

# Cellular and Molecular Mechanisms of Axon Growth and Regeneration

December 14

Tuesday, 12:30pm

Online Webinar

For Researchers



**Speaker:**

**Andrea Tedeschi, Ph.D.**

*Assistant Professor Department of Neuroscience*

*Chronic Brain Injury Discovery Theme*

*The Ohio State University*

*Columbus, OH*

**Host: Jian Zhong, Ph.D.**

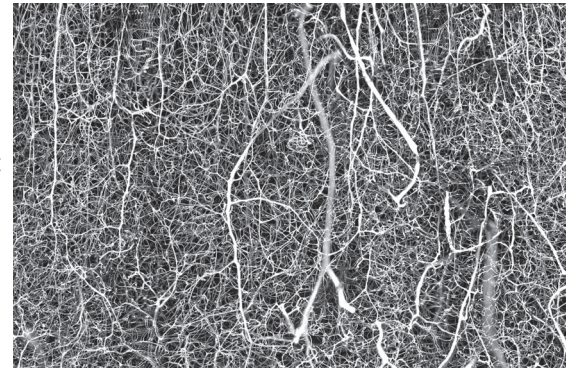
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## Abstract

During later stages of development, neurons experience a drastic decline in axon growth capacity as axons approach their target field. This allows a motile growth cone to differentiate into a pre-synaptic terminal specialized for neurotransmitter release. We questioned whether the transition from a growing to a transmitting phase may represent one of the first key steps in the gradual loss of axon growth and regeneration ability. By using whole transcriptome sequencing and bioinformatic analysis followed by gain- and loss-of-function experiments, we discovered that *Cacna2d2*, the gene encoding the Alpha2delta2 subunit of voltage-gated calcium channels, functions as a developmental switch that limits axon growth and regeneration. *Cacna2d2* gene deletion or silencing promoted axon growth in vitro. In vivo, Alpha2delta2 pharmacological blockade through systemic gabapentinoids administration promoted robust regeneration of sensory dorsal column axons after spinal cord injury (SCI) in adult mice. Gabapentinoids are clinically approved drugs already used to treat various neurological disorders such as neuropathic pain. More recently, we found that Alpha2delta2 negatively regulates axon growth and regeneration of corticospinal neurons, the cells that originate the corticospinal tract. Increased Alpha2delta2 expression in corticospinal neurons contributed to loss of corticospinal regrowth ability during postnatal development and after SCI. In contrast, Alpha2delta2 pharmacological blockade through gabapentinoids administration promoted corticospinal structural plasticity and regeneration in adulthood. Using an optogenetic strategy combined with in vivo electrophysiological recording, we demonstrated that regenerating corticospinal axons functionally integrate into spinal circuits. Mice administered gabapentinoids recovered upper extremity function after cervical SCI. Importantly, such recovery relies on reorganization of the corticospinal pathway, as chemogenetic silencing of injured corticospinal neurons transiently abrogated recovery. We uncovered new evidence that the same treatment strategy effectively promotes structural plasticity of corticospinal neurons and neurological recovery after ischemic cortical infarction in adult mice. Together, these exciting results set up an opportunity to re-purpose gabapentinoids as a novel treatment strategy to repair the injured CNS.



1. Kiyoshi CM, Tedeschi A. Axon growth and synaptic function: A balancing act for axonal regeneration and neuronal circuit formation in CNS trauma and disease. *Dev Neurobiol* doi: 10.1002/dneu.22780.
2. Sun W, Larson MJE, Kiyoshi CM, Annett AJ, Stalker WA, Peng J, Tedeschi A. Gabapentinoid treatment promotes corticospinal plasticity and regeneration following murine spinal cord injury. *The Journal of Clinical Investigation* doi: 10.1172/JCI1130391
3. Tedeschi A, Dupraz S, Laskowski CJ, Xue J, Ulas T, Beyer M, Schultze JL, and Bradke F (2016) The calcium channel subunit Alpha2delta2 suppresses axon regeneration in the adult CNS. *Neuron* 19;92(2):419-434. Cover Article. Faculty 1000 recommended

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