# This Week in The Journal

## Roles for Rab8a and Tuba in Neuronal Polarity

Pamela J. Urrutia, Felipe Bodaleo, Daniel A. Bórquez, Yuta Homma, Victoria Rozes-Salvador, et al.

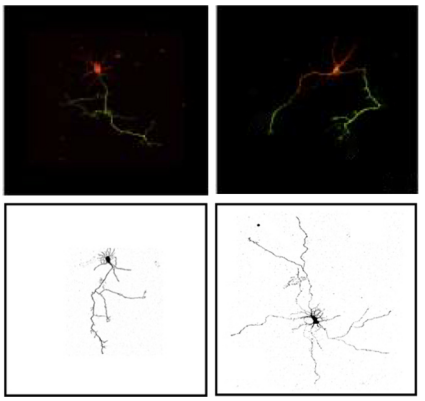
(see pages 1636–1649)

Most cells have distinct subdomains with specialized functions. Epithelial cells, for example, have an apical domain, which typically faces a lumen, and a basolateral domain that faces other cells. Neurons exhibit an extreme form of such polarity, having a single axon specialized to transmit signals and a soma and dendrites specialized to integrate input. Notably, the same molecular processes drive the acquisition of polarity across cell types. These processes include modification of the cytoskeleton and accumulation of polarity-inducing proteins in specific domains.

The small Rho-family GTPase Cdc42, which activates a protein complex that modifies the cytoskeleton, is a key protein in the establishment of polarity in both neurons and epithelial cells. In epithelial cells, Cdc42 accumulation in the apical domain depends on vesicular transport regulated by the GTPase Rab8, as well as on anchoring and activation by the guanine nucleotide exchange factor (GEF) Tuba (Bryant et al., 2010, Nat Cell Biol 12:1035). Urrutia et al. now show that Rab8a and Tuba also contribute to axon specification, the first step in neuronal polarization.

In cultured hippocampal neurons, Tuba levels increased during axon specification, and Tuba became enriched in the nascent axon. Knocking down Tuba or mutating its GEF domain reduced axon formation and growth. A similar phenotype was induced by overexpressing a dominant-negative form of Rab8a. In contrast, overexpressing either full-length Tuba or constitutively active Rab8a increased the number of neurons bearing multiple axons. Notably, constitutively active Rab8a also led to an enrichment of Tuba in the distal axon and increased Cdc42 activity throughout neurons. Knocking out Tuba attenuated Cdc42 activation and suppressed the formation of multiple axons in neurons expressing constitutively active Rab8a. Importantly, knocking down Tuba or expressing dominant-negative Rab8a also suppressed polarization and reduced migration of newborn cortical neurons *in vivo*.

These data suggest that Rab8a contributes to neuronal polarization by promoting transport of Tuba to the distal axon, where it activates Cdc42. Downstream rearrangement of actin in the growth cone is expected to promote neurite elongation, which may lead to additional transport and accumulation of Tuba and Cdc42. Such positive feedback between neurite growth and directed vesicle transport is thought to be essential for neuronal polarization.



Compared with control neurons (left) those overexpressing full-length Tuba (top right) or constitutively active Rab8a (bottom right) are more likely to have multiple axons (green in top panels). See Urrutia et al. for details.

## Brain Areas Linked to Consciousness of Surroundings

Annalotta Scheinin, Oskari Kantonen, Michael Alkire, Jaakko Långsjö, Roosa E. Kallionpää, et al.

(see pages 1769–1778)

Identifying the neural circuits responsible for generating consciousness is a fundamental objective in neuroscience. Studying the neural bases of consciousness is challenging, however, because it requires comparing brain activity in conscious and unconscious states, and demonstrating lack of consciousness is difficult. Failure to respond to probes is insufficient to indicate unconsciousness, because subjects may be conscious of a stimulus but unable to generate a response or may be in a so-called disconnected state, conscious of their own thoughts, yet unresponsive to external stimuli. Moreover, conditions in which people are unconscious, such as sleep or anesthesia, alter brain functions beyond those that are strictly necessary for consciousness.

To minimize these confounds, Scheinin et al. imaged brain activity in the same individuals under various levels of anesthesia and during multiple stages of sleep. Importantly, they not only assessed responsiveness before each scan, but also attempted to arouse individuals immediately afterward to ask whether they had any conscious experience during the scan. Notably, in >70% cases where unresponsive subjects were aroused, they reported having had some kind of experience, either related to the surroundings or disconnected from the world (e.g., dreams or memories). Comparing brain activity patterns in the same subjects across connected and disconnected states at similar anesthesia doses, the authors found that activity in the thalamus, cingulate cortex, and angular gyri was consistently associated with connected consciousness. In contrast, activity in frontoparietal cortex was suppressed under anesthesia regardless of conscious state. Activity in other cortical areas was inconsistent. Importantly, similar effects were seen with two different types of anesthesia, and the same areas were associated with consciousness during natural sleep.

These results suggest that activity in the thalamus, cingulate cortex, and angular gyri underlies connected conscious states, whereas reduction in frontoparietal activity, which is routinely linked to loss of consciousness, is likely an independent effect of anesthesia. Activity in other cortical areas probably contributes to the content of consciousness, that is, what is being experienced, but does not appear to be essential for creating a conscious state. Future work should compare brain activity when people report no conscious experience to activity when subjects report consciousness despite unresponsiveness.

*This Week in The Journal was written by* Teresa Esch, Ph.D.
https://doi.org/10.1523/JNEUROSCI.twij.41.8.2021