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Review

Rab family small GTPases-mediated regulation of intracellular logistics in neural development

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Summary. Rab family small GTPases play essential roles in various cellular events via the regulation of intracellular logistics comprising a large number of membrane traffic pathways. Emerging evidence reveals the physiological roles of Rab proteins in several tissues, including developing brains. Many Rab proteins, such as Rab5, Rab6, Rab7, Rab8, Rab10, Rab11, Rab17 and Rab18, are shown to regulate neurite outgrowth in PC12 cells and/or axon and dendrite formation in primary cultured neurons. Recent studies have also revealed *in vivo* roles of several Rab family small GTPases in brain development and its related neurological disorders. In this review, we introduce the physiological function of Rab family proteins in neural development with particular focus on neurite outgrowth and neuronal migration.

Key words: Brain development, Neurite outgrowth, Neuronal migration, Membrane traffic, Endocytosis, Rab5, Rab6, Rab7, Rab8, Rab10, Rab11, Rab17, Rab18, CdK5, JNK

Introduction

Small GTPases function as regulators for various cellular events by cycling between two nucleotide-states: a GDP-bound inactive form and a GTP-bound active form (Barr and Lambright, 2010; Muller and Goody, 2017). The transition to the active or inactive states is promoted by guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs), respectively. The largest family of small GTPases is a Rab family, which includes around 60 proteins in mammals (Zerial and McBride, 2001; Stenmark, 2009; Pfeffer, 2012). Rab family small GTPases regulate intracellular logistics that comprise various membrane trafficking pathways, such as endocytic trafficking and secretory pathways.

Endocytic trafficking pathways originate from the plasma membrane (Zerial and McBride, 2001; Stenmark, 2009; Kawauchi, 2012; Pfeffer, 2012). Endocytosis can be classified into several types, such as clathrin-mediated, caveolae-mediated and macropinocytosis, but the internalized vesicles from almost all types of endocytosis are basically transported into the early endosomes. Endocytosis, trafficking to the early endosomes and early endosome fusion are regulated by Rab5 and its subfamily members. Early endosomes, which are also known as sorting endosomes, lead to many subcellular compartments, each of which is controlled by different Rab family small GTPases. While Rab4 is involved in a fast recycling pathway from the early endosomes to the plasma membrane, Rab11 regulates a slow recycling pathway via the recycling endosomes. Rab7 regulates the degradation pathway to the late endosomes and lysosomes.

Secretory pathways through the ER, Golgi and *trans*-Golgi network (TGN) are also regulated by Rab family small GTPases, such as Rab3, Rab8, Rab10, Rab13 and Rab27 (Zerial and McBride, 2001; Stenmark, 2009; Pfeffer, 2012; Fukuda, 2013). Mutations in Rab3GAP (which also functions as a Rab18GEF) and Rab27a cause Warburg micro syndrome and type 2

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Griscelli syndrome, respectively. Warburg micro syndrome is an autosomal recessive neurodevelopmental disorder characterized by brain, eye and endocrine abnormalities (Warburg et al., 1993; Aligianis et al., 2005). Griscelli syndrome is an autosomal recessive disorder showing hypopigmentation of the skin and hair caused by defects in melanosome transport of melanocytes and immunodeficiency (Menasche et al., 2000; Fukuda, 2013). Some type 1 Griscelli syndrome patients exhibit severe neurological impairments, although it is unclear whether type 2 Griscelli syndrome patients also show neurological impairments.

In addition, the Rab proteins involved in endocytic pathways, including Rab7 and Rab11, are associated with neurodegenerative diseases (D'Adamo et al., 2014). Mutations in Rab39B are also associated with X-linked mental retardation (Giannandrea et al., 2010). Thus, emerging evidence shows important roles of Rab proteins in brain development and function. In this review, we discuss the roles of Rab family small GTPases in neural development.

Cerebral cortical development and axon and dendrite formation

In the developing mammalian cerebral cortex, neural progenitors are located near the ventricle, the ventricular zone and subventricular zone (Kawauchi and Hoshino, 2008; Heng et al., 2010; Cooper, 2014; Kawauchi, 2015). After the final cell division, immature neurons exhibit multipolar morphology. Subsequently, the multipolar neurons form an axon and undergo the morphological changes into bipolar neurons with an axon and a leading process. The leading process-possessing bipolar neurons, called locomoting neurons, migrate along radial fibers over a long distance. When they approach the pial surface, these migrating neurons change their migration mode from locomotion to terminal translocation and begin dendrite maturation (Fig. 1).

A popular approach to study the molecular mechanisms underlying axon and dendrite formation is using primary cultures of hippocampal and cerebral cortical neurons (Banker and Cowan, 1977; Dotti et al., 1988). Primary cultured hippocampal neurons first extend lamellipodia around the cell body (stage 1), and the lamellipodia are transformed into minor (immature) processes (stage 2). These minor processes exhibit extension and retraction but their total length does not change significantly. About 1.5 days after plating, one of the minor processes begins to elongate quickly and becomes an axon (stage 3). Significant dendritic growth from the remaining immature neurites occurs around 4 days after plating (stage 4). Subsequently, the dendrite maturation is completed at or after 7 days after plating (stage 5). This culture system is frequently applied to many studies examining the mechanisms for neuronal polarity and axon and dendrite formation (Dotti et al., 1988; Arimura and Kaibuchi, 2007).

Involvement of endocytic pathways in neural development

PC12 pheochromocytoma cells exhibit neurite

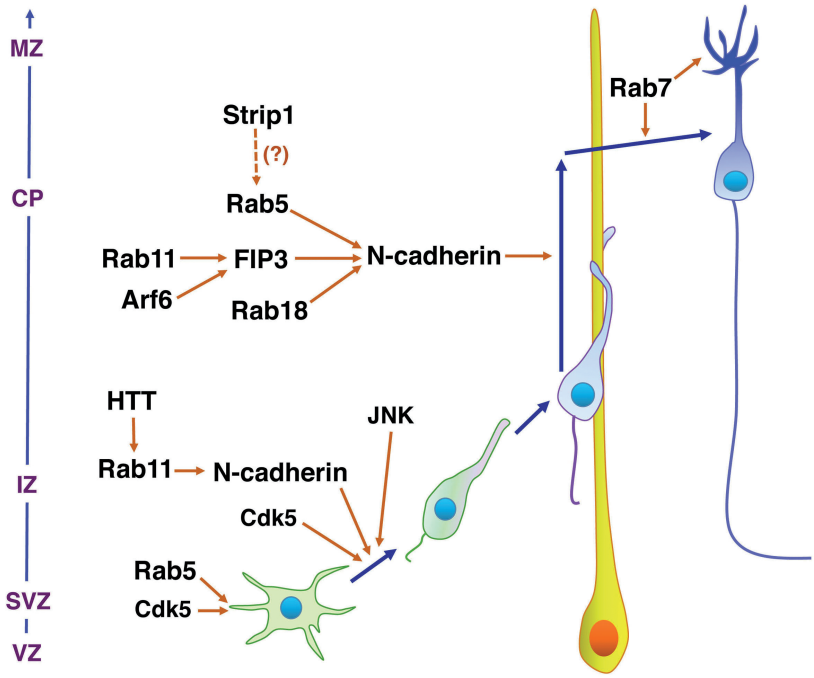

Fig. 1. Roles of Rab GTPases in neuronal migration. Rab5 is required for the multipolar process formation, whereas the HTT-Rab11 pathway controls the multipolar-to-bipolar transition. In addition, Rab5 and Rab11 cooperatively regulate the locomotion mode of neuronal migration. Rab7 controls the final phase of neuronal migration (terminal translocation) and dendrite maturation. See text for detail. MZ: marginal zone, CP: cortical plate, IZ: intermediate zone, SVZ: subventricular zone, VZ: ventricular zone.

outgrowth in response to nerve growth factor (NGF) treatment and are often used as an experimental model for neurite outgrowth. It has been reported that stable (possibly moderate) expression of dominant negative Rab5 (DN-Rab5) promotes NGF-induced neurite outgrowth in PC12 cells (Liu et al., 2007). A constitutive active form of Rab5 (CA-Rab5) and Rabex5, a GEF for Rab5, suppress the neurite extension. On the other hand, in primary cultured mouse hippocampal neurons, knockdown of Rabex-5 or Rab5 reduces both axon and dendrite length, indicating that Rabex-5 and Rab5 are positive regulators for these processes in hippocampal neurons (Mori et al., 2013). Interestingly, Rabex-5 also activates Rab17 and Rab21, in addition to Rab5. The function of endogenous Rab21 remains unclear because its knockdown- and dominant negative-mediated suppression does not affect axon and dendrite length in the hippocampal neurons (Burgo et al., 2009; Mori et al., 2013). Rab17, however, is specifically localized at dendrites and enhances the elongation of dendrites, but not axons (Mori et al., 2013). Rab22, another Rab5 subfamily, is reported to promote neurite outgrowth in PC12 cells (Wang et al., 2011).

In the developing cerebral cortex, axon elongation occurs during the migration of immature neurons. Rab5 has been shown to regulate the neuronal migration *in vivo* (Kawauchi et al., 2010). Rab5 knockdown neurons are unable to extend multipolar processes but normally elongate a leading process. However, leading process-possessing bipolar neurons do not migrate toward the pial surface, indicating that the radial fiber-dependent locomotion mode of neuronal migration is disturbed in the Rab5-knockdown neurons (Fig. 1). Consistently, time-lapse imaging of locomoting neurons in the cortical slice cultures reveals that knockdown of Rab5 impairs neuron-specific morphological changes during the locomotion mode of migration (Nishimura et al., 2014).

Although it is unclear which GEF(s) for Rab5 is a main contributor to the neuronal migration, knockdown of Strip1, a mouse ortholog of *Drosophila* Strip, results in neuronal migration defects (Sakuma et al., 2014). *Drosophila* Strip functions as a molecular linker between Glued, a component of a dynein motor complex, and Sprint, a Rab5GEF, and promotes early endosome clustering. Strip/Strip1 is a component of the STRIPAK complex. Cerebral cavernous malformation 3 (Ccm3), another component of the STRIPAK complex, is reported to regulate neuronal migration in mouse developing cerebral cortex (Louvi et al., 2014).

Unlike mouse cortical neurons, *Drosophila* olfactory projection neurons do not undergo long-distance migration. Strip enhances axon elongation in the *Drosophila* olfactory projection neurons in a Rab5 activity-dependent manner, suggesting that early endosome maturation plays a role in axon elongation *in vivo* (Sakuma et al., 2014). In the mouse developing cerebral cortex, knockdown of Rab5b does not affect the axon length of the upper layer neurons but it rescues a Sema3A-induced axonal growth defect (Wu et al., 2014). In addition, suppression of Rab5b results in defasciculation of corpus callosal axons *in vivo*. These observations suggest that Rab5-dependent endocytic pathways play essential roles in axon and dendrite formation and neuronal migration, but whether it exhibits a positive or negative effect on neurite extension may depend on cell types and/or species.

Roles of recycling endosome-associated Rab proteins

Rab11 is one of the major Rab proteins involved in the regulation of the endocytic recycling pathways via recycling endosomes (Fig. 2). Knockdown of Rab11 decreases the neurite length in PC12 cells (Eva et al., 2010). Rabin8, a GEF for Rab8 and Rab10, is localized at Rab11-positive recycling endosomes in PC12 cells in the absence of NGF. NGF stimulation induces enlargement of an Arf family small GTPase, Arf6-positive recycling endosomes, which become Rabin8-positive. Rabin8 activates Rab8 and Rab10 at the Arf6- and Rab11-positive recycling endosomes, respectively (Homma and Fukuda, 2016). Rab35 is also accumulated at the Arf6-positive endosomes and recruits centaurin-β2 (also known as ACAP2), a GAP for Arf6, which plays an important role in NGF-induced neurite outgrowth (Kobayashi and Fukuda, 2012; Villarroel-Campos et al., 2016). Interestingly, Rabin8 promotes neurite outgrowth in a GEF activity-dependent and independent manner. The GEF activity-independent function of Rabin8 requires its binding to Rab11 (Homma and Fukuda, 2016) (Fig. 2).

Neurite extension and pathfinding largely depend on the growth cone dynamics. Endocytosis and exocytosis at the growth cone are suggested to control its dynamics (Tojima et al., 2011; Tojima and Kamiguchi, 2015). A study using optogenetical control of vesicle/organelle transport have revealed that local activation of kinesin-mediated transport of Rab11-positive vesicles and recycling endosomes in the growth cones promotes axon extension in rat hippocampal neurons (van Bergeijk et al., 2015). Conversely, local activation of its dynein-mediated retrograde transport, which reduces the Rab11-positive compartments at the growth cone, suppresses the dynamics and area of the growth cone (van Bergeijk et al., 2015). In addition, light-induced local aggregation of the Rab5-targeted membrane compartments at the growth cones, which disrupts the dynamics of the target membranes, suppresses the protrusion rate and the area of the growth cones, whereas similar perturbation of the Rab11-targeted membrane compartments reduces the growth cone area, but not the protrusion rate of the growth cones (Nguyen et al., 2016). These observations suggest that local function of Rab5 and Rab11 at the growth cone is important for the growth cone dynamics and thereby proper axon extension and pathfinding.

A recent study shows that GRAB, a GEF for Rab8, recruits Rab8 to the Rab11-positive endosomes in primary cultured cerebral cortical neurons and its GEF

activity is suppressed by an atypical cyclin-dependent kinase, Cdk5-dependent phosphorylation (Furusawa et al., 2017) (Fig. 2). GRAB is transported to the growth cones via Rab11-positive vesicles, where it is dephosphorylated and activates Rab8 at the growth cones. Cdk5 also phosphorylates LMTK1 at Ser34, which negatively regulates the trafficking of Rab11a-positive vesicles in axons and dendrites, and thereby suppresses axon and dendrite elongation in cultured mouse cerebral cortical neurons (Takano et al., 2012, 2014).

Cdk5 is a key regulator for multi-step neuronal migration (Su and Tsai, 2011; Kawauchi, 2014). Cdk5 regulates the formation of both multipolar and leading processes, the multipolar-to-bipolar transition and the radial fiber-dependent locomotion mode of neuronal migration (Kawauchi et al., 2006; Ohshima et al., 2007; Nishimura et al., 2010, 2014) (Fig. 1). Rab11 is also reported to control neuronal migration in the developing cerebral cortex through the continuous recycling of N-cadherin to the plasma membrane (Kawauchi et al., 2010) (Fig. 1). FIP3, a downstream effector for Rab11, is required for N-cadherin trafficking and the locomotion mode of neuronal migration (Hara et al., 2016). Interestingly, FIP3 also functions as an effector for Arf6 and both Rab11- and Arf6-binding sites on FIP3 are required for proper neuronal migration (Hara et al., 2016).

Rab11 activity is reduced in a mouse model for Huntington's disease, a neurodegenerative disease caused by polyglutamine expansion in huntingtin protein (HTT) (Li et al., 2009). Recently, it has been reported that HTT regulates Rab11-dependent N-cadherin trafficking and neuronal migration in the developing cerebral cortex, whereas a pathological HTT with expansion of polyglutamine repeat impairs the neuronal migration (Barnat et al., 2017).

Rab7-mediated regulation of neurite outgrowth and dendrite maturation

Some parts of internalized membrane proteins are sorted to the late endosomes and lysosomes in a Rab7-dependent manner. Rab7 is associated with TrkA, a receptor for NGF, in PC12 cells (Saxena et al., 2005). Expression of DN-Rab7 enhances the activation of TrkA and its downstream target Erk1/2, possibly due to retarded trafficking of TrkA on signaling endosomes to lysosomes. In addition, DN-Rab7 potentiates neurite outgrowth in the PC12 cells briefly stimulated with NGF.

Charcot-Marie-Tooth disease type 2B (CMT2B)-associated Rab7 mutants (L129F, K157N, N161T or V162M), but not wild type-Rab7, suppress neurite formation in N1E-115 mouse neuroblastoma cells. This phenotype can be restored by treatment with valproic acid (VPA), a mood stabilizing drug that is known to inhibit histone deacetylases (HDACs) (Yamauchi et al., 2010). Interestingly, this effect is mediated by the modulation of a JNK signaling pathway, but not the suppression of histone deacetylase activity (Yamauchi et al., 2010).

While JNK is known to control the leading process formation and neuronal migration *in vivo* (Kawauchi et al., 2003), knockdown of Rab7 or DN-Rab7 inhibits only the final phase of neuronal migration and has little effect on the long-distance migration of leading process-possessing locomoting neurons (Kawauchi et al., 2010), suggesting that Rab7 and JNK regulate different cellular pathways at least in the migrating neurons in the developing cerebral cortex. Neurons undergoing the final phase of migration begin branching of their leading process to form dendrites. *In vivo* knockdown of Rab7 in cortical neurons results in defects in dendrite maturation (Kawauchi et al., 2010) (Fig. 1). Consistently,

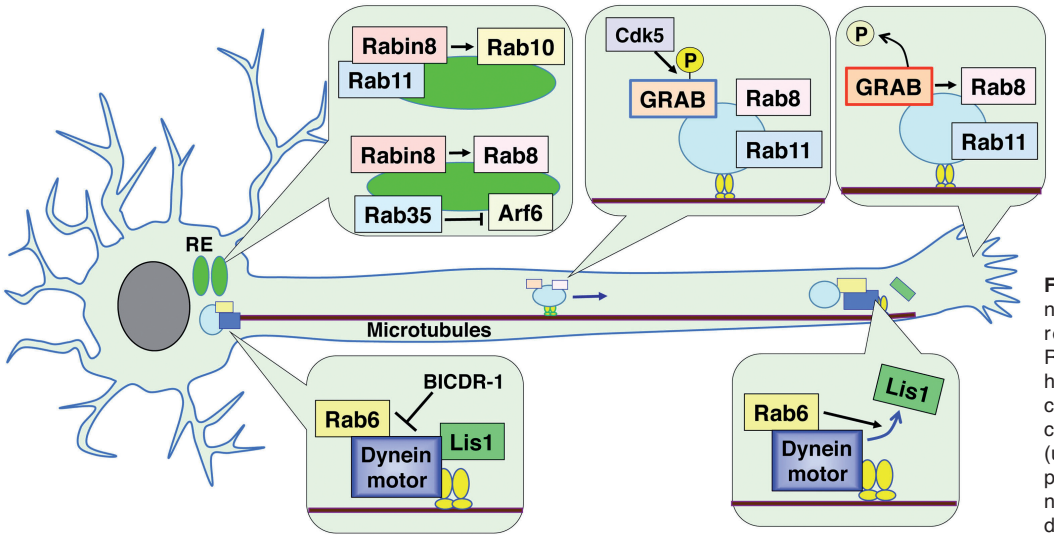

Fig. 2. Roles of Rab GTPases in neurite outgrowth. Two types of recycling endosomes (RE), Rab11-positive and Arf6-positive, have been identified in PC12 cells (upper left panel). In primary cultured neurons, Rab11, Rab8 (upper panels) and Rab6 (lower panels) are reported to regulate neurite outgrowth. See text for detail.

conditional targeting of WDR91, an effector of Rab7, in brains leads to the reduction of the total length and complexity of the dendrites in the dentate gyrus of the hippocampus as well as the cerebral cortex (Liu et al., 2017).

Roles of the Rab proteins associated with ER or Golgi

Newly synthesized membrane proteins are transported to the plasma membrane through the ER, Golgi and TGN. Rab6, a Golgi-associated Rab protein, is shown to promote neurite outgrowth in primary rat hippocampal neurons (Schlager et al., 2010) (Fig. 2). Knockdown of both Rab6a and Rab6b decreases neurite length. COH1/Vps13B, a downstream effector of Rab6, is associated with Cohen syndrome, an autosomal recessive neurodevelopmental disorder characterized by postnatal microcephaly and intellectual disability, and its knockdown decreases neurite length in primary rat hippocampal neurons (Seifert et al., 2015).

Rab6a is shown to activate a dynein motor (Yamada et al., 2013). Lis1, a causative gene product of lissencephaly (smooth brain), forms a dynein idling complex and suppresses the dynein-mediated retrograde transport (Yamada et al., 2008). Rab6 promotes the dissociation of Lis1 from the dynein idling complex to activate the retrograde transport (Yamada et al., 2013). Bicaudal-D-related protein 1 (BICDR-1) interacts with Rab6 and the dynein/dynactin retrograde motor complex and suppresses the trafficking of secretary vesicles at the early stage of neuronal differentiation, resulting in pericentrosomal accumulation of Rab6-positive secretory vesicles in cultured rat hippocampal neurons (Schlager et al., 2010). Subsequently, however, the expression level of BICDR-1 is decreased at mid- and late stages of neuronal differentiation and "unlocked" secretory vesicles begin to undergo the anterograde transport in neurites. Consistently, overexpression of BICDR-1 reduces both axon and dendrite length (Schlager et al., 2010) (Fig. 2).

Rab18 is required for the formation and/or maintenance of the ER and Golgi structure (Dejgaard et al., 2008; Gerondopoulos et al., 2014). Rab18 and Rab3GAP, a heterodimer complex composed of Rab3GAP1 and Rab3GAP2, are associated with Warburg Micro Syndrome, a neurodevelopmental disorder (Warburg et al., 1993; Aligianis et al., 2005; Bem et al., 2011). Rab3GAP exhibits a GEF activity for Rab18, in addition to a GAP for Rab3 (Gerondopoulos et al., 2014). Importantly, the Warburg Micro Syndrome-associated mutants of Rab3GAP1 (T18P and E24V) retain their GAP activity for Rab3a and Rab3b but exhibit no GEF activity for Rab18 (Gerondopoulos et al., 2014). Rab18 is required for both axon and dendrite formation in cultured cortical neurons and neuronal migration *in vivo* (Wu et al., 2016). Rab18 is partially colocalized with Rab7, implying that Rab18 may also play a role in the lysosomal degradation pathway. Knockdown of Rab18 decreases the cell surface level of N-cadherin and the acceleration of N-cadherin degradation (Wu et al., 2016). In contrast, Rab11 knockdown results in abnormal accumulation of N-cadherin at the recycling endosomes without affecting the total expression level of N-cadherin in 2 day-*in vitro* cultured cortical neurons (Kawauchi et al., 2010).

Conclusion

In this review, we introduce some recent advances revealing roles of Rab family proteins in neural development with particular focus on neurite outgrowth and neuronal migration. To date, many Rab proteins involved in these developmental events have been reported. However, Rab family small GTPases comprise around 60 members and therefore we are still on our way to gaining a complete understanding of membrane trafficking-mediated regulation in neural development. Future goals should be to shed light on less characterized Rab proteins and their upstream and downstream molecules and to gain more in depth understanding of the mechanisms underlying the roles of "major" Rab proteins in neurite formation and neuronal migration.

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