Using light to make single cells self-destruct

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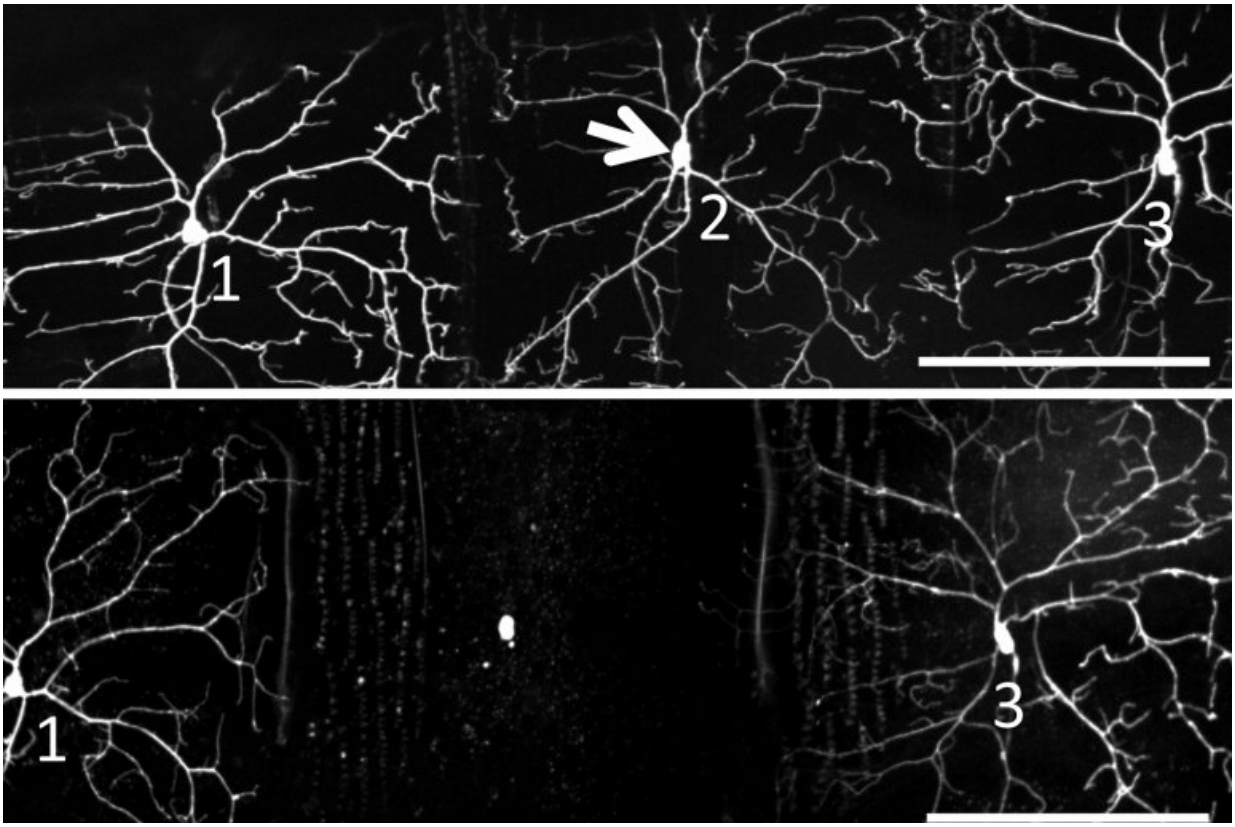

Top: Three genetically modified peripheral neurons in a fruit fly 10 minutes after neuron number two was exposed to a particular wavelength of blue light. Bottom: Twenty-four hours later, the neuron exposed to the light is gone. Credit: Xiaokun Shu

The human brain may be the most complex object in the universe – 86 billion cells of many different types making more than 100 trillion

information-bearing connections. This complexity is a daunting prospect for researchers hoping to unravel how the brain's intricately interwoven networks produce both normal cognition and neurological disease.

As usual when confronted with an overwhelming problem, it's best to start small. In the past 10 years, neuroscientists have developed so-called "optogenetic" tools that let them use beams of light to turn particular cells or networks of cells on and off with both genetic and spatial precision. Using these tools, researchers hope to reverse engineer the principles of brain function.

Now researchers at UC San Francisco have developed a new optogenetic tool that can be used to completely eliminate single cells from brain networks in live animals. The researchers believe the new tool – called miniSOG2 – will enable exquisitely precise experiments to help researchers understand how each cell contributes to the whole.

In an experiment, researchers used peripheral neurons in a live fruit fly that were genetically modified to express miniSOG2 as well as a protein that makes the cells glow. The researchers then exposed the number two neuron to a particular wavelength of blue light that triggers miniSOG2 to generate reactive oxygen specifies, and thus exposing the cell to the toxic molecules and eventually leading the cell to self-destruct. In a second image taken 24 hours later, this neuron has vanished, but the other two neurons that were not exposed to blue light remain intact.

In a second experiment, the researchers set out to show that the new technique could be used to study all kinds of cells – not just neurons. They found that getting rid of certain developing cells in the fly larva led to specific changes in the structure of the wings of the adult fly, demonstrating the utility of the new technique for studing how individual cells contribute to the development of the organism.

"Many diseases are caused by death of certain important cells," said Xiaokun Shu, PhD, an assistant professor of pharmaceutical chemistry in the UCSF School of Pharmacy and senior author of a new study about the new optogenetic tool that was published in *Cell Chemical Biology* on Jan. 5, 2017. "For example, Parkinson's disease is caused by death of a specific group of neurons called dopaminergic neurons in part of the brain called the substantia nigra. We can use our probe to model the loss of particular types of neurons in animals, which should lead to a more precise understanding of these cells' normal functions, as well as new ways to test therapeutics against this kind of disease."

More information: Kalpana Makhijani et al. Precision Optogenetic Tool for Selective Single- and Multiple-Cell Ablation in a Live Animal Model System, *Cell Chemical Biology* (2017). DOI: 10.1016/j.chembiol.2016.12.010

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