdU, a synthetic nucleotide that binds with DNA and leaves an unmistakable mark on it, much like a tattoo. (Nucleotides are the structural units of DNA and RNA.) When the adult stem cells divided into daughter cells as part of the worms' normal cell regeneration, the BrdU was passed to the daughter cells in their DNA, allowing the researchers to track these cells. By detecting which genes were expressed in which BrdU-labeled cells, the collection of identified genes allowed the researchers to work out for the first time the lineage of stem cells in planarians.

They found that the daughter cells that move on to differentiate into different cell types do so by going through at least two steps. Although the daughter cells, which the researchers labeled categories 2 and 3, are indistinguishable by appearance, they play different roles in cell

differentiation

"It seems as if category 2 cells make category 3 cells," Sánchez Alvarado said. "We don't know which differentiated cells they make, but category 3 cells likely differentiate into many different cell types."

These findings open a window to understanding how multipotent stem cells take differentiation decisions. "This allows us to begin to understand how adult stem cells decide what their daughter cells will become when they grow up," Sánchez Alvarado said. "These molecular markers will help us identify specific differentiated cells and help us determine how a stem cell population decides how many of each of the differentiated cell types it needs to make."

The next big step for Sánchez Alvarado and his colleagues is to identify the molecules that act to restrict cell types into serving specific functions.

Source: University of Utah