Study outlines an activity-regulated genetic program underlying the formation of synapses during development

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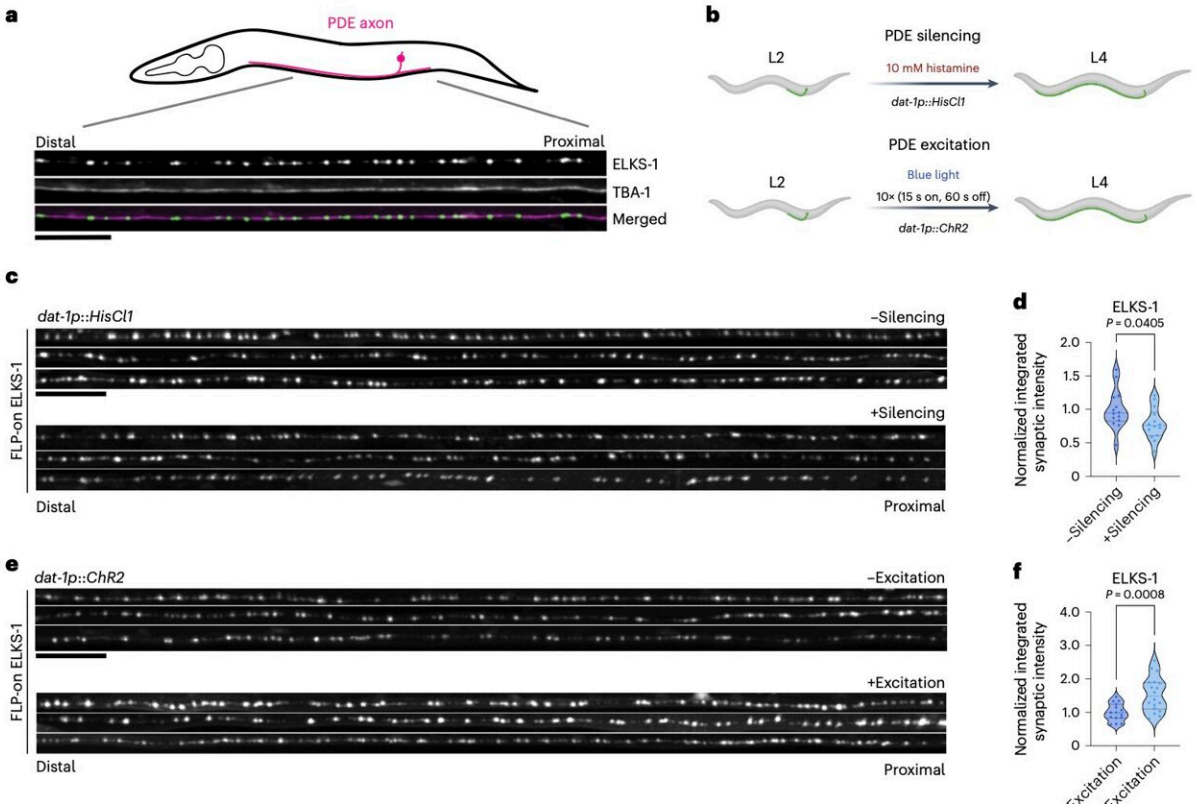

Neuronal activity modulates synapse formation in the developing PDE axon. a, Schematic representation and line scan of the PDE axon and its synapses labeled using a combinatorial approach. Endogenous FLP-on (FRT) GFP::ELKS-1 labels active zones and endogenous FLP-on (FRT3) mScarlet::TBA-1 labels microtubules (for axon morphology) when combined with a transgene expressing a dopaminergic-specific flippase (dat-1p::FLP). b, Top: schematic representation

of PDE-silencing experiments. Transgenic animals expressing dat-1p::HisCl1 were placed on media containing histamine at the L2 stage and imaged at the L4 stage. Bottom: schematic representation of PDE-excitation experiments. Transgenic animals expressing dat-1p::ChR2 were subjected to blue light at the L2 or L4 stage and imaged either 2 h or 48 h post-treatment. This schematic was created with BioRender.com. c, Line scans of ELKS-1 in the PDE axon of animals carrying wyEx8629(dat-1p::HisCl), treated with 0 mM or 10 mM histamine. d, Quantification of ELKS-1 in PDE of animals shown in c (n = 14 for both conditions). e, Line scans of ELKS-1 in the PDE axon of animals carrying wyEx10629(dat-1p::ChR2), treated with or without blue light. f, Quantification of ELKS-1 of animals shown in e (n = 19 for both conditions). Credit: *Nature Neuroscience* (2024). DOI: 10.1038/s41593-024-01728-x

Synapses are junctions via which neurons communicate with each other or with other types of cells. Synapses are formed throughout the course of a person's life, yet their strength and numbers change over time, a phenomenon known as synaptic plasticity.

While past neuroscience studies have shed much light on the composition and function of synapses, the genetic mechanisms that orchestrate their formation remain poorly understood. Experimental findings suggest that the activity of neurons plays a key role in the formation of synapses, yet the interaction between this activity and genetic mechanisms remains widely unexplored.

Researchers at Stanford University, Stony Brook University and other institutes in the U.S. recently carried out a study aimed at filling this gap in the literature, by examining dopaminergic neurons from the multi-cellular organism Caenorhabditis elegans. Their paper, published in *Nature Neuroscience*, unveils a robust genetic program that could underlie the formation of synapses via neuronal activity.

"Although the molecular composition and architecture of synapses have been widely explored, much less is known about what genetic programs directly activate synaptic gene expression and how they are modulated," wrote Callista Yee, Yutong Xiao and their colleagues in their paper. "Using Caenorhabditis elegans dopaminergic neurons, we reveal that EGL-43/MECOM and FOS-1/FOS control an activity-dependent synaptogenesis program."

Yee, Xiao and their colleagues proposed the idea that synaptic genes are controlled by two different mechanisms. One of these consists of programs that regulate gene expression patterns during development, while the other is dependent on neuronal activity.

Their recent study was aimed at better understanding how these two different mechanisms converge to support the formation of synapses during development. To do this, they carried out experiments on Caenorhabditis elegans, a small roundworm that is often used as a model organism in biological research.

The researchers modulated the activity of dopaminergic neurons in this organism using optogenetic and chemogenetic techniques, to then observe how this impacted the expression of presynaptic proteins. The results they collected suggest that neuronal activity played a key role in the formation of synapses.

Subsequently, the team set out to identify neuronal activity-regulated genetic programs that drive the formation of synapses. This led them to uncover two genes/proteins that control an activity-regulated process through which new synapses are formed, namely EGL-43/MECOM and FOS-1/FOS.

"Loss of either factor severely reduces presynaptic protein expression," wrote the researchers. "Both factors bind directly to promoters of

synaptic genes and act together with CUT homeobox transcription factors to activate transcription. egl-43 and fos-1 mutually promote each other's expression and increasing the binding affinity of FOS-1 to the egl-43 locus results in increased presynaptic protein expression and synaptic function. EGL-43 regulates the expression of multiple transcription factors, including activity-regulated factors and developmental factors that define multiple aspects of dopaminergic identity."

The recent work by this research team demonstrates a mechanism through which neuronal activity modulates genetic programs that control synapse formation in Caenorhabditis elegans. While this mechanism has so far only been observed in dopaminergic neurons, the team believes that similar ones also exist in different types of neurons.

In their next studies, they plan to study how the genetic program they uncovered is regulated over time. In addition, they could explore how this program interacts with other molecular processes to support the expression of synaptic genes.

More information: Callista Yee et al, An activity-regulated transcriptional program directly drives synaptogenesis, *Nature Neuroscience* (2024). DOI: 10.1038/s41593-024-01728-x