Coordination of AMPA receptor trafficking by Rab GTPases

Angelika Hausser and Katalin Schlett

Institute of Cell Biology and Immunology, University of Stuttgart, Stuttgart, Germany; 6Stuttgart Research Center Systems Biology, University of Stuttgart, Stuttgart, Germany; 7Department of Physiology and Neurobiology, Eötvös Loránd University, Budapest, Hungary; 8MTA-ELTE NAP B Neuronal Cell Biology Research Group, Eötvös Loránd University, Budapest, Hungary

ABSTRACT

Synaptic connections in the brain are continuously weakened or strengthened in response to changes in neuronal activity. This process, known as synaptic plasticity, is the cellular basis for learning and memory, and is thought to be altered in several neuronal disorders. An important aspect of synaptic plasticity is the tightly controlled trafficking and synaptic targeting of the AMPA-type glutamate receptors, which are the major mediators of fast excitatory transmission in the brain. This review addresses the role of Rab GTPases in AMPA receptor trafficking in neurons under basal conditions and during activity-induced synaptic plasticity, especially during long-term potentiation (LTP) and long-term depression (LTD). We highlight the importance of the tight spatio-temporal control of Rab activity and suggest that this is critical for proper neuronal functions. We also discuss how abnormal AMPA receptor trafficking and malfunctioning of Rabs can lead to neurologic disorders or memory problems.

Introduction

Overview on Rab proteins

Rab proteins are small monomeric GTPases forming the largest subgroup of the Ras superfamily. Originally, they were named as ras genes from rat brain but they are ubiquitously expressed in mammalian cells. Up to date almost 70 different Rab proteins have been identified in humans, playing a central role in the regulation of intracellular membrane traffic. A particular characteristic of Rab proteins is that they specifically mark different membranes and play critical role in ensuring the correct delivery of membrane-bound cargo from the donor to the acceptor compartment (for recent reviews, see refs. 2-4).

In general, Rab GTPases are molecular switches cycling between an inactive form bound to GDP and an active form bound to GTP (see Fig. 1 for an overview of the regulation of Rab activity). Rab proteins can associate with membranes due to the posttranslational covalent attachment of prenyl groups to their C-terminus. Once the prenylgeranylation of a Rab protein takes place, a GDP dissociation inhibitor (GDI) factor chaperones it within the cytosol. GDIs take part in the delivery of inactive, GDP-bound Rab proteins to specific membrane compartments through interactions with membrane-bound GDI displacement factors (GDFs). GDFs recognize GDI-Rab complexes specifically and promote GDI release, thereby facilitating the association of a particular Rab protein with its target membrane. The activation of the GDP-bound Rabs is mediated by guanine nucleotide exchange factors (GEFs), which catalyze the conversion from the GDP-bound to the GTP-bound form. In certain cases, membrane-bound GEFs can be sufficient to lead to the accumulation of Rab GTPases without the involvement of GDFs. Active, GTP-bound Rab proteins exert their function through their effector proteins, providing a diverse array of pathways (see below). As a negative regulator of Rab signaling, the intrinsic GTP hydrolysis of Rab proteins is enhanced by GTPase-activating proteins (GAPs) leading to Rab inactivation. Inactive, GDP-bound Rabs are then removed from their target membrane and kept soluble in the cytoplasm by GDIs (reviewed in refs. 5-7).

A diverse set of proteins serves as Rab effectors including motor proteins, kinases and phosphatases, tethering factors or sorting adaptors. There is increasing evidence that each Rab signals through a set of different effectors, allowing the compartment-specific coordination of vesicle transport, budding or fusion as well as...
We will discuss the role of Rab proteins and the life-cycle of Rab proteins. Inactive, GDP-bound Rab is recognized by the Rab–GDI complex and mediates the insertion of the Rab into the target membrane through its prenyl tails (red wavy lines) resulting in release of the GDI into the cytosol. The activation of GDP-bound Rab is mediated by the guanine nucleotide exchange factor (GEF), which mediates the exchange of GDP with GTP. Active, GTP-bound Rab exerts its function through its effector protein(s). Intrinsic GTP hydrolysis of Rab is enhanced by the GTPase-activating protein (GAP) leading to Rab inactivation. Subsequently, inactive, GDP-bound Rab is removed from the membrane and kept in the cytoplasm by GDI.

Receptor signaling. Generally, Rab5 allows entry into the early endosome, whereas Rab4 and Rab11 activate the machinery that is necessary for sorting and recycling membranes and receptors back to the plasma membrane. Rab7 specifically marks late endosomes containing cargo directed toward lysosomal degradation. Regarding secretory transport, Rab1 and Rab2 regulate vesicular traffic between the endoplasmic reticulum (ER) and the Golgi complex, and Rab8 is involved in transport processes from the trans-Golgi network (TGN) toward the plasma membrane (for detailed overview on general Rab activity see refs. 2, 3, 7-9).

**Rab proteins in neurons**

In neurons, elaborated axonal and dendritic branching generates an extreme surface to volume ratio and an enormous flux of membrane traffic, with a need of tightly controlled and activity-dependent delivery of vesicles toward specific membrane compartments. Up to date, approximately 20 Rab proteins have been identified to play important regulatory roles during normal neuronal functions, including axonal outgrowth, synaptic vesicle recycling, vesicular transport to and from the Golgi complex and postsynaptic functions (extensively reviewed in refs. 9-12; Table 1 summarizes data on Rab interactors identified in neuronal cells). So far, the role of only a few Rab proteins and their corresponding GEF, GAP or effectors have been identified during AMPAR vesicular trafficking (interactor proteins are highlighted together with their proven importance in AMPA receptor trafficking in Table 1). In this review we provide an overview on different trafficking routes of AMPAR and how these are coordinated by small GTPases of the Rab family. We also discuss how malfunctioning of Rabs and abnormal AMPAR trafficking can contribute to neurologic disorders or memory problems.

**AMPA receptors and neuronal plasticity**

In the central nervous system, most excitatory transmission is mediated by the AMPA-type ionotropic glutamate receptors (AMPARs). Upon binding glutamate that is released from the presynaptic terminals, AMPARs open and become permeable to Na\(^{+}\), K\(^{+}\) and – depending on the subunit composition – to Ca\(^{2+}\) ions, leading to membrane depolarization. The number and the properties of the available AMPARs at the postsynaptic membrane determine the extent of excitatory postsynaptic currents (EPSCs) formed within the dendritic spines. It is now widely accepted that the amount and composition of AMPA receptors within the postsynaptic density (PSD) of dendritic spines determine synaptic efficacy and affect the excitability of the neuron (reviewed in ref. 13).

AMPA receptors are tetrameric structures composed of 4 types of subunits, namely GluA1, GluA2, GluA3 and GluA4. The GluA1, GluA2, and GluA3 subunits are expressed during embryonic development, whereas the GluA4 subunit is mainly present in the late postnatal development and in adults. Most AMPARs in the brain contain the GluA2 subunit co-assembled with GluA1 or GluA3, while receptors with GluA4 subunit show a more restricted and developmentally regulated expression. The logistics of the delivery, retention and removal of individual AMPARs with defined subunit compositions at specific synapses is highly complex and fundamentally influences both Hebbian and homeostatic plasticity (reviewed in ref. 15). The most studied forms of Hebbian plasticity in the brain are long-term potentiation (LTP) and long-term depression (LTD), which lead to the long-lasting increase and decrease of synaptic strength, respectively. Homeostatic plasticity, however, regulates synaptic activity in a way to keep neuronal activity within a limited range to preserve the stability of neuronal circuits. These mechanisms depend on the number of AMPARs at synapses, which is determined according to the relative rates of exocytosis and endocytosis at the postsynaptic membrane. Although it is highly likely that similar molecular machinery is involved in regulating AMPAR trafficking during Hebbian and homeostatic plasticity, some aspects of AMPAR endocytosis clearly differ between events leading to homeostatic scaling or during LTD. We will discuss the role of Rab proteins during activity-dependent regulation of AMPAR trafficking only in relation to LTP and LTD as most of the available data deal with these events.
Table 1. Rab GTPase interactors in neuronal cells. Rab GTPase interactor proteins with a reported role in neurons are listed according to their GEF, GAP or effector functions and to their Rab GTPase partners. Major neuronal functions of these proteins are summarized according to literature data. Proteins with a proven role in AMPA receptor trafficking are highlighted in bold lettering.

| Protein | Rab GTPase | Neuronal function | Reference |
|---------|------------|-------------------|-----------|
| **GEF** |            |                   |           |
| RIN1    | Rab5       | - Increases endocytosis of EphA4 receptors  
|         |            | - Enhances GluA1 endocytosis during chemically induced LTD  
|         |            | - Lack of RIN1 leads to increased mEPSCs in cultured neurons and to enhanced amygdala fear conditioning  | 36,77-79 |
| ALS2    | Rab5       | - Endosomal transport of trophic receptors  | 82 |
| Rabex-5 | Rab5       | - Semaphorin3A-induced axon guidance during brain development  
|         | Rab17      | - Regulates neurite morphogenesis  | 83,84 |
| Rabin8  | Rab8, Rab10| - Promotes neurite outgrowth in NGF-treated PC12 cells  
|         |            | - Regulates spine development  | 85,86 |
| **GAP** |            |                   |           |
| TBC1D20 | Rab1b/Rab2a| - Essential for neuronal autophagic flux and adult-onset motor function  | 87 |
| TBC-8   | Rab2       | - Required for DCV maturation  | 88 |
| TBC-2   | Rab5       | - Separation of Rab5 and Rab10 domains at the Golgi-endosomal interface, required for DCV secretion  | 89 |
| TBC-4   | Rab10      | - Separation of Rab5 and Rab10 domains at the Golgi-endosomal interface, required for DCV secretion  | 90 |
| TBC1d15 | Rab7       | - Required for normal presynaptic growth and postsynaptic organization at the neuromuscular junction.  
|         |            | - Regulates levels of the postsynaptic glutamate subunit GluRIIA  | 91 |
| Skywalker| Rab35      | - Controls endosomal trafficking of synaptic vesicles at Drosophila neuromuscular junction boutons  | 91 |
| **Effector protein** |            |                   |           |
| RIC-19/ICA69 | Rab2    | - Dense core vesicle maturation  | 92 |
| Rim     | Rab3a      | - Regulator of synaptic-vesicle fusion  | 93 |
| Rabphilin3A | Rab3a | - Dense core vesicle secretion  | 94 |
| GRASP-1 | Rab4       | - Necessary for AMPA receptor recycling, maintenance of spine morphology and synaptic plasticity  
|         |            | - Coordinates the coupling of Rab4 to Rab11-positive recycling endosomes  | 39 |
| Huntingtin/HAP40 | Rab5 | - Regulates endosome motility and endocytic activity  | 95 |
| FHF     | Rab5       | - Contributes to neuronal polarity through dynein-dependent retrieval of somatodendritic proteins e.g. AMPA receptors from the axon  | 96 |
| APPL1   | Rab5       | - Mediates Rab5 overactivation in Down Syndrome and AD through interaction with /CCTF  | 68 |
| BICDR-1 | Rab6       | - Restricts secretory trafficking to inhibit neuritogenesis  | 97 |
| COH1    | Rab6       | - Required for neurite outgrowth  | 98 |
| Optineurin | Rab8    | - Binds to huntingtin protein and attenuates mGluR1a G-protein coupling  
|         |            | - Inhibits receptor endocytosis  
|         |            | - Controls post-Golgi trafficking  | 32,33 |
| JIP1    | Rab10      | - Couples Rab10-positive vesicles to kinesin-1 light chain required for anterograde axonal transport  | 99 |

(continued on next page)
| Protein         | Rab GTPase | Neuronal function                                                                 | Reference |
|-----------------|------------|-----------------------------------------------------------------------------------|-----------|
| MARCKS          | Rab10      | Mediating membrane targeting of plasmalemmal precursor vesicles during axon development | 100       |
| Rab11-Fip5      | Rab11      | Required for hippocampal LTD                                                        | 8         |
| MyoVb           | Rab11      | Required for BDNF/TrkB-induced dendritic branching                                 | 101       |
| Rab11-Fip3      | Rab11      | Controls BDNF – mediated TrkB trafficking                                            | 102,103   |
|                 |            | Regulation of dendritic formation and arborization                                  |           |
| RCP             | Rab11      | Trafficking of β1-integrin during axonal growth                                      | 104       |
| SH3TC2          | Rab11      | Involved in Schwann cell myelination                                                | 105       |
| Rabaptin-5      | Rab22, Rab5 | Required for NGF-induced neurite outgrowth                                          | 93, 84    |
|                 |            | Semaphorin3A-induced axon guidance during brain development                         |           |
| Rabphilin and Noc2 | Rab27A | Involved in neuropeptide Y secretion                                                | 106       |
| ACAP2/centaurin-γ2 | Rab35 | NGF-induced neurite outgrowth                                                       | 107       |
| PICK1           | Rab39B     | Controls surface expression of GluA2 at the ER-Golgi interface                     | 23        |
Rab proteins regulating AMPAR trafficking under basal conditions

Already in the ER, AMPA receptors assemble as dimers, which then form heterotetrameric structures leaving the ER. The assembly of the tetramer and the exit from the ER is controlled by a RNA editing step in the GluA2 subunit: the Q/R editing in the pore loop blocks tetrameric assembly and retains the GluA2 protein at the ER whereas the unedited subunits immediately assemble and traffic to their postsynaptic target via the Golgi complex (Fig. 2A, enlarged neuronal soma). On the other
hand, GluA1, which lacks the ER retention motif found in GluA2, is rapidly exported from the ER. The RNA editing also contributes to the functionality of the receptors because Q/R edited GluA2 subunits are impermeable to Ca\(^{2+}\) ions (reviewed in ref. 18).

AMPAR receptor trafficking from the neuronal cell body to the synapse is also controlled by other mechanisms such as interaction with auxiliary proteins including the stargazing/transmembrane AMPAR regulatory proteins (TARPs)\(^{19}\) or the cornichon family.\(^{20}\) The length and phosphorylation of the intracellular C-terminal domains of AMPA receptors have been considered as further critical determinants of trafficking. Long-tailed AMPAR subunits (GluA1 and GluA4) were reported to rapidly proceed from the ER to the synapse whereas the short-tailed subunits (GluA2 and GluA3) are trafficked more slowly. Recent data, however, questioned the importance of the C-terminal tail, especially during the regulation of the GluA1 transport (reviewed in ref. 13; see also refs. 21, 22). Among Rab proteins, so far only Rab39B has been identified to regulate AMPAR exit from the ER toward the Golgi complex\(^{23}\) (see Table 1). Rab39B localizes to the Golgi and interacts with protein interacting with C-kinase 1 (PICK1), which is necessary for GluA2 transport from the ER to Golgi compartment by selectively binding GluA2/GluA3 heterodimers. Silencing of Rab39B in hippocampal neurons leads to a decrease in surface GluA2 density and an increase in Ca\(^{2+}\) ion permeable GluA1 AMPAR subunits, elevating miniature EPSC amplitudes. Importantly, Rab39B is not involved in activity-dependent AMPAR recycling and endocytosis as Rab39B knock down did not influence LTD.

Surface AMPA receptors can be delivered to the plasma membrane along different trafficking pathways, such as the de novo exocytotic pathway originating from the Golgi apparatus and from recycling pathways involving early and recycling endosomes. Under basal conditions, AMPARs are known to shuttle between internal and surface compartments, with a steady-state of continuous exocytosis and endocytosis\(^{24-26}\) (see the enlarged spines in Fig. 2B). Golgi outposts located in dendritic branch points as well as local protein synthesis from mRNA can also participate in the de novo exocytotic pathway (reviewed by ref. 27). Interestingly, local protein synthesis is primarily involved during long-term changes in activity, leading to homeostatic scaling.\(^{23}\)

AMPAR delivery to the plasma membrane from the trans-Golgi network (TGN) or from the Golgi outposts located within the dendritic shaft is regulated principally by Rab8.\(^{28,29}\) Although mainly trans-Golgi network (TGN)-localized, Rab8 is also found in close proximity to the postsynaptic plasma membrane and the postsynaptic density\(^{29}\) and has been indicated to direct the Golgi to plasma membrane delivery of AMPARs during de novo exocytotic pathway under basal conditions\(^{25}\) as well as during activity-dependent stimuli.\(^{28}\) Although real-time observations promote the findings that AMPARs are inserted extrasynaptically to the plasma membrane, followed by lateral diffusion to the postsynaptic regions, some work has shown a direct insertion of AMPARs through Rab8-mediated transport within the spines.\(^{28,30}\) Rabin8 has been described as a Rab8 GEF\(^{31}\) and optineurin as a Rab8 effector\(^{32,33}\) in neuronal cells, but so far neither of them has been investigated in relation to AMPAR trafficking.

The recycling pathway of GluA subunit turnover is regulated by a tight, spatially and temporally controlled balance between the rapid internalization of AMPARs associating with the early endosomes and the delivery of AMPARs from the recycling endosomes toward the plasma membrane (depicted within the dendritic shaft of

**Figure 2.** (see previous page) Rab proteins regulating intracellular trafficking of AMPA receptors (AMPARs) in neurons during basal conditions and synaptic plasticity. (A) Enlarged neuronal soma summarizes neuron-specific, Rab-mediated actions in relation to different trafficking steps (see text for details). (B-D) enlarged spines depict Rab-dependent events in the basal state (B), during long-term potentiation (LTP; C) or long-term depression (LTD; D). (B) In the basal state, de novo transport from the Golgi or from the Golgi outposts take place through Rab8-associated exocytotic vesicles (designated as E). Exocytosis occurs at the extrasynaptic membrane, mostly at the dendritic shaft, although some data suggest direct delivery of AMPARs to the perisynaptic membrane (dashed arrow). Extrasynaptic AMPARs diffuse laterally toward the synaptic membrane where they get immobilized within the PSD. Clathrin-mediated endocytosis of AMPARs into Rab5-positive early endosomes (indicated by EE) occurs at the endocytotic zone, located perisynaptically or within the dendritic shaft. Clathrin-independent and Rab10-regulated endocytosis of AMPAR-type subunits from lipid rafts was reported in C. elegans neurons, as well. Besides de novo trafficking, continuous recycling directly from Rab4-positive endosomes or through Rab11-associated recycling endosomes (designated as RE) provides the supply for synaptic AMPARs inside the spines as well as within the shafts (depicted in details only inside the spine heads). (C) upon LTP, the amount of synaptic AMPARs is increased by upregulating de novo trafficking toward the plasma membrane and lateral diffusion of newly inserted AMPARs (indicated by thicker arrows). During activity-dependent recycling, the endosomal compartment is increased in size and recycling through Rab11-positive recycling endosomes is elevated. The role of Rab4-dependent delivery to the membrane has yet to be proven during LTP. It is yet unclear how Rab5-dependent endocytosis is changed during LTP. (D) in case of LTD, the loss of synaptic AMPARs is due to increased Rab5-dependent endocytosis. Rab11-positive recycling is reduced, and a large portion of the endocytosed AMPARs is directed to the Rab7-associated late endosome system and toward lysosomal degradation. During this time, Rab11-dependent recycling is still ongoing.
the enlarged spine regions in Fig. 2). Endocytotic removal of AMPARs occurs at the extrasynaptic membrane within the shaft, or at the perisynaptic endocytotic zone within the spines. During clathrin-mediated internalization, Rab5 regulates uncoating and directs internalized AMPARs toward early endosomes. In C. elegans neurons, there is an additional, clathrin-independent endocytosis of the GLR-1 AMPAR-type subunit. This Rab5-independent endocytosis is mediated by lipid rafts, and AMPARs endocytosed through this mechanism are recycled by Rab10.

While a role for Rab10 in AMPAR recycling in mammalian neurons remains unclear, the closely related Rab4, as well as Rab11, mediate continuous recycling of endocytosed AMPARs from sorting and recycling endosomes, respectively, during normal conditions. Rab4-positive compartments play critical role in spine maintenance during normal conditions. GRASP-1, a Rab4 effector has been implicated to mediate the fusion between Rab4 and Rab11 positive endosomes via syntaxin 13 bridging. Knockdown or overexpression of GRASP-1 perturbs normal spine morphology and leads to abnormal endosomal functions. Rab11 selectively labels recycling endosomes and has been shown to regulate the continuous recycling of previously endocytosed GluA1 subunits to the postsynaptic membrane via frequent entry to and exit from the spines depending on myosin Vb-directed transport. Rab11 is not solely responsible for targeting recycled AMPARs back to the plasma membrane, as internalized GluA2 subunits can return to the surface directly from the Rab4 positive compartments, as well. Increase in the surface amount of AMPARs during corticosterone-induced acute stress also depends on the Rab4-mediated delivery of the AMPARs, regulated by the phosphorylation of its GD1. Somewhat contradictory to these data, earlier studies analyzing GluA1 delivery showed that neither dominant-negative Rab4S22N nor Rab11S25N altered AMPAR-mediated basal synaptic transmission, although Rab4-dependent membrane trafficking was critical for spine size maintenance during normal conditions.

During normal conditions, most of the endocytosed AMPARs return back to the synaptic membrane and therefore transport to the Rab7-labeled late endosomes and toward lysosomal degradation is not a common phenomenon. In accordance with this, dominant-negative Rab4N125S did not cause significant differences in the amount of surface AMPARs in hippocampal slices. A special way of recycling has been described in C. elegans neurons: the retromer complex sequesters GLR-1 AMPARs into endosomal tubules, where RAB-6.1 and RAB-6.2 regulate the trafficking of the cargo vesicles back to the Golgi or to dendritic Golgi outposts (depicted as Rab6 on Fig. 2). Subsequently, cargo is transported back to the plasma membrane. In case of rat hippocampal neurons, Golgi-associated dominant-negative Rab6T22N did not grossly alter glycine-evoked AMPAR insertion to the plasma membrane suggesting that the retrograde transport is negligible under these conditions. Very recently, a function for the retromer complex in AMPAR trafficking was also confirmed in mammalian neurons. Here, Temkin and colleagues showed that retromer function is required for exocytosis of AMPAR during LTP but not for basal synaptic transmission in mature hippocampal neurons. Whether Rab6 is required for AMPAR trafficking under these conditions, however, still needs to be addressed.

**Rab proteins regulating AMPAR trafficking under LTP**

Long-term potentiation is accompanied by a rapid increase in the amount of surface AMPARs within the postsynaptic membrane, which confers increased synaptic strength. Increased mobility and lateral diffusion of extrasynaptic AMPARs provide an important supply for newly inserted synaptic AMPARs. Additionally, exocytosis from recycling endosomes and/or from the Golgi complex increased AMPAR insertion into the synaptic membrane within minutes. These events are regulated at different levels, including interaction with scaffold proteins and molecular motors, formation of the exocyst complex and regulated release from endosomal compartments (reviewed in more detail by refs. 53-55).

Elevated de novo transport of AMPAR subunit (see the thickened arrows on the enlarged spine in Fig. 2C) requires proper Rab8 functioning, as dominant-negative Rab8T22N selectively impairs AMPA receptor currents and abolishes LTP in hippocampal slices. Interestingly, Rab8T22N highly elevates the relative amount of GluA1 in spines compared with the dendritic shaft following the expression of constitutively active CaMKII, implicating phosphorylation-dependent regulation of Rab8 functions. LTP is accompanied by structural changes, including expansion of the spine head and enlargement of the endocytotic compartment. It seems that Rab4-associated sorting endosomes are not primarily involved in activity-induced recycling of AMPAR subunits during LTP, as dominant-negative Rab4T22N only slightly reduced EPSC amplitudes in organotypic hippocampal slice cultures. Despite the lack of a proven role in LTP, dominant negative Rab4 regulates synaptic efficacy under stress conditions. It is known that acute stress
increases AMPAR-mediated synaptic transmission and surface positioning in pyramidal neurons. Corticosterone activates serum- and glucocorticoid-inducible kinase (SGK), which phosphorylates GDI1, regulating the cycling of Rab proteins between membranes and cytosol.\textsuperscript{45} Thus, in the prefrontal cortex, corticosterone stimulates the formation of the GDI1/Rab4 complex via SGK1-mediated phosphorylation of GDI1, which facilitates Rab4-dependent AMPAR delivery to the surface and potentiates synaptic transmission.\textsuperscript{45,46}

In the case of Rab11, it is widely accepted that its association with recycling endosomes facilitates the delivery of previously endocytosed AMPARs back to the synaptic membrane,\textsuperscript{44} interacting with myosin Vb and the endosomal adaptor Rab11-FIP2 upon glycine-induced LTP.\textsuperscript{43} Accordingly, dominant-negative Rab11 inhibits the elevation in synaptic AMPARs induced by cholesterol depletion or during chemically induced LTP,\textsuperscript{44,56} depletes mobile AMPARs at synapses\textsuperscript{57} and blocks LTP formation.\textsuperscript{58,44} Interestingly, overexpression of wild-type Rab11 leads to robust glycine-induced AMPAR insertion\textsuperscript{44} while short-term removal or addition of Rab11 recycling endosomes from spines does not impair spine expansion during chemically induced LTP in hippocampal neurons.\textsuperscript{41}

Although dominant-negative Rab5\textsuperscript{S34N} does not influence LTP formation in organotypic cultures,\textsuperscript{28} it is highly likely that Rab5-mediated endocytosis takes place during LTP. Chemical LTP (cLTP) was shown to increase the synaptic delivery of Ca\textsuperscript{2+}-permeable AMPARs selectively and within minutes, which is followed by a subsequent exchange to Ca\textsuperscript{2+}-impermeable AMPARs.\textsuperscript{58} Although Rab5-mediated endocytosis was not investigated directly, selective removal of GluA2-free AMPARs during the consolidation phase of cLTP is most probably mediated by Rab5-dependent endocytosis. Importantly, selective retention of GluA2-containing AMPARs during the early phase of LTP is mediated by their association to PICK1 in the endosomal compartments. Upon elevated intracellular Ca\textsuperscript{2+} ion levels PICK1 is phosphorylated and released from the membrane allowing GluA2 containing AMPARs to insert into the synaptic membrane.\textsuperscript{58,59} Another study, however, showed that PICK1 is not necessary for maintenance of the basal synaptic complement of AMPARs or NMDAR-dependent LTP. Instead, PICK1 function in AMPAR trafficking seems to be specific to NMDAR-dependent LTD.\textsuperscript{60} Whether the PICK1-dependent GluA2 retention is of physiological relevance for LTP thus requires further investigation.

So far, we are not aware of any data showing a contribution of Rab7-mediated lysosomal degradation of AMPARs in LTP. However, we assume that basal protein turnover of AMPARs takes place also during LTP, albeit it might not be important for the strengthening of the synapse.

### Rab proteins regulating AMPAR trafficking under LTD

During LTD formation (see the enlarged spine in Fig. 2D), synaptic efficacy is reduced due to the loss of synaptic AMPARs, which is often accompanied by structural changes inside the spines, leading to shrinkage (reviewed in more detail in ref. 13). During this process, synaptic AMPARs are taken back by Rab5-dependent endocytosis, leading to the formation of Rab5-positive early endosomes containing ex-synaptic AMPARs.\textsuperscript{35,61} Rab5 activity is a key mediator of AMPAR endocytosis and LTD formation, as blocking Rab5 function by infusing anti-Rab5 antibody or expressing dominant-negative Rab5\textsuperscript{S53N} inhibited serotonin-facilitated LTD formation in the prefrontal cortex. In line with these findings, constitutively active Rab5\textsuperscript{Q79L} caused a gradual depression of mEPSC amplitude, indicating increased endocytic activity.\textsuperscript{62} The surface level of AMPARs and its downregulation during chemically evoked LTD in cultured hippocampal neurons was shown to be dependent on the intact Rab5 effector functions of Ras and Rab interactor protein 1 (RIN1), as well.\textsuperscript{36}

Internalized AMPARs are sorted along the recycling or retention pathways, according to neuronal activity.\textsuperscript{48,61} Blockade of Rab7-dependent trafficking by the dominant-negative Rab7\textsuperscript{N123I} produced a significant reduction in the extent of LTD,\textsuperscript{47} indicating that Rab7-driven trafficking of AMPARs to lysosomes is important during LTD. Blocking the transport of AMPARs from the recycling endosomes to the postsynaptic membrane by the dominant negative Rab11\textsuperscript{S25N} produced a significant increase in LTD, indicating that a certain amount of internalized AMPARs upon LTD induction recycles back toward the synaptic membrane.\textsuperscript{47} This is in accordance with previously published data, where vesicles containing AMPARs from the cell surface colocalize with TfR (transferrin receptor) or Rab4,\textsuperscript{61} highlighting the importance of the recycling pathways even during LTD formation. Rab8, finally, has not been mentioned so far in relation to the development and formation of LTD.

### Improper regulation of Rab activity and AMPA receptor trafficking in neuronal disorders

AMPA receptor dysfunction has been reported in a couple of neuronal disorders, with Alzheimer disease (AD) representing the best studied disease so far. Here, amyloid β (Aβ) treatment of neurons induces a...
reduction of AMPA receptor surface expression through increased endocytosis. Accordingly, Aβ treatment facilitates hippocampal LTD and impairs synaptic plasticity and memory. Some of the earliest neuronal responses in AD are endosomal abnormalities which are associated with an upregulation of Rab5 expression, which most likely results in enhanced endocytosis. Furthermore, enhanced Rab7 levels might promote lysosomal degradation of AMPA receptors. So far the molecular mechanisms leading to pathological Rab5 activity have not been well understood. A recent study suggested that elevated levels of βCTF induce APPL1-mediated Rab5 activation on endosomes in AD, a process that is independent from Aβ. How Aβ disturbs endocytic signaling thus still awaits investigation.

In the past years, malfunctioning of Rab GTPases and their regulators and effectors has also been implicated in several neurodegenerative and neurodevelopmental disorders. For example, mutations in the Rab5 GEF ALS2 are associated with amyotrophic lateral sclerosis, missense mutations in Rab7 cause the Charcot-Marie-Tooth type 2B disease, whereas Rab8 has been linked to Huntington’s disease through its effector optineurin. Here, mutant huntingtin disrupts the Rab8-optineurin complex resulting in an overall deficit in post-Golgi trafficking. Furthermore, nonsense or missense mutations of the X-chromosome localized RAB39B resulted in X-linked intellectual disability and early onset Parkinson disease in affected males. Although it is likely that alteration of Rab GTPase activity cause the deregulated AMPA receptor trafficking that contributes to these diseases, substantial evidence for this is still missing. In a recent paper, we have shown that the Rab5 GEF RIN1 enhances GluA1 endocytosis due to its Rab5 GEF activity and plays a critical role in AMPAR internalization upon LTD. RIN1 is highly expressed within the dendrites of hippocampal neurons and regulates EphA4 receptor internalization. Importantly, RIN1−/− mice have deficits in fear learning and extinction and were proposed as a potential model for posttraumatic stress disorder, characterized by enhanced retention of fear-related memories. Thus, the lack of RIN1 leads to increased amount of AMPARs at the plasma membrane, which cannot be downregulated upon NMDA-dependent cLTD. Because AMPAR downregulation is required during fear extinction in the amygdala, one interesting possibility is that prolonged fear memory of RIN1−/− mice as well as their inability to forget aversive memories are due to the increased surface level of AMPARs and the inability to downregulate their levels during LTD and fear extinction through Rab5-dependent endocytosis.

Summary and conclusion

Taken together, in the past years several members of the RabGTPase family have been shown to control the trafficking of AMPA receptors under basal and activity-dependent conditions. Because of partially redundant functions within the Rab subfamilies, it can be assumed that even more RabGTPases contribute to exo- and endocytosis of AMPA receptors. While it is intuitively clear that Rab GTPases must be tightly regulated in a spatial and temporal manner to ensure proper trafficking of AMPA receptors and hence synaptic plasticity, the identification of the responsible GEFs and GAPs is still in its infancy. Similarly, only a few Rab effector proteins involved in AMPA receptor trafficking have been characterized so far. Rab effectors are very heterogeneous, and each Rab isofrom has many effectors through which it carries out multiple functions, making their identification still challenging. Similarly, several GAPs and GEFs control the activity of a single Rab isofrom. Large interactions screens are required to provide more detailed information on the interaction network of RabGTPases in the orchestration of AMPA receptor trafficking under normal and pathological conditions.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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ORCID

Angelika Hauser [http://orcid.org/0000-0002-4102-9286] Katalin Schlett [http://orcid.org/0000-0001-9265-4236]

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