alpha2-Chimaerin is an essential EphA4 effector in the assembly of neuronal locomotor circuits

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The assembly of neuronal networks during development requires tightly controlled cell-cell interactions. Multiple cell surface receptors that control axon guidance and synapse maturation have been identified. However, the signaling mechanisms downstream of these receptors have remained unclear. Receptor signals might be transmitted through dedicated signaling lines defined by specific effector proteins. Alternatively, a single cell surface receptor might couple to multiple effectors with overlapping functions. We identified the neuronal RacGAP alpha2-chimaerin as an effector for the receptor tyrosine kinase EphA4. alpha2-Chimaerin interacts with activated EphA4 and is required for ephrin-induced growth cone collapse in cortical neurons. alpha2-Chimaerin mutant mice exhibit a rabbit-like hopping gait with synchronous hindlimb movements that phenocopies mice lacking EphA4 kinase activity. Anatomical and functional analyses of corticospinal and spinal interneuron projections reveal that loss of alpha2-chimaerin results in impairment of EphA4 signaling in vivo. These findings identify alpha2-chimaerin as an indispensable effector for EphA4 in cortical and spinal motor circuits.
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