Critical importance of RAB proteins for synaptic function

Maria Lidia Mignogna and Patrizia D’Adamo

Molecular Genetics of Intellectual Disabilities Unit, Division of Neuroscience at IRCCS San Raffaele Scientific Institute, Milan, Italy

ABSTRACT

Neurons are highly polarized cells that exhibit one of the more complex morphology and function. Neuronal intracellular trafficking plays a key role in dictating the directionality and specificity of vesicle formation, transport and fusion, allowing the transmission of information in sophisticated cellular network. Thus, the integrity of protein trafficking and spatial organization is especially important in neuronal cells. RAB proteins, small monomeric GTPases belonging to the RAS superfamily, spatially and temporally orchestrate specific vesicular trafficking steps.

In this review we summarise the known roles of RAB GTPases involved in the maintenance of neuronal vesicular trafficking in the central nervous system. In particular, we discriminate the axonal pre-synaptic trafficking and dendritic post-synaptic trafficking, to better underline how a correct orchestration of vesicle movement is necessary to maintain neuronal polarity and then, to permit an accurate architecture and functionality of synaptic activity.

Introduction

Neurons are the most sophisticated cells able to discriminate and process an enormous variety of events in the environment, forming a complex network in the nervous system. The complex morphology and the specialized compartments, in the form of cell body, multiple dendrites, one axon and pre- and post-synaptic buttons, are necessary for synaptic transmission. The formation and conservation of the asymmetric domains as well as the generation and the maintenance of connectivity need a continuous membrane supply, a correct distribution of membrane receptors, adhesion molecules and intracellular mediators. Thus, the integrity of protein trafficking and spatial organization are especially important in neuronal cells, because they crucially determine morphogenesis and connectivity, information processing and synaptic plasticity.

RAB proteins, small monomeric GTPases belonging to the RAS superfamily, are involved in correct vesicle sorting, fission, transport, tethering, docking and fusion, by the interaction with effector proteins.

RAB proteins count for more than 60 members in eukaryotes and act as a network to orchestrate the transport of specific vesicles both spatially and temporally. They coordinate this function from the ability to switch from an inactive Guanosine-5’-DiPhosphate (GDP)-bound state to an active Guanosine-5’-TriPhosphate (GTP)-bound state. To ensure the correct coordination between GDP release and GTP hydrolysis, accessory regulatory proteins are necessary to guarantee and accelerate the switch. RAB GDP dissociation inhibitor (GDI), Guanine nucleotide exchange factor (GEF) and GTPase-activating protein (GAP). Additionally, RAB GTPases are physically associated with specific organelles, becoming the first true molecular markers to discriminate the membrane compartments of the endocytic and secretory pathway. However, the exact cellular localization and tissue expression profile of many RABs remain unidentified. To date, 24 RAB proteins are documented to play a role in brain, driving different and sequentially steps of neuronal trafficking.

In this review we focus on a status update on the role played by RAB GTPases in intracellular neuronal vesicular trafficking in the central nervous system. The intrinsic complexity of RAB family proteins and the sophisticated neuronal morphology and specialized compartmentalization, require a systematic description of RAB GTPases-mediated trafficking, from the cell body, to reach, by traveling through the axon and dendrites, the final destination, the pre- and post-synaptic compartments for synaptic function. Indeed, a complete and overall perspective of how RAB GTPases operate in neurons is crucial for a better understanding of the molecular mechanisms underlying the neuronal phenotypes in the context of intellectual disabilities.

ARTICLE HISTORY

Received 21 December 2016
Revised 13 December 2016
Accepted 21 December 2016

KEYWORDS

axon; dendrite; neuronal cells; neuronal trafficking; post-synaptic; pre-synaptic; RAB GTPases; synaptic function; vesicle transport

CONTACT Patrizia D’Adamo dadamo.patrizia@hsr.it
San Raffaele Scientific Institute, Via Olgettina, 58, 20132, Milan, Italy.

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comprehension of multiple aspects of neuronal physiology and pathophysiology.

**RAB GTPases involved in the first steps of neuronal trafficking: at the cell body**

The importance of the entire neuronal trafficking, from the cell body to the synaptic sites, for synaptic activity was well described by Waller during a lecture he delivered at the Royal Institution of Great Britain in 1861: “A nerve cell would be to its effluent nerve fibers what a fountain is to the rivulet which trickles from it – a center of nutritive energy.” The nutritive energy comes from the protein synthesis that initially occurs in the cell body where they start their route.

Initially, proteins take on secretory pathway where a series of RAB GTPases work together regulating anterograde, such as RAB1,19 RAB2,20 RAB8,21 RAB39B22 and retrograde, such as RAB7,23 RAB6,24 RAB33B,25 RAB26 vesicular trafficking/transport. Here, impairments in the activity of RAB proteins perturb Endoplasmic Reticulum (ER) and Golgi structures26 leading to alterations in axonal and dendritic outgrowth, as well as impacting on a correct synaptic formation.27–29

Then, traffic though the Golgi compartment is responsible for secretion of proteins targeted to the membrane. In particular neurons count several types of secreted vesicles that are differentially targeted to dendrites and/or to the axon to maintain cellular polarity. Dendritic transport polarization is well established because vesicles containing dendritic proteins are bi-directionally transported via microtubules in dendrites but not in axons. Axonal polarization is more complicated because some vesicles containing axonal proteins undergo toward axon but also dendrites; the polarity is guaranteed by endocytosis that avoid the accumulation of axonal proteins of dendritic surface.30,31

For neuronal cells it is important to maintain a well-regulated dendritic and axonal transport to establish and preserve the correct polarized morphology. A right cell polarization is in turn essential for the organization and maintenance of synaptic activity.5

**RAB GTPases involved in axonal trafficking**

The secretory process in neurons is strictly similar to that in other cells but the axon-terminal, the primary target of secretion, is greatly distant from the cell body (up to a meter in length). Two types of vesicle traffic exist in the axon: slow and fast transport.32 Cytosolic and cytoskeletal proteins move in the anterograde direction by the slow axonal transport with kinetics of 0.01-0.001 μm/sec. Instead membranous organelles move in the anterograde and retrograde direction by fast axonal transport at 1-5 μm/sec.33 Several RAB GTPases control protein transport in the axon to guarantee, at first, the right axonal development and then, a proper pre-synaptic functionality.

**RAB proteins-mediated trafficking during neuronal development for axonal polarization**

Some RAB proteins are key masters of axonal polarization and elongation through membrane precursor vesicles or neurotrophic receptors transport.

RAB10 is involved in regulating activities to induce axonal polarization and elongation. Following RAB10 release from GDI by Lgl1,34 RAB10 mediates trafficking from trans-Golgi network (TGN) to the plasma membrane of membrane precursor vesicles by MyosinVb35 and kinesin-depending movement.28 Finally RAB10 binds to Myristoylated Alanin-Rich C-Kinase Substrate (MARCKS) at the plasma membrane to make the docking and fusion to the plasma membrane of RAB10-exocytic carriers, resulting in axonal outgrowth.36 It has been demonstrated that the expression of wild type (WT) or constitutively active form of RAB10 (RAB10-Q68L) leads to axonal arborization; in contrast the dominant negative form of RAB10 (RAB10-T23N) inhibits this process.34,37 Moreover in RAB10 – null mouse, target disruption of Rab10 leads abnormal endosomes and ER hyperplasia disturbing the general balance of membrane trafficking, resulting to early embryonic lethality (from E9.5).38

RAB33A, a TGN-related RAB protein, mediates anterograde synaptophysin-positive vesicles trafficking impacting on axonal outgrowth. In particular, in hippocampal neurons RAB33A downregulation negatively affects neuronal polarization, at contrary the overexpression of the constitutively active mutant (RAB33A-Q95L) leads to multi-axonic neurons.39

RAB4 and RAB11 are involved in axonal outgrowth by working in endosome recycling, which can be classified in fast and slow routes depending on the presence of RAB4- and RAB11-positive recycling endosomes, respectively.8

In Xenopus retinal ganglion cells, RAB4 is recruited to the endosomes in the growth cone, and RAB4 downregulation or the dominant negative RAB4 mutant (RAB4-N1211) decrease axonal elongation.40 RAB4 upregulation was found in patients with Alzheimer’s disease and mild cognitive disorder,41,42 indicating that deficits in neuronal endosomal sorting may establish these disorders.43

In rat cortical neurons, RAB11 improves axonal elongation following the upstream activation of signaling cascade controlled by cyclin-dependent protein kinase 5.
(CDK5). Overexpression of RAB11 WT and the RAB11 constitutively active mutant (RAB11-Q70L) promote axonal elongation in rat cultured cortical neurons. In contrast RAB11 downregulation or dominant negative expression form of RAB11 (RAB11-S25N) in the striatum and cortex of normal mice lead to decreased axonal length causing neuropathology and motor dysfunction. Moreover, alteration in RAB11 GDP to GTP conversion was described in a mouse model for Huntington’s disease, supporting the idea that defects in vesicle formation impact on early stages of the synaptic dysfunctions. Indeed Huntington’s disease phenotype was partially rescued upon enhancing RAB11 activity. However, in Nerve Growth Factor (NGF)-stimulated PC12 cells it was described an increase in the interaction between phosphorylated protrudin and the inactive GDP-bound form of RAB11. This evidence raises some question on which form of RAB11, the GDP- or GTP-bound form, impacts on axonal outgrowth. Given that the majority of RAB11 studies have found that RAB11-GTP enhances axonal elongation, it is conceivable that protrudin promotes RAB11-GDP to the cell periphery before its activation. Recently, it was showed that RAB11 works together with RAB25 and RAB14 in the N2A cells in regulating axonal outgrowth, however additional work is necessary to clarify this mechanism.

RAB5 and RAB7 have been shown to sequentially mediate the retrograde transport of NGF and neurotrophin receptors. After internalisation by clathrin-mediated endocytosis or micropinocytosis, neurotrophin receptors are clustered into RAB5-positive early endosomes thanks to Phosphatidil Inositol 3-kinase (PI3K) activity. Indeed, PI3K allows a production of Phosphatidil Inositol 3-Phosphate (PI(3)P) which binds the Early Endosome Antigen 1 (EEA1) tethering factor, which in turn permits the RAB5-positive endosomes fusion in order to concentrate cargos and consequently the advance into the RAB7-controlled late endosomal pathway. RAB7 is considered a marker for the axonal retrograde transport. The expression of RAB7 dominant negative mutant (RAB7-T22N) allows an accumulation and a prolonged persistence of internalized neurotrophin receptors, leading to axonal degeneration. Misregulation of both RAB5 and RAB7 were also found associated with human neurodegenerative diseases, such as Alzheimer’s disease and Down Syndrome, leading an enlargement of the endosomes in neuronal cells, finally causing the cell death. In particular they were upregulated in specific human post-mortem brain regions, as basal forebrain, frontal cortex, and hippocampus but not in cerebellum and striatum. Upregulation of endosomal vesicle trafficking is also associated to Parkinson’s disease where an increased RAB5 was found in the striatal neurons. These evidences raised the hypothesis that a tight link between protein-compartment-marker and the vulnerability of cell types within selective brain regions exists.

A new role played by RAB7 is in neurite outgrowth, by interconnecting secretory and endocytic pathway by permitting repeated late endosomes (LE)-ER contacts. RAB7, binding the ER protein protrudin, mediates transfer of vesicles to LE and promotes the microtubule-dependent translocation of LEs to the cell periphery and subsequently synaptotagmin-VII-dependent fusion with the plasma membrane in PC12 cell lines. Moreover expression of mutated forms of RAB7, mutations causing Charco-Marie-Tooth type 2B (CMT2B) neuropathy, leads a marked inhibition of neurite outgrowth in PC12 and N2A cells.

The anterograde transport of neurotrophin receptors, in particular of TrkB, is regulated by RAB27B. Given to the generation of LacZ-Rab27b knockout mouse, RAB27B was found to be the isoform of RAB27 higher expressed in mammalian neurons. RAB27B together with Slp1/CRMP-2 complex directly moves TrkB-containing vesicles to the neuronal membrane, by Kinesin-1 dependent transport. Downregulation of RAB27B decreases the axonal membrane targeting of TrkB, however the Rab27b mouse model shows a normal development and behavior.

RAB35 has a role also in neurite outgrowth in PC12 cell line. It determines the localization of MICAL-L1, a multiple RAB-binding protein, to Arf6-positive recycling endosomes. In turn MICAL-L1 functions as a scaffold for the recruitment of RAB8, RAB13 and RAB26. In particular RAB35 permits axonal elongation in rat primary neurons thanks to Microtubule-associated protein 1B (MAP1B) which, interacting with p53-related protein kinase (PRPK), protects RAB35 from ubiquitin-proteasome degradation pathway.

RAB13, as mentioned before, supports neurite outgrowth in PC12 and DRG cell lines, regulating the transport of membrane-containing vesicles from TGN to recycling endosomes. In cultured Dorsal Root Ganglion (DRG) neurons, RAB13 co-localizes with the Growth Associated Protein 43 (GAP43) in neurites and nerve terminals, promoting neurite extension in the PC12 cell line when stimulated with NGF. At contrary the downregulation of RAB13 by RNA interference inhibits neurite outgrowth in NGF-treated PC12 cells. In particular RAB13, together with Corinin1b, is required for axonal regeneration in mice following the transcriptional regulation control of the tumor suppressor p53. Indeed after facial nerve axotomy, a model for neuronal regeneration, p53 null mice did not show...
expression of Coronin1b and RAB13 in axonal sprouts in regenerating facial nuclei as in WT mice.72

**RAB proteins-mediated trafficking for pre-synaptic function**

At last, a proper pre-synaptic functionality is ensured by the organelles trafficking including vesicles of the constitutive secretory pathway, synaptic vesicle precursor membranes, mitochondria and elements of smooth ER and in particular neurotransmitters. Neurotransmitters are packaged into synaptic vesicles (SVs) and clustered at the pre-synaptic membrane in the axon-terminal, on the pre-synaptic side of a synapse. In response to a local transient increase in Ca2+ concentration at the active zone following the arrival of an action potential, SVs, that enclose neurotransmitters and are properly docked and primed, fuse with the pre-synaptic membrane and release the content in the synaptic cleft.74 The recycling of SVs by endocytosis ensures the refilling of SV reserve. For any SV cycling step, there are specific RAB GTPases that guarantee the timing and the correct directionality for vesicles.

SV docking and exocytosis are controlled by RAB3 subfamily and RAB27B.

RAB3 subfamily is composed of RAB3A, RAB3B, RAB3C and RAB3D. They are highly expressed in the murine brain74 and it is the first group of RAB GTPases associated with a neuronal specific pathway.27 RAB3A, the most investigated RAB of RAB3 subfamily, is required for the assembly and transport of vesicles in fast anterograde axonal transport by a Kinesin1-dependent transport.75 One of the RAB3 known effector protein is RIM1, considered the core component of the active zone. It forms a trimeric complex with RAB3 and MUNC13 recruiting SVs to the active zone and organizing them for release.77 Single, double, triple and quadruple Rab3 KO mice were generated and they succumb when one of deleted Rab3 is Rab3A. In particular quadruple Rab3 KO mice, that are born alive and die to respiratory failure, show no apparent changes in synapse structure or brain composition except for a mild reduction of 30% in neurotransmitter release.78 This may be due to role played by RAB27B, which is structurally tight related to Rab3. RAB27B localization partially overlaps with Rab3 wherewith shares regulator and effector proteins.79,80 Overexpression of constitutive active (RAB27B-Q78L) or inactive (RAB27B-N133I) RAB27B mutants in murine neurons causes a strong reduction in SV recycling79 however the mechanism has to be further investigated.

Recycling of SVs by endocytosis is directed through several pathways. One is identified as kiss-and-run and vesicles are undocked and recycled locally. Three mechanisms of SV retrieval consist in full fusion of vesicles with the plasma membrane: clathrin-mediated endocytosis (CME), which retrieves SVs during mild synaptic stimulation,81 clathrin-independent bulk endocytosis (CIE), which permits invagination of a large region of the plasma membrane during an intense stimulus,82 and ultra-fast endocytosis, which retrieves single, large endocytic vesicles next to the pre-synaptic densities (speed: 50-100 ms) in response to a single stimulus or during mild stimulation.83,84

Endocytic events are regulated by RAB4, RAB5, RAB10, RAB11, RAB14, RAB35 and RAB7.29,85 RAB5 localizes to a subset of SVs and it is principally involved in SV retrieval, recycling and SV uniformity size control: it orchestrates early endosomes by step-wise recruitment of effector proteins (Rabaptin5/Rabex5/PI (3)P/Vps34/EEA1/Rabenosyn5) to endosomal micro-domains.86-88 Alterations in RAB5 affect formation and composition of endosomal compartment at the nerve terminal and impair SV recycling leading to altered synaptic transmission in *Drosophila*.87 In rat hippocampal neurons overexpression of RAB5A reduced the recycling pool size by 50%.89

A functional screen on *Drosophila*90 and *C. elegans*81,92 models to assess the impact of a battery of constitutively active RABs on SV cycling, identified RAB35, RAB7, RAB11 and RAB10 as putative regulators of post-endosomal trafficking of SVs. RAB4, RAB5 and RAB11 collaborate in regulating different steps of the endosome recycling80 RAB7, driving LE-positive vesicles from Rab5-positive EE participates in several steps of the autophagic pathway: from maturation to the trafficking process of autophagosomes and amphisomes.93 RAB10 and RAB14 are implicated in clathrin-coated traffic and recycling pathways.80,94,95

RAB35, previously described having a role in axonal and neurite outgrowth, is important for regeneration of new SVs, indeed the expression of the constitutively active RAB35 mutant or loss-of-function of its GAP, TBC1D24/Skywalker, allows a recovery of SVs via endosomal intermediates and increases synaptic transmission.2,90 However, how these RABs operate in mammalian pre-synaptic buttons remains to be investigated.85

RAB35 also plays a role in SV degradation and turnover. In cultured rat hippocampal neurons GTP-RAB35 recruits the Endosomal Sorting Complex Required for Transport (ESCRT)-0 protein Hsr to SV pools to initiate ESCRT complex formation, then mediating the degradation of SV integral membrane proteins SV2 and VAMP2.96
Recent studies provided the link between SV-associated RAB26 and the autophagic pathway. RAB26 binds the autophagosomal markers ATG16L1, the complex was found in a subset of Synaptobrevin and RAB3A-positive vesicles suggesting that RAB26 covers the gap between recycling and autophagic pathway. Moreover, RAB26 overexpression leads to SV clustering and engulfment by autophagosomes. RAB33B, ubiquitously presents in murine organs, shares the binding to ATG16L1 with RAB26 regulating autophagosomes.
formation.\textsuperscript{39,98,99} If RAB26 and RAB33B overlap their role or sequentially work in regulating SV recycling and autophagy, remain to be demonstrated.

All the RAB GTPases described to be involved in axonal and pre-synaptic trafficking are essential for a correct synaptic activity formation and maintenance. Indeed, mutations and physiological abnormalities affecting synaptic RABs, and their regulator and effector proteins, lead to neurodevelopmental and neurodegenerative disorders.

**RAB GTPases involved in dendritic trafficking**

Neuronal dendrites play a critical role in integrating synaptic inputs, so that they may determine an action potential. For these reasons it is important, at first, to study how the dendritic outgrowth is regulated and maintained. Dendrites are specialized compartments that receive signals from the axonal termini of other neurons; this occurs where pre-synaptic buttons contact dendritic spines, situated through the dendritic tree.\textsuperscript{100,101} Indeed, dendrites are strewed with spines that exhibit different types of Ligand-Gated Ion Channels classified into three families: Cys-loop receptors, ionotropic receptors and Adenosine Tri-Phosphate (ATP)-gated channels.\textsuperscript{102} In the brain, the most excitatory transmission is mediated by $\alpha$-Amino-3-hydroxy-5-Methyl-4-isoxazole-Propionic Acid (AMPA)-type ionotropic glutamate receptors; they have the highest influence on the strength of the synaptic response and are crucially involved in synaptic plasticity and learning and memory processes.\textsuperscript{103}

**RAB proteins-mediated trafficking during neuronal development for dendritic polarization**

One of the first studies on this issue described the role of RAB8 in dendrite-specific transport. It has two different isoforms, RAB8A and RAB8B, which compensates for each other.\textsuperscript{104} RAB8 localizes in neurites of cultured hippocampal neurons in early developmental stages; in mature neurons it localizes in dendrites, but not in axon.\textsuperscript{27,105,106} RAB8 regulates membrane precursor-vesicle trafficking from TGN to the plasma membrane playing a crucial role in neurite outgrowth. In neuronal cells, downregulation of RAB8 inhibits anterograde formation and transport of vesicles and avoids neurite outgrowth.\textsuperscript{106,107} However Rab8 knock-out mouse model dies prematurely, not for alterations in its role in neurons but, for its role played in the development of intestinal epithelial cells triggering its ubiquitously tissue expression.\textsuperscript{104} A recent study described that RAB8 shares its GEF Rabin8 with RAB10 and RAB11 in regulation of neurite outgrowth. However Rabin8 regulates RAB10 and RAB11 by a GEF-dependent and -independent mechanism, respectively.\textsuperscript{108}

It was reported that RAB11 also controls dendritic arborisation in rat hippocampal neurons, regulating the trafficking of TrkB via MyosinVb. In particular, it permits the TrKB retention in dendrites, increasing the local signal needed for arborisation. Indeed, the overexpression of the constitutively active form of RAB11 (RAB11-Q70L) leads to increase dendritic branching, with an accumulation of TrkB in dendrites.\textsuperscript{109}

**Figure 1.** (see previous page) RAB GT Pas orchestrate different neuronal trafficking steps. Graphical representation of RAB GTPas-mediated intracellular vesicular trafficking steps in different neuronal cell compartments. Section A (in red) represents the cell body compartment with RAB GTPas that mediate ER-Golgi pathway and vice versa. RAB1, RAB2, RAB6, RAB33B and RAB2 play a role in retrograde transport. Section B (in blue) shows RAB proteins involved in dendritic vesicle trafficking. RAB8, RAB10, RAB11 controls constitutive Membrane Precursors Vesicle (MPV) trafficking in secretory pathway from cell body to the cell periphery. RAB17 acts at early neuronal developmental stage in secretory pathway through MPV for dendritic morphogenesis. RAB21 controls the exocytic vesicle transport to the cell periphery. A specialized function is showed for RAB11 in TrkB receptor (white rectangle) internalisation leading to local receptor signal increase for dendritic arborisation. Section C (in yellow) recapitulates RAB GT Pas involved in axonal vesicle trafficking. Transport vesicles (TV) and recycling endosomes (RE) are involved in axonal outgrowth. RAB10, RAB33A and RAB27B mediate TV trafficking. RAB10 controls the vesicle transport from TGN to the plasma membrane. RAB27B regulates the anterograde transport of neurotrophin receptors and RAB33A mediates anterograde synaptophysin-positive vesicles. RAB4, RAB11, RAB35 and RAB13 are involved in RE pathway. RAB4 and RAB11 control RE fast and slow recycling route, respectively. RAB25 and RAB14 collaborate with RAB11. RAB35 permits neurite and axon elongation together with RAB8, RAB13 and RAB26. RABs reported in italic, represent the RAB GTPases that mediate ER-Golgi pathway and vice versa. RAB1, RAB2, RAB6, RAB33B and RAB2 play a role in retrograde transport. Section B (in blue) shows RAB proteins involved in dendritic vesicle trafficking. RAB8, RAB10, RAB11 controls constitutive Membrane Precursors Vesicle (MPV) trafficking in secretory pathway from cell body to the cell periphery. RAB17 acts at early neuronal developmental stage in secretory pathway through MPV for dendritic morphogenesis. RAB21 controls the exocytic vesicle transport to the cell periphery. A specialized function is showed for RAB11 in TrkB receptor (white rectangle) internalisation leading to local receptor signal increase for dendritic arborisation. Section C (in yellow) recapitulates RAB GT Pas involved in axonal vesicle trafficking. Transport vesicles (TV) and recycling endosomes (RE) are involved in axonal outgrowth. RAB10, RAB33A and RAB27B mediate TV trafficking. RAB10 controls the vesicle transport from TGN to the plasma membrane. RAB27B regulates the anterograde transport of neurotrophin receptors and RAB33A mediates anterograde synaptophysin-positive vesicles. RAB4, RAB11, RAB35 and RAB13 are involved in RE pathway. RAB4 and RAB11 control RE fast and slow recycling route, respectively. RAB25 and RAB14 collaborate with RAB11. RAB35 permits neurite and axon elongation together with RAB8, RAB13 and RAB26. RABs reported in italic, represent the finding of their presence on RE without a well-defined role in neuron. RAB5 and RAB7 have been shown to sequentially mediate the retrograde transport of NGF and neurotrophin receptors from RAB5-positive Early Endosomes (EE) to RAB7-positive Late Endosomes (LE), leading to axonal degeneration. Section D recapitulates RAB proteins involved in pre- (green) and post- (orange) synaptic functions. At pre-synaptic site, RAB3 and RAB27B play a role in specific steps of SV docking and exocytosis at the pre-synapse. Recycling of SVs by endocytosis is directed through several pathways, represented are kiss-and-run and clathrin-mediated endocytosis (CME). The first step of CME is mediated by RAB5, RAB10 and RAB14. Then, RAB10 and RAB14 control the SVs direct pathway and RAB5 directs the endosomal pathway via RE. RAB5-mediated RE trafficking involves at the end, RAB4, RAB11 and RAB35 in SV regeneration. RAB7, driving LE-positive vesicles from RAB5-positive EE, links endosomal-recycling pathway to the autophagic process. RAB26, RAB33B and RAB35 are involved in SV degradation and delivery. RAB11 is the mediator of recycling endosomes and contributes with RAB8 to AMPAR delivery. RAB5, controlling EE, is involved in a clathrin-dependent receptor internalization. Through RAB4 and RAB11 receptors are recycled to the plasma membrane, and through RAB7-dependent late endosomes they are transported toward lysosomes.
Dendritic outgrowth is also regulated by RAB17 and RAB21. RAB17 is specifically expressed in dendrites of mouse hippocampal neurons, it localizes at dendritic growth cones, shafts, filopodia and mature spines.\textsuperscript{110} RAB17 mediates the dendrite growth and branching thanks to its GEF Rabex-5,\textsuperscript{111} found to be also one of RAB5 GEF, suggesting an inter-play between these RABs. Downregulation of RAB17, by shRNA technology, decreases synaptic branching in mouse hippocampal neurons.\textsuperscript{111}

RAB21 controls the exocytic vesicle transport to the cell periphery in mouse hippocampal neurons through its GEF protein VARP and the non-canonical SNARE Vesicle-Associated Membrane Protein 7 (VAMP7).\textsuperscript{112}

**RAB proteins-mediated trafficking for post-synaptic function**

RAB8, RAB11 and RAB17, previously described to play a role in dendrite outgrowth, participate also in receptor trafficking and recycling.

RAB8 is involved in GluA1-AMPA receptors trafficking from ER to the Golgi complex, and their delivery at the post-synapse.\textsuperscript{113,114} In central neurons RAB8 works in accordance with RAB11, present at the base of the dendritic spines.\textsuperscript{115} RAB11 is well known as the mediator of recycling endosomes: interestingly it also mediates the activity-dependent delivery of GluA1-containing AMPA receptors to synapses.\textsuperscript{116} Neuronal activity-dependent insertion or removal of AMPA receptors from the postsynaptic plasma membrane triggers the phenomenon of long-term Potentiation (LTP) and long-term Depression (LTD).\textsuperscript{27} Dominant negative form of RAB11 (RAB11-S25N) is able to block AMPA receptor recycling and LTP.\textsuperscript{116}

RAB17 promotes GluK2-kinate receptor surface expression thanks to syntaxin-4 in mouse hippocampal neurons. Indeed, RAB17 downregulation leads to syntaxin-4 redistribution away from dendrites and reduction of surface expression of GluK2-kinate receptors, while overexpression of the constitutively active form of RAB17 (RAB17-Q77L) endorses an accumulation of syntaxin-4 in dendrites and an increase of dendritic surface insertion of GluK2-kainate receptors.\textsuperscript{117}

AMPA receptor internalization is controlled by RAB5 in Cornus Ammonis 1 (CA1) hippocampal neurons: it drives the internalization of AMPARs in a clathrin-dependent manner. In fact RAB5 is rapidly and transiently activated during N-Methyl-D-Aspartate (NMDA)-dependent LTD induction.\textsuperscript{118} AMPARs recycling is controlled by RAB4. It binds the neuronal specific GRIP-associated proteins 1 (GRASP1) performing a key role in the coordination of recycling endosome maturation in dendrites: in particular it plays a role in AMPARs recycling and in connecting early and late recycling endosomal compartments.\textsuperscript{119,120} Conversely, the transport of AMPA receptors, via RAB7-dependent late endosomes, ensures receptor removal from the synaptic membrane toward lysosomes.\textsuperscript{121} Another RAB GTPase involved in AMPA receptor trafficking is the neuronal specific protein RAB39B. It coordinates the secretory pathway of the AMPA receptor hetero-tetramer formed by GluA2-GluA3 subunits, leading to a correct AMPA receptor composition at the post-synaptic site. The downregulation of RAB39B in murine hippocampal neurons leads to an increase in Ca\textsuperscript{2+}-permeable GluA2-lacking AMPA receptors at the neuronal surface, allowing impairments in excitatory post-synaptic currents.\textsuperscript{22} Moreover loss- or gain-of-function mutations in RAB39B cause Intellectual Disability\textsuperscript{122-124} and early onset Parkinson’s disease.\textsuperscript{125-127}

Finally, a correct orchestration by RAB proteins of dendritic and post-synaptic trafficking is essential for the architecture and maintenance of synaptic plasticity. In fact mutations in human RAB GTPases are described to cause neurodevelopmental and neurodegenerative disorders.

**Conclusive remarks**

The knowledge about the expression profile and the consequent role of RAB GTPases has considerably grown in recent years. In particular the isolation of RAB regulators and their effector proteins is providing the opportunity to understand, at first, their subcellular localization and consequently how RAB proteins work together.

In this review it well emerges how RAB GTPases communicate with each other thanks to common effectors, even if they localize in different neuronal compartments, and then how they efficiently coordinate the several steps of vesicular trafficking building up the cellular conditions for a correct synaptic function. A summary of described RAB proteins, that play a role in formation and maintenance of polarized neuronal synaptic architecture in the central nervous system, is schematically showed in Fig. 1.

The models used from different work-groups gave the opportunity to start to explore the role of several RAB GTPases in intracellular trafficking of central neurons, where the complexity of cellular morphology and activity is translated in a sophisticated and intricate coordination of vesicular traffic. It remains essential to generate animal models of different RAB proteins to better comprehend, not only the expression profile but also, the specific role of RABs in different tissues of the central nervous system. In particular the exact definition of multiple intracellular
trafficking steps in neurons raises the groundwork in understanding the mechanisms involved in several neuro-pathological conditions. These open the way to the development of effective therapeutic strategies.

**Abbreviations**

AMPA $\alpha$-Amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid  
ATP Adenosine Tri-Phosphate  
CA1 Cornus Ammonis 1  
CDK5 Cyclin-Dependent protein Kinase 5  
CIE Clathrin-independent bulk endocytosis  
CME Clathrin-mediated endocytosis  
CMT2B Charco-Marie-Tooth type 2B  
DRG Dorsal Root Ganglion  
EEA1 Early Endosome Antigen 1  
ER Endoplasmic Reticulum  
ESCRT Endosomal Sorting Complex Required for Transport  
GAP GTPase-Activating Protein  
GAP43 Growth Associated Protein 43  
GDI GDP Dissociation Inhibitor  
GDP Guanosine-5'-DiPhosphate  
GEF Guanine Nucleotide Exchange Factor  
GRASP1 GRIP-Associated Protein 1  
GTP Guanosine-5'-TriPhosphate  
LE Late Endosome  
LTD long-term Depression  
LTP long-term Potentiation  
MAP1B Microtubule-Associated Protein 1B  
MARCKS Myristoylated Alanin-Rich C-Kinase Substrate  
NGF Nerve Growth factor  
NMDA N-Methyl-D-Aspartate  
PI3K Phosphatidyl Inositol 3-kinase  
PRPK p53-Related ProteinKinase  
PtdIns(3)P Phosphatidyl Inositol 3-Phosphate  
SV Synaptic vesicle  
TGN trans-Golgi network  
VAMP7 Vesicle-Associated Membrane Protein 7  
WT wild type

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

**Acknowledgments**

We thank S. Mignogna for graphic support. M.L. Mignogna is supported by Fondazione Umberto Veronesi fellowship program 2016.

**Funding**

This work was supported by Ministero della Salute RF-2013-02355326.

**ORCID**

Maria Lidia Mignogna [1] http://orcid.org/0000-0001-9144-6363  
Patrizia D’Adamo [2] http://orcid.org/0000-0002-0312-5541

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