Modular and Distinct Plexin-A4/FARP2/Rac1 Signaling Controls Dendrite Morphogenesis

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Abstract

Diverse neuronal populations with distinct cellular morphologies coordinate the complex function of the nervous system. Establishment of distinct neuronal morphologies critically depends on signaling pathways that control axonal and dendritic development. The Sema3A-Nrp1/PlxnA4 signaling pathway promotes cortical neuron basal dendrite arborization but also repels axons. However, the downstream signaling components underlying these disparate functions of Sema3A signaling are unclear. Using the novel *PlxnA4*$^{KRK\text{-}AAA}$ knock-in male and female mice, generated by CRISPR/cas9, we show here that the KRK motif in the PlxnA4 cytoplasmic domain is required for Sema3A-mediated cortical neuron dendritic elaboration but is dispensable for inhibitory axon guidance. The RhoGEF FARP2, which binds to the KRK motif, shows identical functional specificity as the KRK motif in the PlxnA4 receptor. We find that Sema3A activates the small GTPase Rac1, and that Rac1 activity is required for dendrite elaboration but not axon growth cone collapse. This work identifies a novel Sema3A-Nrp1/PlxnA4/FARP2/Rac1 signaling pathway that specifically controls dendritic morphogenesis but is dispensable for repulsive guidance events. Overall, our results demonstrate that the divergent signaling output from multifunctional receptor complexes critically depends on distinct signaling motifs, highlighting the modular nature of guidance cue receptors and its potential to regulate diverse cellular responses.

SIGNIFICANCE STATEMENT The proper formation of axonal and dendritic morphologies is crucial for the precise wiring of the nervous system that ultimately leads to the generation of complex functions in an organism. The Semaphorin3A-Neuropilin1/Plexin-A4 signaling pathway has been shown to have multiple key roles in neurodevelopment, from axon repulsion to dendrite elaboration. This study demonstrates that three specific amino acids, the KRK motif within the Plexin-A4 receptor cytoplasmic domain, are required to coordinate the downstream signaling molecules to promote Sema3A-mediated cortical neuron dendritic elaboration, but not inhibitory axon guidance. Our results unravel a novel Semaphorin3A-Plexin-A4 downstream signaling pathway and shed light on how the disparate functions of axon guidance and dendritic morphogenesis are accomplished by the same extracellular ligand *in vivo*.