Glia guide brain development in worms

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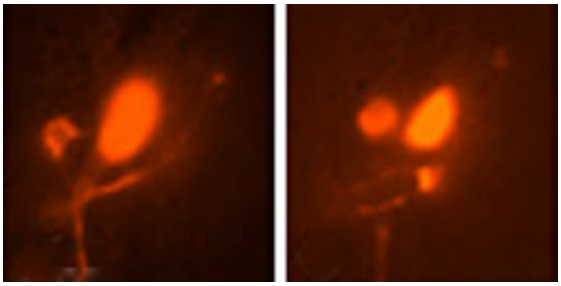

Mind-blowing. In C. elegans, fluorescent images show that when brain cells called glia are zapped — and killed — with a microscopic laser, neurons (red) survive but are highly abnormal (right) compared to normal ones (left).

Again and again, experiments confirmed it. Without glia, neurons die. So scientists who wanted to study in living animals what glia — the most abundant brain cells — do for neurons besides keep them alive were out of luck. But now, a breakthrough.

A system unveiled and described by Rockefeller University scientists shows that in the Caenorhabditis elegans worm, neurons live on despite the absence of glia, a landmark discovery that paves the way for scientists to explore the dialogue between these team players in their natural environment.

“As far as we know, this is the first system where removing glia does not affect neuronal survival,” says Shai Shaham, head of the Laboratory of Developmental Genetics, who made the discovery along with graduate

student Satoshi Yoshimura. “So now we can study glia and the contributions they make in the developing brain in this in vivo context.”

In the 1990s, glia took on a new level of importance as researchers found that most brain tumors and many neurodegenerative diseases, such as Alzheimer’s Disease, may arise from these cells, suggesting the possibility that glia are more than mere support cells that cater to the needs of neurons, that in fact a more dynamic dialogue between glia and neurons takes place. Since then, scientists inferred as much. But now, as similarities between vertebrate and invertebrate glial cells continue to surface, this newly revealed system gives scientists an entry point from which to study this intricate cross-talk in its natural environments — and what happens when it goes wrong.

Yoshimura, Shaham and colleagues have already started. In two separate sets of experiments, when the team either zapped two of the animal’s four brain-ensheathing glia with a microscopic laser or mutated genes required for these glia’s normal development, they found that while neurons didn’t die, they were abnormal — and grossly so. Their dendrites were dramatically shortened and their axons, unable to branch to their expected locations, failed to make the right connections. Moreover, the team showed that neurons located closer to the removed glia have a more abnormal pattern of axon branching compared to those farther away, suggesting that a chemical glia secrete does, in fact, tell axons where to go and, perhaps, how to get there.

The scientists’ most dramatic finding, however, was the effect the loss of these glia, called cephalic sheath cells, had on the organization of C. elegans’s entire brain, a tight bundle of neurons called the nerve ring. Instead of developing one nerve ring, 20 percent of the animals developed a chain of multiple bundles. Likewise, cell bodies that normally appear behind the nerve ring were dispersed throughout the head, a defect that can impair how the brain receives and sends

information.

“If you get rid of these cells, the nervous system doesn’t develop properly,” says Shaham. “It’s the first time this has been shown in a living animal where survival effects did not have to be taken into account.”

While differences in glia between invertebrates and humans exist, the team showed uncanny similarities between the two, particularly expression patterns and intricate transcriptional cascades of key molecules that lead to the development of glia. “Because these glia resemble vertebrate glia, not only molecularly but also morphologically and functionally, this finding and future ones can help us ask the right questions as we work to understand more about brain development and disease in humans,” says Shaham.

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Source: Rockefeller University