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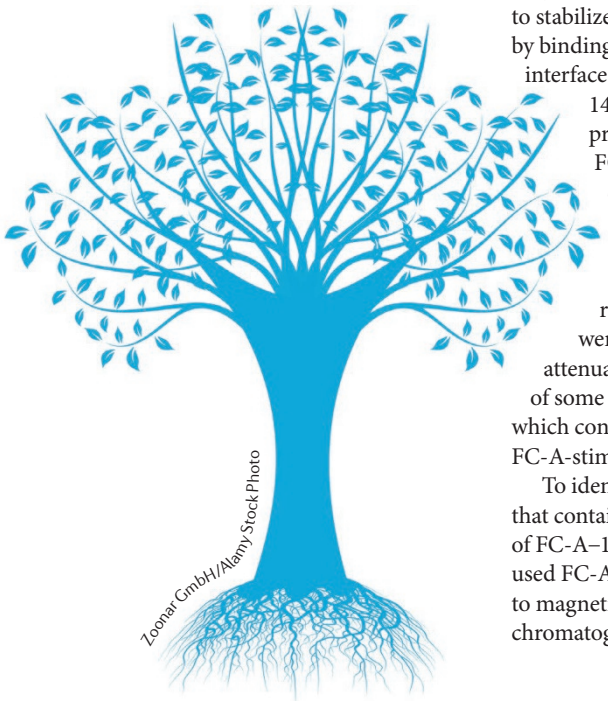
REGENERATIVE MEDICINE

Targeting adaptor protein interactions for nerve regrowth

CNS neurons show limited capacity for spontaneous repair after injury, which hampers functional recovery in conditions such as stroke and traumatic brain injury. Now, a study in *Neuron* has shown that a small molecule, fusicoccin A (FC-A), promotes axon growth after injury in mice by modulating adaptor protein–protein interactions, suggesting a new therapeutic approach.

Kaplan *et al.* focused on the 14-3-3 family of cytosolic adaptor proteins, which bind to various client proteins and thereby modulate cell signalling, including pathways involved in neurodevelopment and axon guidance. Treatment of embryonic day 18 rat cortical neurons with BV02, an inhibitor of 14-3-3 protein–protein interactions, impaired neurite outgrowth. Interestingly, the authors noted that phosphorylation of 14-3-3, which blocks dimerization and binding to client proteins, was upregulated from postnatal week 2 in mice, which could account in part for the decline in the intrinsic capacity of neurons to grow.



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Next, the authors studied the neuronal effects of FC-A, which is a fusicoccane made by the fungus *Diaporthe amygdali*. FC-A is known to stabilize 14-3-3–client complexes by binding to a pocket created by the interface of the binding groove of 14-3-3 and the docked client protein. Treatment with FC-A stimulated dose-dependent neurite outgrowth in rodent cortical neurons and human primary fetal neurons. These neuronal effects were abolished by BV02 and attenuated by RNA knockdown of some 14-3-3 family members, which confirms a role for 14-3-3 in FC-A-stimulated nerve growth.

To identify specific client proteins that contain potential binding motifs of FC-A–14-3-3, the researchers used FC-A chemically coupled to magnetic beads for affinity chromatography, followed by mass spectrometry. The most promising candidate from this analysis was general control of amino-acid synthesis 1-like protein 1 (GCN1), which is a regulator of translation in response to cell stress. *In vitro* studies in cortical neurons indicated that stabilization by FC-A enhanced 14-3-3-mediated sequestration of GCN1 and increased proteasomal GCN1 degradation. RNA knockdown confirmed that loss of GCN1 function contributes to FC-A-induced neurite outgrowth.

Importantly, in mice with dorsal hemisection spinal cord injury, immediate application of FC-A to the injury site significantly reduced axonal die-back compared with control mice. Moreover, in the optic nerve crush model, two intravitreal injections of FC-A (at the time of injury and at day 7) caused significant axon regeneration up to 500 μm from the lesion site compared with control mice. Western blot analysis showed that GCN1 expression was significantly downregulated following FC-A injection.

Together, these findings highlight a new small-molecule approach to harness the potential of adaptor protein interactions and promote nerve regeneration after injury.

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ORIGINAL ARTICLE Kaplan, A. *et al.* Small-molecule stabilization of 14-3-3 protein-protein interactions stimulates axon regeneration. *Neuron* **93**, 1082–1093.e5 (2017)