Report

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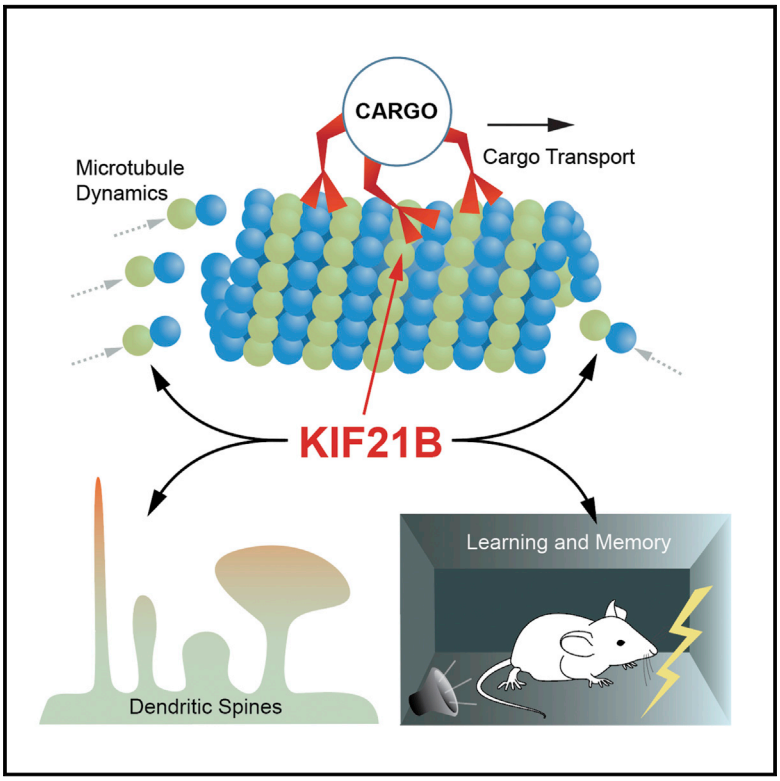
The Kinesin KIF21B Regulates Microtubule Dynamics and Is Essential for Neuronal Morphology, Synapse Function, and Learning and Memory

Graphical Abstract



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In Brief

Muhia et al. investigate the physiological functions of the kinesin-4 member KIF21B. They show that KIF21B is a processive motor protein regulating microtubule dynamics. They also demonstrate that KIF21B depletion alters neuronal morphology by decreasing dendritic branching and spine number. In addition, *Kif21b* knockout mice are impaired in learning and memory.

Highlights

- KIF21B is a processive kinesin that regulates microtubule dynamics
- KIF21B depletion alters neuronal dendritic tree branching and spine formation
- *Kif21b* knockout mice exhibit learning and memory deficits

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The Kinesin KIF21B Regulates Microtubule Dynamics and Is Essential for Neuronal Morphology, Synapse Function, and Learning and Memory

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SUMMARY

The kinesin KIF21B is implicated in several human neurological disorders, including delayed cognitive development, yet it remains unclear how KIF21B dysfunction may contribute to pathology. One limitation is that relatively little is known about KIF21B-mediated physiological functions. Here, we generated *Kif21b* knockout mice and used cellular assays to investigate the relevance of KIF21B in neuronal and in vivo function. We show that KIF21B is a processive motor protein and identify an additional role for KIF21B in regulating microtubule dynamics. In neurons lacking KIF21B, microtubules grow more slowly and persistently, leading to tighter packing in dendrites. KIF21B-deficient neurons exhibit decreased dendritic arbor complexity and reduced spine density, which correlate with deficits in synaptic transmission. Consistent with these observations, *Kif21b*-null mice exhibit behavioral changes involving learning and memory deficits. Our study provides insight into the cellular function of KIF21B and the basis for cognitive decline resulting from KIF21B dysregulation.

INTRODUCTION

Kinesin superfamily proteins (KIFs) share a common ATP-binding "motor" domain, fused to divergent tail domains that specify intracellular localization and function. Many kinesins utilize chemical energy derived from ATP hydrolysis to propel directional transport of various cargoes along the microtubule (MT) cytoskeleton (Hirokawa et al., 2009). Kinesins have also been shown to regulate MT dynamics. For example, kinesin-4 and -8 family members adopt dual roles as cargo translocators and regulators of MT dynamics (Drummond, 2011; Walczak et al., 2013). These findings highlight a kinesin-MT interplay in mediating intracellular cargo transport (Hirokawa et al., 2009).

MTs are composed of α- and β-tubulin and bind specific protein complexes at their plus and minus ends (Jiang and Akhmanova, 2011; Yau et al., 2014). The plus ends of cellular MTs can dynamically remodel through stochastic length fluctuations. These events, termed as dynamic instability, comprise periods of persistent MT growth interrupted by occasional rapid shrinkage: switching between these states of growth and shortening is termed catastrophe and rescue (Gardner et al., 2013).

Studies from several mouse mutant lines have unraveled essential roles for kinesins and other MT binding proteins in neuronal development, survival, and higher brain function. Further, abnormalities in kinesin function and the MT cytoskeleton are reflected in a wide spectrum of human diseases, including neurodegeneration and cognitive disability (Franker and Hoogenraad, 2013; Hirokawa and Tanaka, 2015).

Kinesin-4 family members KIF21A and KIF21B were previously described to share little identity with other KIFs beyond the conserved motor domain, suggesting that they may play unique roles in vivo (Marszalek et al., 1999). KIF21A is expressed ubiquitously, and displays robust processive activity in vitro (Cheng et al., 2014). KIF21A binds to KANK1 (*ANKRD15*, KN motif, and ankyrin repeat domains 1) and co-clusters with liprins and components of the MT attachment complex at the cellular cortex. It inhibits MT growth and engages in organizing MT arrays at the cell edge (van der Vaart et al., 2013).

By contrast, KIF21B protein expression is restricted to the brain, spleen, and testes (Marszalek et al., 1999). Within neurons, KIF21B is present in axons and dendrites, with particular enrichment in growth cones of developing neurons (Huang and Banker, 2012; Marszalek et al., 1999). KIF21B binds E3 ubiquitin ligase TRIM3 (tripartite motif protein 3) to regulate $GABA_A$ receptor surface delivery (Labonté et al., 2013, 2014). Micro-duplications in the chromosomal region 1q32.1, including the *Kif21b* gene, have been described in individuals with delayed motor and