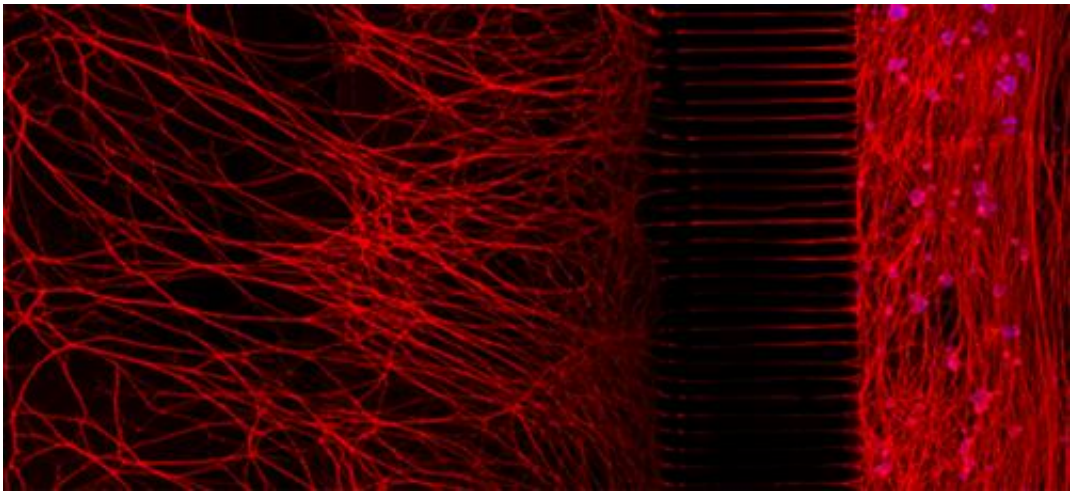
MedicalXpress

The secret lives, and deaths, of neurons

May 23 2013



Neurons can be cultured in one compartment of a microfluidic chamber (right side) and extend their axons through very small grooves into a separate compartment (left side). Using this technology, study co-author Corey L. Cusack and colleagues were able to separate and study the distinct pathways that mediate whole-cell degeneration versus axon-specific degeneration in neurons. Credit: Deshmukh Lab, UNC School of Medicine

As the human body fine-tunes its neurological wiring, nerve cells often must fix a faulty connection by amputating an axon—the "business end" of the neuron that sends electrical impulses to tissues or other neurons. It is a dance with death, however, because the molecular poison the neuron deploys to sever an axon could, if uncontained, kill the entire cell.

Researchers from the University of North Carolina School of Medicine have uncovered some surprising insights about the process of axon

amputation, or "pruning," in a study published May 21 in the journal *Nature Communications*. Axon pruning has mystified scientists curious to know how a neuron can unleash a self -destruct mechanism within its axon, but keep it from spreading to the rest of the cell. The researchers' findings could offer clues about the processes underlying some neurological disorders.

"Aberrant axon pruning is thought to underlie some of the causes for neurodevelopmental disorders, such as schizophrenia and autism," said Mohanish Deshmukh, PhD, professor of cell biology and physiology at UNC and the study's senior author. "This study sheds light on some of the mechanisms by which neurons are able to regulate axon pruning."

Axon pruning is part of normal development and plays a key role in learning and memory. Another important process, apoptosis—the purposeful death of an entire cell—is also crucial because it allows the body to cull broken or incorrectly placed neurons. But both processes have been linked with disease when improperly regulated.

The research team placed mouse neurons in special devices called microfluidic chambers that allowed the researchers to independently manipulate the environments surrounding the axon and cell body to induce axon pruning or apoptosis.

They found that although the nerve cell uses the same poison—a group of molecules known as Caspases—whether it intends to kill the whole cell or just the axon, it deploys the Caspases in a different way depending on the context.

"People had assumed that the mechanism was the same regardless of whether the context was axon pruning or apoptosis, but we found that it's actually quite distinct," said Deshmukh. "The neuron essentially uses the same components for both cases, but tweaks them in a very elegant way

so the neuron knows whether it needs to undergo apoptosis or axon pruning."

In apoptosis, the neuron deploys the deadly Caspases using an activator known as Apaf-1. In the case of axon pruning, Apaf-1 was simply not involved, despite the presence of Caspases. "This is really going to take the field by surprise," said Deshmukh. "There's very little precedent of Caspases being activated without Apaf-1. We just didn't know they could be activated through a different mechanism."

In addition, the team discovered that neurons employ other molecules as safety brakes to keep the "kill" signal contained to the axon alone. "Having this brake keeps that signal from spreading to the rest of the body," said Deshmukh. "Remarkably, just removing one brake makes the neurons more vulnerable."

Deshmukh said the findings offer a glimpse into how nerve cells reconfigure themselves during development and beyond. Enhancing our understanding of these basic processes could help illuminate what has gone wrong in the case of some neurological disorders.

Provided by University of North Carolina Health Care