Scientists discover stem cells that build a fly's nervous system

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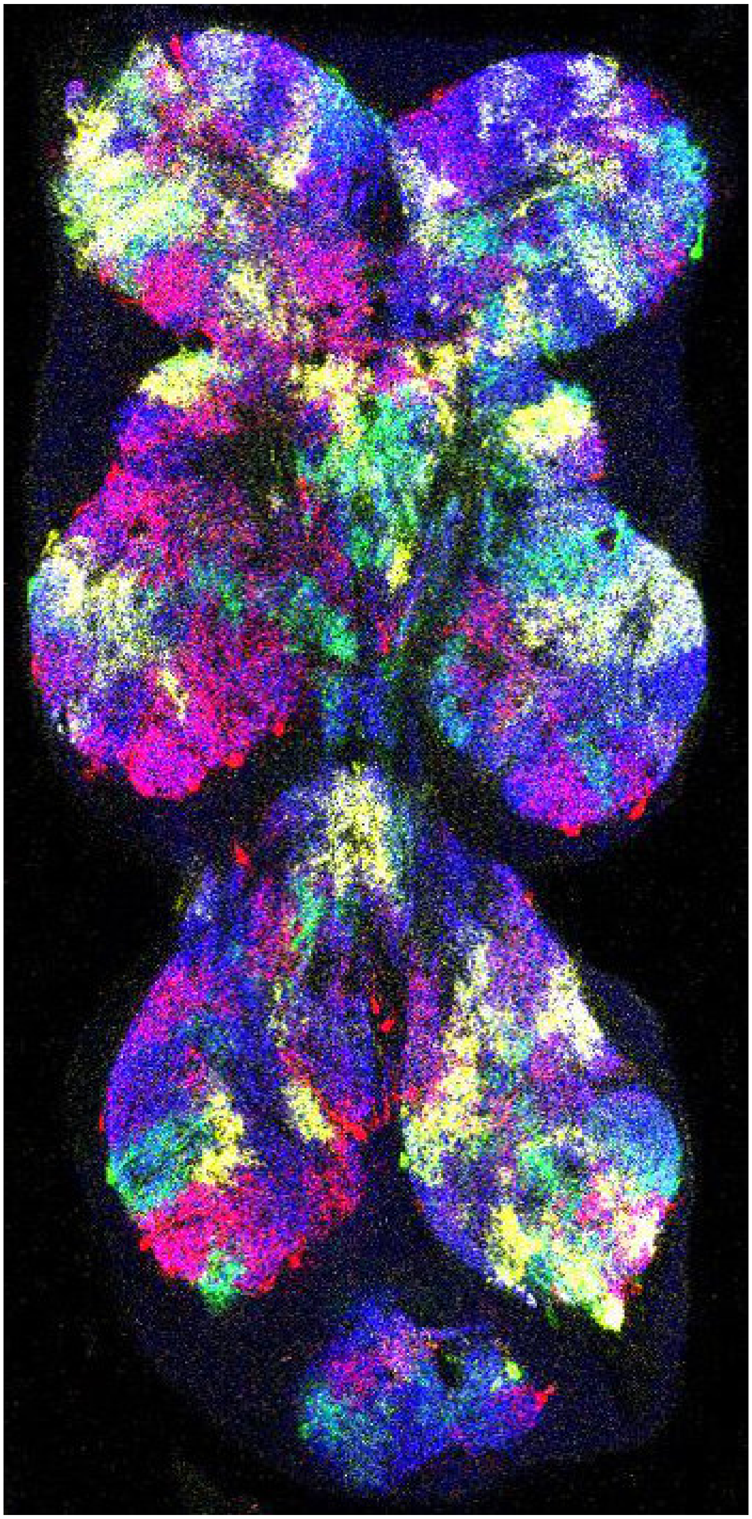

Single glial cells that surround and innervate the adult Drosophila nervous system are randomly labeled in different colors. These glia are derived from the very same stem cells that also give rise to the motor neurons that control leg movements. Credit: Jon Enriquez/Mann Lab/Columbia's Zuckerman Institute

Scientists at Columbia's Zuckerman Institute have uncovered new insights into how stem cells transform into brain cells that control leg movements. The surprising details of this process, observed in the brains of fruit flies, could shed light on how the human brain develops—and what happens when problems arise. Stem cells hold tremendous promise for medicine; their ability to metamorphose into other kinds of cells make them useful for repairing injuries—from heart attacks to brain damage. By providing key insight into how stem cells develop and mature, this research should help scientists in their quest to use stem cells to heal.

The results of this study were published today in *Neuron*.

"For an animal to develop from egg to infant, everything must end up in the right place at the right time. But how a single system exhibits both the necessary precision and flexibility to achieve this—particularly in the face of developmental and environmental challenges—remained unclear," said Richard Mann, PhD, principal investigator at Columbia's Mortimer B. Zuckerman Mind Brain Behavior Institute and the paper's senior author. "Here, we identified an ingenious solution, in which two critical and interacting types of brain cells, born from the same stem cell, facilitate the construction of a mature motor system."

To understand the development of the human brain, the researchers looked to a much simpler animal, the fruit fly, in which they could control and observe cells more easily. They started with stem cells, the undifferentiated cells that then develop into virtually any cell type in the body. The researchers traced stem cells as they matured into motor neurons, which are the type of nerve cells that control muscle movement. In particular, they focused on the approximately 50 motor neurons that control the movement of each of a fruit fly's six legs.

While studying the stem cells as they developed into motor neurons in fruit fly larvae, they noticed that in the midst of this process, some of these stem cells took a detour. Instead of developing into motor neurons like the others, some of their progeny, or offspring, became glial cells. Glial cells are critical components of the nervous system, acting to guide their growth and connectivity with other neurons. What's more, these glial cells were the ones that specifically build the scaffolding for the motor neurons that were born from the same stem cells and ultimately control leg movement.

"This process resembles a separated-at-birth reunion," Dr. Mann, who is also the Higgins Professor of Biochemistry and Molecular Biophysics at Columbia University Irving Medical Center. "There are many examples in developmental biology where cells from different origins will come together and form a coherent structure. But here, we have cells born of the same parent that each diverge down their own path—only to be reunited during development".

Even more interesting, once early-stage motor neurons and glia diverged, they have dramatically different properties. The development of each motor neuron was hardwired; each cell was always born in the same order and achieved the identical shape.

Glial development, on the other hand, was more plastic. The number of glial cells produced by each stem cell could vary. Moreover, the glia did not have rigid birth orders or shapes. And yet somehow the final total number of glia always came to the same number—280—and they always fully infiltrated the bundle of motor neurons they needed to support.

"It's just gorgeous to see this kind of coordinated dance of these two cell types being orchestrated over the course of development," Dr. Mann said.

While the hardwired motor neuron development allows for the precise control that muscle coordination requires, the flexible development of glia makes the system more robust. If a mutation or an injury occurs during larval development, the glia can adapt and still support the motor neurons.

The researchers were able to trace the development of these two cell types with unprecedented clarity by advancing very powerful imaging techniques that are available in the fruit fly.

Jon Enriquez, PhD, the paper's first author, who now runs his own lab at IGFL, France, is "very creative at using and tweaking the existing technologies to answer important questions," Dr. Mann says. "By harnessing the lineage tracing methods that are available in the fly, he was able to adapt them to label the glia and motor neurons that are born from the same stem cell in two different colors." Carol Mason, PhD, another Zuckerman Institute principal investigator, contributed expertise in electron microscopy, a powerful technology that allows individual cells to be observed in high resolution.

Going forward, Dr. Mann hopes to explore how the glia coordinate with each other without the benefit of hardwiring like motor neurons; perhaps they communicate with each other, or with the motor neurons. He wants to know if similar parings of hardwired and plastic development exist in vertebrates such as humans. And he hypothesizes that the glia may be able to repopulate if they become damaged due to disease or injury.

Understanding the coordinated development of motor neurons and glia may inform ways to prod stem cells into generating more glia after someone suffers an injury with nerve damage. But basic science comes first.

"If you want to try to harness the potential of stem cells to treat disease or to recover from an injury," Dr. Mann said, "It's important to know what the behavior of these stem cells is in an animal during normal development."

More broadly, understanding how the nervous system grows might shed light on how it operates in adults, the way visiting an auto factory might give you a better understanding of cars than merely peeking under the hood.

"I sum it up this way: development informs function," Dr. Mann added. "Building the system is part of the deal."

More information: "Differing strategies despite shared lineages of motor neurons and glia to achieve robust development of an adult neuropil in Drosophila." *Neuron* (2018).

Provided by Columbia University