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# Asymmetric Golgi Repositioning: A Prerequisite for Appropriate Dendrite Formation in Adult-Born Neurons

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Review of Rao et al.

Adult-born granule cells (GCs) are continuously generated in the subgranular zone of the dentate gyrus and become integrated into the dentate circuitry. These adult-born neurons are thought to be important for hippocampal functions such as spatial learning (Clelland et al. 2009). Within 2 weeks of their birth, adult-born neurons develop a granule cell-like morphology with a primary dendrite directed toward the molecular layer. Over the next 2 weeks, the primary dendrite of the adult-born neurons form branches (Espósito et al. 2005; Zhao et al. 2006; Kelsch et al. 2008). After passing through several morphological changes, the adult-born neurons become functionally integrated into the granular cell layer within 4 weeks after their birth. The later stages of morphological development of adult-born dentate GCs (DGCs), including dendritic branching, pruning, synapse formation, and spine morphogenesis have been extensively studied. Much less is known about changes occurring during the first 2 weeks after neurons are generated. Rao et al. (2018) addressed this question in a recent article in *The Journal of Neuroscience*.

To document the time course of neurite formation and elimination by adult-born GCs, Rao et al. (2018) expressed GFP in newborn cells in the subgranular zone of 4- to 6-week-old mice and analyzed their morphology at 7, 10, and 14 d postinjection (dpi) of viral vectors. Most adult-born GCs formed multiple neurites between 7 and 10 dpi (Rao et al., 2018, their Fig. 1*B*,*C*), but by 14 dpi only the primary dendrite and one or two hilar neurites remained.

The growth of neurites requires new membrane and proteins as well as cytoskeletal dynamics. Membrane and associated proteins are trafficked to growing neurites from the Golgi apparatus, which is present not only in the soma, but also in "outposts" in dendrites. These outposts are thought be a source for acentrosomal microtubule nucleation (Ye et al., 2007). Previous studies using cultured pyramidal neurons have shown that the Golgi apparatus is polarized along the longest dendrite, and this helps to guide the movement of post-Golgi secretory cargo into dendrites. The disruption of Golgi outposts causes dendrites to shrink and simplify (Horton and Ehlers, 2003; Horton et al., 2005). Furthermore, the overexpression of the Golgi cisternae stacking protein GRASP65 induces Golgi vesiculation and dispersal into multiple dendrites, which in turn causes neurons to produce symmetric dendritic arbors, lacking a single principal dendrite (Horton and Ehlers, 2003). Therefore, Rao et al. (2018) assessed the contribution of the Golgi apparatus to changes in dendritic morphology and neuritic rearrangement in newborn DGCs.

The authors first analyzed the distribution of Golgi apparatus in newborn neurons by immunostaining GFP-labeled cells for GRASP65 and found that the Golgi apparatus preferentially localized at the base of the primary neurite at 5 and 7 dpi. By 14 dpi, however, the Golgi apparatus had completely translocated into the shaft of the primary dendrite (Rao et al., 2018, their Fig. 1*D–F*). These results are consistent with the recent finding that Golgi outposts are located along the dendrites of *Drosophila* DA neurons during dendritic morphogenesis (Ori-McKenney et al., 2012). Together, the results suggest that the repositioning of Golgi apparatus and Golgi outposts is required for the establishment of the primary dendrite.

Rao et al. (2018) next examined factors regulating the repositioning of the Golgi apparatus in polarized DGCs. They first analyzed single-cell transcriptomes of adult-born granule cells (Gao et al., 2017) to detect Golgi-associated genes (for review, see Yadav and Linstedt, 2011). Interestingly, Rao et al. (2018) found robust

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expression of the following two main regulators of Golgi repositioning: the STE20 family serine/threonine kinase (STK25) and the adaptor protein STE20-related pseudokinase (STRAD; Rao et al., 2018, their Fig. 2*A*). Previous studies in cultured mouse hippocampal neurons have demonstrated that the STK25–STRAD pathway regulates the outgrowth of dendrites by promoting Golgi movement into dendrites (Preisinger et al., 2004; Matsuki et al., 2010, 2013). To assess the role of this signaling pathway in the development of adult-born granule cells, Rao et al. (2018) knocked down STK25 expression in the dentate gyrus of 4- to 6-month-old mice. STK25 knockdown resulted in mispositioning of the Golgi apparatus in adult-born neurons (Rao et al., 2018, their Fig. 2*C*). Moreover, after STK25 knockdown, nearly 82% of adult-born granule cells had more than two neurites, compared with only 25% in control cells (Rao et al., 2018, their Fig. 3*B*,*F*). Knocking down the STK25 adaptor protein STRAD resulted in a similar dispersion of the Golgi apparatus and dendritic abnormality (Rao et al., 2018, their Fig. 4*B*,*C*,*F*). These data support the hypothesis that Golgi repositioning is required for the elimination of supernumerary neurites during maturation of adult-born neurons.

STK25 and STRAD regulate Golgi apparatus localization through phosphorylation of the Golgi matrix protein GM130. Therefore, Rao et al. (2018) asked whether the STK25–STRAD–GM130 association caused asymmetric Golgi repositioning in adult-born DGCs. They first observed that STK25 colocalized with STRAD at the base of the apical dendrite in adult-born neurons. Furthermore, STK25 was found to colocalize with the Golgi marker GRASP62 (Rao et al., 2018, their Fig. 5*C*,*D*). Interestingly, immunoblotting of HEK-293 whole-cell lysates coexpressing STK25-dTom or STRAD-GFP and GM130-FLAG showed almost a twofold greater expression of GM130-FLAG than control cells expressing only GM130-FLAG. These data suggest that the association of GM130 with either STRAD or STK25 leads to a significant stabilization of the GM130 protein (Rao et al., 2018 their Fig. 5*B*). Indeed, the expression of a mutated version of STRAD (Δ180) prevented the STRK25–GM130 complex formation, disrupted Golgi positioning, and resulted in impaired neurite elimination in adult-born neurons (Rao et al., 2018, their Figs. 5*F*, 6*E*,*F*). Together, the findings Rao et al. (2018) indicate that the association of STK25 and STRAD contributes to the somatic Golgi repositioning in adult-born neurons by promoting the recruitment and stabilization of GM130.

Rao et al. (2018) conclude that repositioning of the Golgi apparatus leads to the elimination of secondary neurites. Moreover, the Golgi-associated protein STK25 is required to reposition the Golgi apparatus via association with the GM130 in the presence of STRAD as a cofactor. A previous study using HeLa cells (Preisinger et al., 2004) showed that a mutated version of STK25 with impaired binding to GM130 resulted in dispersion of the Golgi apparatus. However, the exact binding mechanism was not clear. The findings of the study by Rao et al. (2018) suggest that STRAD acts as a key protein to form the STK25–GM130 complex, resulting in the repositioning of the Golgi apparatus toward dendrites.

In contrast to the results of the study by Rao et al. (2018), a previous study showed that STRAD promoted axon initiation in cultured hippocampal neurons in association with Liver Kinase B1 (LKB1), an activator of STRAD (Shelly et al., 2007), and that the inhibition of LKB1 caused the formation of excessive neurites in cultured hippocampal neurons, indicating a role of STRAD in both axon and dendrite development. One possible reason for observing the extensive dendrites after the deletion of LKB1 (Shelly et al., 2007) is that freely available STRAD might bind to STK25 and form the STK25–GM130 complex. It is possible that the stabilization of GM130 and STK25 with STRAD leads to dendritic morphogenesis through Golgi repositioning (Rao et al., 2018), whereas formation of the STRAD–LKB1 complex leads to axon formation in neuronal development (Shelly et al., 2007).

These results also align with those of another study showing that a knockdown of *STK25* causes symmetric Golgi deployment in all neurites of the cultured hippocampal neuron. Interestingly, this effect was rescued by the overexpression of Reelin, a neuronal migratory signaling molecule, which decreases Golgi dispersion, axon specification, and dendrite growth in hippocampal and neocortical pyramidal neurons (Matsuki et al., 2010). Overall, these findings suggest that STK25 induces dendritic morphogenesis in adult-born DGCs through a well programmed asymmetric Golgi repositioning.

In humans, homozygous recessive *STRAD* mutations cause polyhydramnios, megalencephaly, and symptomatic epilepsy (PMSE), a rare disorder (Orlova et al., 2010; Parker et al., 2013) associated with abnormal brain development and intractable epilepsy. However, little is known about the status of Golgi positioning in PMSE patients. In rat cortical neurons, the application of kainic acid not only induces recurrent seizures, but also causes Golgi fragmentation (Kaneko et al., 2016). Furthermore, rat cortical or hippocampal neurons showed Golgi fragmentation under hyperexcitable conditions, confirming the direct relation between the fidelity of Golgi organization and the pathogenesis of epilepsy (Thayer et al., 2013; Kaneko et al., 2016). Observations from Rao et al. (2018), along with other reports, thus hint at a possible mechanism by which *STRAD* loss of function prevents the stabilization of GM130 and results in Golgi fragmentation, consequently producing epilepsy. Together, these findings indicate that a loss of *STRAD* function in newborn neurons might produce more than one principal dendrite with less complex branches, resulting in their poorer integration into the hippocampal circuit. Further functional studies on new adult-born DGCs with deletion of STRAD might help to identify the underlying causes of abnormal brain development.

Many important questions remain to be addressed. What are the molecular mechanisms enabling the Golgi apparatus to find the primary dendrites? How does the Golgi repositioning trigger the elimination of secondary neurites? Does Golgi repositioning play a role in other polarized cell types in the developing brain, such as dividing radial glial progenitors? Without doubt, future studies will answer the questions raised by these new findings of Rao et al. (2018).

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