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Scientists have captured the elusive cell that can regenerate an entire flatworm

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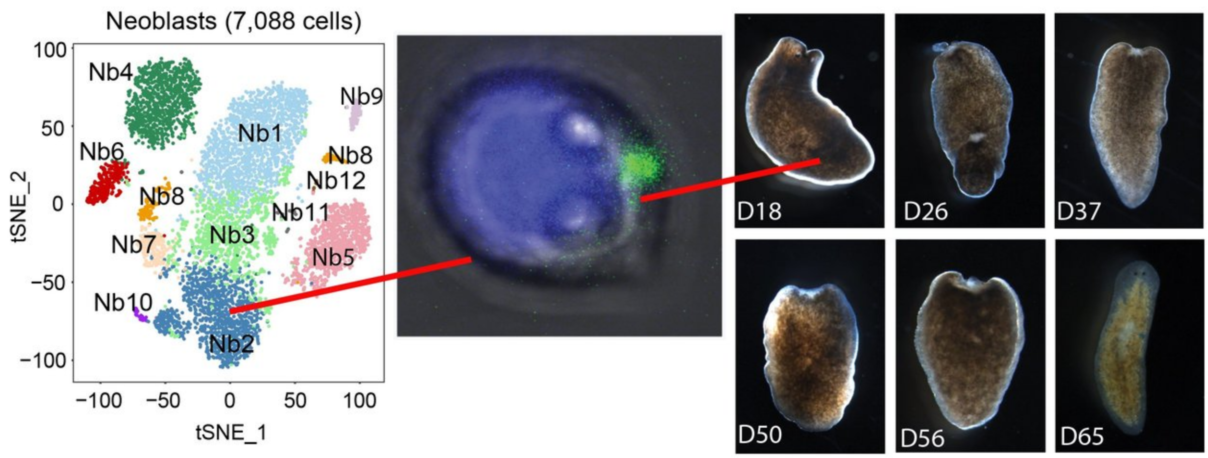

Planarian flatworm adult stem cells known as neoblasts can be clustered based on their gene expression profiles (left panel). A neoblast subpopulation termed Nb2 expresses the cell membrane protein TSPAN-1 (center panel, a representative Nb2 cell with TSPAN-1 protein shown in green and DNA in blue). Nb2 neoblasts can repopulate stem cell-depleted animals (right panel, representative animals at different time points after Nb2 single-cell transplants). Credit: Sánchez Alvarado Lab

Researchers at the Stowers Institute for Medical Research have captured the one cell that is capable of regenerating an entire organism. For over a century, scientists have witnessed the effects of this cellular marvel, which enables creatures such as the planarian flatworm to perform death-defying feats like regrowing a severed head. But until recently, they lacked the tools necessary to target and track this cell, so they could watch it in action and discover its secrets.

Now, by pioneering a technique that combines genomics, single-cell analysis, flow cytometry and imaging, scientists have isolated this amazing regenerative cell—a subtype of the long-studied adult pluripotent stem cell—before it performs its remarkable act. The findings, published in the June 14, 2018, issue of the journal *Cell*, will likely propel biological studies on highly regenerative organisms like planarians and also inform regenerative medicine efforts for other organisms like humans that have less regenerative capacity.

"This is the first time that an adult pluripotent stem cell has been isolated prospectively," says Alejandro Sánchez Alvarado, Ph.D., an investigator at the Stowers Institute and Howard Hughes Medical Institute and senior author of the study. "Our finding essentially says that this is no longer an abstraction, that there truly is a cellular entity that can restore regenerative capacities to animals that have lost it and that such entity can now be purified alive and studied in detail."

Every multicellular organism is built from a single cell, which divides into two identical cells, then four, and so on. Each of these cells contains the exact same twisted strands of DNA, and is considered pluripotent—meaning it can give rise to all possible cell types in the body. But somewhere along the way, those starter cells—known as embryonic stem cells—resign themselves to a different fate and become skin cells, heart cells, muscle cells, or another cell type. In humans, no known pluripotent stem cells remain after birth. In planarians, they stick around into adulthood, where they become known as adult pluripotent stem cells or neoblasts. Scientists believe these neoblasts hold the secret to regeneration.

Though neoblasts have been the subject of scientific inquiry since the late 1800's, only in the last couple of decades have scientists been able to characterize this powerful cell population using functional assays and molecular techniques. Their efforts showed that this seemingly homogenous cell population was actually a conglomeration of different subtypes, with different properties and different patterns of gene expression.

"We might have to transplant over a hundred individual cells into as many worms to find one that is truly pluripotent and can regenerate the organism," says Sánchez Alvarado. "That's a lot of work, just to find the one cell that fits the functional definition of a true neoblast. And if we want to define it molecularly by identifying the genes that cell is expressing, we have to destroy the cell for processing. There was no way to do that and keep the cell alive to track it during regeneration."

Sánchez Alvarado and his team began searching for a distinguishing characteristic that could identify this elusive cell ahead of time. One feature that had long been used to distinguish neoblasts from other cells is a stem cell marker known as piwi-1, so Postdoctoral Research Associate An Zeng, Ph.D., decided to start there. First, he separated the cells that expressed this marker from those that did not. Then he noticed the cells could be separated into two groups—one that expressed high levels of piwi (aptly called piwi-high) and another that expressed low levels of piwi (called piwi-low). When Zeng studied the members of these two groups, he found only those that were piwi-high fit the molecular definition of neoblasts. So he discarded the rest.

"This kind of simultaneous quantitative analysis of gene expression and protein levels had never been done before in planarians," says Sánchez Alvarado. "We could not have done it without the amazing scientific support facilities here at Stowers, including molecular biology, flow cytometry, bioinformatics, and imaging groups. Many researchers had assumed that all cells expressing piwi-1 were true neoblasts, and it didn't matter how much of the marker they expressed. We showed it did matter."

Next, Zeng selected 8,000 or so of the piwi-high cells and analyzed their gene expression patterns. To his surprise, the cells fell not into just one or two, but 12 different subgroups. Through a process of elimination, Zeng excluded any subgroups with genetic signatures indicating that the cells were destined for a particular fate, like muscle or skin. That left him with two subgroups that could still be pluripotent, which he named Nb1 and Nb2.

Conveniently, the cells in subgroup Nb2 expressed a gene coding for a member of the tetraspanin protein family, a group of evolutionarily ancient and poorly understood proteins that sit on the surface of cells. Zeng made an antibody that could latch onto this protein, pulling the cells that carried it out of a mixture of other suspected neoblasts. He then transplanted the single purified cell into a planarian that had been subjected to lethal levels of radiation. Not only did these cells repopulate and rescue the irradiated animals, but they did so 14 times more consistently than cells purified by older methods.

"We have enriched for a pluripotent stem cell population, which opens the door to a number of experiments that were not possible before," says Sánchez Alvarado. "The fact that the marker we discovered is expressed not only in planarians but also in humans suggests that there are some conserved mechanisms that we can exploit. I expect those first principles will be broadly applicable to any organism that ever relied on stem cells to become what they are today. And that essentially is everybody."

Provided by Stowers Institute for Medical Research

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