Scientists shed light on long-distance signaling in developing neurons

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A longstanding puzzle in neurodevelopment may have yielded up a key secret. A team led by scientists at Weill Cornell Medical College says they have determined how events at the very tips of the developing neuron's long, skinny axon affect gene transcription back in the cell's distant nucleus.

The study also revealed the first-ever evidence of a transcription factor -- proteins that influence gene activity -- working outside the cell's nucleus.

The findings, published in the Feb. 1 issue of *Nature Cell Biology*, could bring neuroscientists a much better understanding of how nerve cells grow and connect during healthy development, and how these processes might go astray in neurological disease.

"We have found a process whereby the growth cone at the developing axon's tip sends key signals back to the cell nucleus to ensure the neuron's survival," explains senior study author Dr. Samie R. Jaffrey, associate professor of pharmacology at Weill Cornell Medical College. "In this way, the human nervous system develops over time, choosing viable neural pathways over neurological 'dead ends.' This process hinges on the type of communication between the growth cone and the nucleus that we now describe."

As Dr. Jaffrey explains, the developing fetus carries many times more neurons than it will retain after birth. These newly formed neurons send

out long branches called axons that seek specific targets -- a toe, for example, or a kidney or an eye. In recent years, scientists discovered that as the axon reaches its target -- which may be many centimeters away from the nucleus -- it senses a signal called nerve growth factor (NGF), which is made by target tissues.

"Most axons never make it to their proper destination and the neurons die off in a preprogrammed way," Dr Jaffrey says. "But the axons that correctly navigate to their destinations detect NGF which 'says' to the neuron 'No, you've made it, you can survive.' In these rarer cases, the neuron lives to become part of the nervous system."

But how does this critical information get passed from the growth cone at the tip of the axon back to the cell's "command center," the nucleus?

"That was the central mystery we sought to clear up in this work," Dr. Jaffrey says.

To do so, his team examined axonal growth cones for messenger RNA (mRNA) -- bits of genetic material that help produce specific proteins. The team used an innovative new technique developed by study lead author Dr. Llewellyn J. Cox, a postdoctoral researcher in Dr. Jaffrey's lab. He coaxed axons to grow in such a way that the scientists were able to sample mRNA in the growth cones alone.

"By doing so, we were able to build a library of mRNA found in those growth cones," Dr. Cox said.

The experiment yielded one big surprise: a type of mRNA that produces a transcription factor called CREB.

"Prior research elsewhere has shown that CREB is essential to neuronal survival," Dr. Jaffrey says. "But no one had ever thought it might be

active in the axon."

The team next used cutting-edge fluorescent technology to track CREB's activity in the presence of the "survival signal," NGF.

"We watched CREB being produced in the growth cone and then saw it travel back to the nucleus," Dr. Jaffrey says. "This was astounding -- it suggested that the axonally-synthesized protein could have a role in the nucleus, a very long distance away."

It is this axonally produced CREB that appears to be key to switching off the neuron's self-destruct mechanism, he says. "The axonal CREB enters the nucleus, where it induces gene expression that ensures that the developing neuron will survive," Dr. Jaffrey says.

This was confirmed in a later experiment where the team selectively abolished CREB mRNA from the axons but not the rest of the neuron. "When that happened, the neurons died, even in the presence of NGF," Dr. Jaffrey says. "This proves that axonal CREB, not CREB in the nucleus, is the key player here."

The findings may have big implications for neuroscience going forward. First of all, they shed important new light on how the complex system of interconnected neurons develops over time, and how aberrations in this axon-to-nucleus relationship might impair that development.

"We are also wondering if the type of phenomenon we have observed might occur at other points in development, such as when axons navigate through tissues to find their targets or when axons arrive at targets and create synapses -- the electrochemical bridges between neurons, and target cells," Dr. Jaffrey says. "This newly discovered property of the axon -- its ability to produce its own functional transcription factors -- might allow axons to communicate with the nucleus throughout

neurodevelopment."

And because runaway neuronal death is a hallmark of Alzheimer's disease, spinal cord injury and other neurological injuries or illness, insights into mechanisms controlling neuronal survival are bound to be useful for medical research, the scientists say.

"We believe other mRNAs, and other transcription factors, may play key roles as well," Dr. Jaffrey says. "This exciting work marks a big step forward in our understanding of neurodevelopment, as well as neurological health and disease."

Source: New York- Presbyterian Hospital