Chapter 17
Principles Driving the Spatial Organization of Rho GTPase Signaling at Synapses

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Abstract The Rho proteins play critical roles in numerous aspects of neuronal development, and mutations in their regulators (GEFs and GAPs) and effectors underlie multiple neurodevelopmental and neurological disorders. How Rho GTPase-mediated signaling can have a hand in regulating so many different neurobiological processes remains a challenging question. An emerging theme is that GAPs and GEFs, through their spatial/temporal regulation and/or through additional protein–protein interactions, cooperate in making connections between upstream signals and the downstream signaling output, engaging distinct effector proteins. This chapter focuses on recent evidence illustrating distinct modes of regulation and specialized roles of Rho regulators particularly in the context of synaptic structure, function, and plasticity, and how their dysregulation affects behavioral processes and contributes to disease.

Keywords Rho regulators • Rho effectors • Neuronal development • Synaptic structure and function • Brain disorders

17.1 Introduction

Rho-family GTPases (typified by Rho, Rac, and Cdc42) are a branch of the Ras superfamily of small G-proteins, consisting of 22 different Rho GTPases. They function as intracellular molecular switches that, among other functions, rapidly activate actin polymerization and reorganization in vivo (Van Aelst and D'Souza-

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A. Wittinghofer (ed.), *Ras Superfamily Small G Proteins: Biology and Mechanisms 1*,
DOI 10.1007/978-3-7091-1806-1_17,

Schorey 1997; Hall 2012). Rho-family GTPases are active when bound to GTP, which induces a conformational alteration that realigns two surface regions, known as switch one and two regions (Abdul-Manan et al. 1999). Upon realignment, the switch regions bind to and modulate the activity of a wide variety of downstream effectors, including kinases and regulators of actin polymerization (Bishop and Hall 2000). Activation of Rho GTPases is mediated by Guanine Nucleotide Exchange Factors (GEFs), while inactivation is accelerated by GTPase Activating Proteins (GAPs) (Cook et al. 2013; Bos et al. 2007; Cherfils and Zeghouf 2013).

The birth of the Rho-family GTPase field was the discovery of Rho (*R*as *ho*molog) (Madaule and Axel 1985), the founding member of the Rho family. Interestingly, Rho was first identified from the sea slug Aplasia, using a low stringency screen for homologs of the alpha subunit of human chorionic gonadotropin (hCG). The resulting cDNA clone however showed no significant similarity to hCG but to Ras and was evolutionally conserved in humans, distinguishing it as a new branch of the Ras superfamily of GTPases. It was subsequently shown in the 1990s by Alan Hall's laboratory to potently regulate actin formation in cells (Paterson et al. 1990). These seminal observations drove the formation of a new field of study, which rapidly expanded, and has shown that the breadth of cellular functions regulated by Rho-family GTPase activity is truly remarkable.

Almost 1 % of human proteins are either regulators or effectors for the 22 different Rho GTPases (Jaffe and Hall 2005). Consistent with the wide variety of interaction partners, the regulation of Rho-family GTPase signaling pathways drive many key functions of developing and mature neural networks, including polarization, axonal guidance, dendritic arborization, intracellular trafficking, migration, and synapse formation and plasticity (Govek et al. 2005; Luo 2000; Tolias et al. 2011; Tahirovic and Bradke 2009; Guan and Rao 2003; Hall and Lalli 2010; Saneyoshi et al. 2008; Lai and Ip 2013; Colgan and Yasuda 2013). The dysregulation of Rho-family GTPase pathways are also associated with some of the most enigmatic neuropsychiatric disorders, including intellectual disability, schizophrenia, and autism (Newey et al. 2005; Tolias et al. 2011; van Galen and Ramakers 2005; van Bokhoven 2011; Boda et al. 2010; DeGeer and Lamarche-Vane 2013; Nadif Kasri and Van Aelst 2008).

Yet the discoveries that the Rho GTPases occupy a central role in so many different neurobiological functions have also led to several conundrums. For example, how can specificity be achieved downstream of the activation of Rho, Rac, or Cdc42 when they seemingly have a role in so many cell functions? This problem is exemplified by one of the remarkable features of the Rho-family GTPases, which is their ability to interact with many different regulators and effectors. For example, Rac activity is regulated by several different GEFs or GAPs, many of which are co-expressed in the same cell. Furthermore, once activated, Rac can bind to and modulate the activity of an even larger number of different downstream effectors.

The large excess of regulators and effectors when compared to Rho GTPases means that individual GTPases do not function as simple binary switches. Rather, they behave as signaling multiplexers that can pair a given upstream cue with a

specific cellular effector. The most important unanswered question in the field is how a GTPase achieves specificity when faced with such a large diversity of potential interactions? Assembling the correct complement of regulators and effectors to fulfill specific neuronal functions is a major challenge in the field. Here we review literature to propose that specificity of neuronal Rho GTPase functions is achieved by three general mechanisms: (1) *Input Targeting*—interactions between GAPs and GEFs with receptors; (2) *Signaling Clustering* by scaffolding and linker proteins; and (3) *Effector Clustering*—linking GAPs and GEFs to downstream Rho GTPase targets. For space considerations we primarily focus on examples of these mechanisms that operate to regulate the functions of synapses. However these mechanisms are also used to drive many other important tasks, including neural migration and axonal outgrowth and guidance.

17.2 Input Targeting

Initial responses to external stimuli are transduced by the initial engagement of neuronal transmembrane receptors, resulting in the rapid organization of adhesion, trans-synaptic morphogenesis, and electrical responses to neurotransmitters. Thus, an efficient mechanism to integrate specific responses to ligand binding is to physically couple signaling molecules to receptors, ensuring the spatial and temporal specificity between the initiation and propagation of synaptic signals. Recent studies have uncovered several mechanisms by which GEFs and GAPs for Rho GTPases are specifically tethered to receptors, and in many cases regulated by neuronal receptor activity (Fig. 17.1a). These studies reveal that receptor binding is an important mechanism to specify the timing of synapse development as well as distinguish between excitatory versus inhibitory synapses.

17.2.1 Bidirectional Regulation of Excitatory Synapse Formation by Eph Receptor and GEF Complexes

Eph receptors represent a large class of receptor tyrosine kinases that are classified as either EphA or EphB receptors by their preference for a certain type of ephrin ligands (Lai and Ip 2009). EphR-ephrin interactions are critical for excitatory synaptogenesis, a process that must be regulated to allow for coordinated pre- and postsynaptic specialization at the correct time and place during development (Sheffler-Collins and Dalva 2012; Hruska and Dalva 2012). The molecular mechanisms by which EphB receptors regulate postsynaptic development have been elucidated by several studies, which highlight a central role for receptor tethering of Rho-family GEFs. Surprisingly, differential GEF anchoring to these receptors is important for both the inhibition and promotion of dendritic spine formation. Thus,

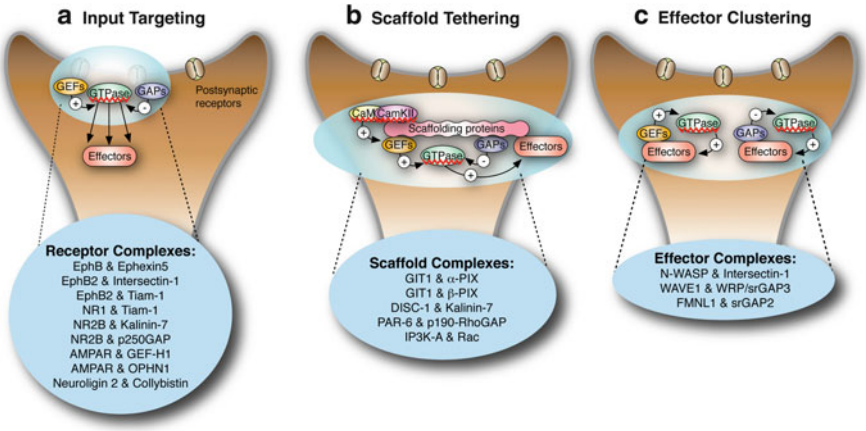

Fig. 17.1 Schematic of the organizational principles directing Rho-family GTPase signaling at synapses. Three different mechanisms to organize Rho-family GTPase-based signaling complexes are shown. In each panel the postsynaptic dendritic spine is shown with different schematics of signaling complexes. Note that some complexes exist within inhibitory synapses (i.e., Neuroligin 2 and Collybisitin) rather than excitatory spines. (**a**) Input targeting representing protein–protein complexes of Rho-family GTPase regulators (GEFs and GAPs) with different receptors present at synapses. (**b**) Scaffold tethering representing the formation of complexes of GEFs or GAPs along with downstream Rho-family effector proteins within a single protein complex. Note scaffolding proteins such as GIT1 also incorporate regulators of GEFs and GAPs such as kinases to these protein complexes. (**c**) Effector clustering occurs when GAPs or GEFs are in physical complex with Rho-family GTPase effectors. This can allow for specific pairing of GTPase regulators to individual downstream targets. Specific examples of protein interactions representing each mode of signaling regulation are shown below

it appears the sequential recruitment of different GEFs to EphB receptors coordinate the developmental timing of synapse development.

Early in dendritic development, before the initiation of spinogenesis, EphB receptors are present but are likely to remain unbound to ephrins until a presynaptic bouton makes contact. In this pre-synaptogenesis state, EphB receptors are in complex with the GEF ephexin-5 (E5) (Margolis et al. 2010). E5 functions to specifically activate RhoA. Active RhoA inhibits dendritic spine formation (Luo 2000; Nakayama et al. 2000; Tashiro et al. 2000). Mice lacking E5 have significantly reduced levels of activated RhoA, indicating it is a major regulator of neuronal RhoA in vivo. E5 knockout mice exhibit elevated numbers of excitatory synapses, indicating that the GEF activity of E5 limits synaptogenesis. Importantly, EphB receptor activation by ephrin binding (which promotes spine formation) initiates the tyrosine phosphorylation of E5, triggering its recognition as a substrate by the ubiquitin ligase Ube3a. Ube3a-mediated ubiquination leads to proteasomal degradation and loss of E5, alleviating the E5-activated RhoA brake on synaptogenesis. Loss of Ube3a is the primary cause of Angelman's Syndrome (Kishino et al. 1997; Matsuura et al. 1997), suggesting that altered regulation of E5 levels may contribute to the synaptic abnormalities in these syndromes.

Consistent with this possibility, Ube3a mutant mice, a model for Angelman's syndrome, have elevated levels of E5 (Margolis et al. 2010).

GEF-EphB interactions, however, orchestrate not only the RhoA inhibition of synaptogenesis but also the subsequent promotion of synaptogenesis (Irie and Yamaguchi 2002). EphB2 ligand binding potently stimulates Cdc42 activation in neurons in a time course that corresponds with EphB2 auto-phosphorylation, suggesting that activation of EphB2 is closely linked to Cdc42 activation. Co-immunoprecipitation analysis demonstrated that EphB2 activates Cdc42 by binding to the N-terminal region of Intersectin-1, which is a brain enriched Cdc42 GEF (Irie and Yamaguchi 2002; Thomas et al. 2009). Intersectin-1 has very low basal activity, which is stimulated upon its binding to EphB2. Importantly, Cdc42 activity is critical for the maturation of spines, in part by activating the Cdc42 effector protein N-WASP. N-WASP is a member of larger family of proteins (including WAVE1) whose activation stimulates Arp2/3-dependent polymerization of branched actin filaments that are required for spine head development during the transition from dendritic filopodia to spines (Wegner et al. 2008; Hotulainen et al. 2009). As discussed in the effector clustering section, Intersectin-1 interacts with N-WASP as well (Hussain et al. 2001), suggesting a model of tight spatial and temporal regulation of Cdc42 activation and effector binding within an EphB2 complex. Interestingly, activation of EphB2 also triggers the recruitment of the Rac GEF Tiam-1 to sites of new synaptic contacts, resulting in the phosphorylation of Tiam-1 and subsequent activation of Rac, the latter being important for spine formation (Tolias et al. 2011). Thus Rac and Cdc42 activities downstream of EphB2 are likely to cooperate to facilitate spine formation.

17.2.2 Focal Regulation of Rac by NMDA Receptor Tethering of GEFs and GAPs

Upon maturation, excitatory postsynaptic spines contain a protein-rich postsynaptic density (PSD) containing arrays of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)- and *N*-methyl-D-aspartate (NMDA)-type glutamate receptors. These receptors organize signaling complexes of Rho-family GTPase regulatory proteins and are anchored within the PSD by several associated actin cytoskeletal proteins (Tada and Sheng 2006; Newpher and Ehlers 2009).

NMDA receptors (NMDARs) are tetramers predominately composed of NR1 and NR2 subunits. Their synaptic activity-dependent activation produces modification of synaptic AMPARs and forms the basis of the well-established LTP (long-term potentiation) and LTD (long-term depression) forms of synaptic plasticity (Sudhof and Malenka 2008; Kessels and Malinow 2009; Huganir and Nicoll 2013). NMDARs mediate calcium influx into the spine and are required for Rho-family GTPase activation and actin polymerization during spine structural plasticity associated with LTP (Govek et al. 2005; Cingolani and Goda 2008; Tolias et al. 2011;

Kiraly et al. 2010a; Carlisle and Kennedy 2005). One mechanism driving this is the specific association between the aforementioned Rac GEF Tiam-1 and the NR1 NMDAR subunit (Tolias et al. 2005). Activation of NR1 induces the rapid phosphorylation and activation of Tiam-1, presumably by calcium activation of CaMKII. Tiam-1 activation of Rac mediates the induction of dendritic arborization and spine development downstream of NR1 activity. The importance of Tiam-1 tethering to NR1 could be to facilitate its phosphorylation by CaMKII, which binds to the NR2B subunit and is thereby locked in an active conformation (Bayer et al. 2001; Sanhueza et al. 2011). Localization of Tiam-1 to NR1 may also bias its activation by placing it within NMDAR local calcium micro-domains in the spine. In this way, Tiam-1 can be positioned for the rapid phosphorylation by NMDA-mediated CaMKII activation. As Tiam-1 forms also a stable interaction with EphB2, it is noteworthy that EphB2 is important for NMDAR clustering and function (Dalva et al. 2000; Takasu et al. 2002), thus placing Tiam-1 as a bridge between these receptors.

NMDARs are also anchored within the postsynaptic density to actin by the actin binding and crosslinking protein, α-actinin-2 (Wyszynski et al. 1997). Activity-dependent rundown of NMDAR current is enhanced by destabilizing actin and is blocked by stabilizing actin filaments, suggesting that tethering of NMDAR to the actin cytoskeleton reduces its synaptic turnover (Rosenmund and Westbrook 1993). Kalirin-7 is a PSD enriched Rac-specific GEF. It plays a role in spine development and structural and functional plasticity (Penzes and Jones 2008) and stabilizes the NMDAR through a specific interaction with the juxtamembrane region of the NR2B subunit (Kiraly et al. 2011). It is thought that this binding may be competitive with an AP2-binding site on NR2B that is important for stimulating NMDAR endocytosis. Indeed, Kalirin-7 knockout mice have reduced levels of synaptic NR2B, supporting the notion that it normally stabilizes the receptor at the synapse. Importantly, Kalirin-7- and NR2B-deficient mice exhibit overlapping behavioral phenotypes, including a deficit in conditioned place preference for cocaine (Lemtiri-Chlieh et al. 2011; Kiraly et al. 2010b; Kiraly et al. 2011). This suggests that the loss of Kalirin-7 interaction with NR2B in the Kalirin-7 knockout mice may be important for the learning involved in this aspect of addiction.

The intracellular tail of NR2B additionally tethers the Rho-family GAP p250GAP (also known as RICS) (Nakazawa et al. 2003; Okabe et al. 2003). p250GAP knockdown increases Rac activity and increases spine number and miniature excitatory postsynaptic potential (mEPSP) frequency, suggesting that this GAP is important for regulating synaptogenesis via inhibition of Rac activity (Impey et al. 2010). Importantly, the effect of p250GAP knockdown requires the activity of Kalirin-7. Thus, the intriguing possibility exists that p250GAP and Kalirin-7 coordinate both the activation and inactivation of Rac by local clustering via NR2B. It is unclear if such a complex would be important for regulating synaptogenesis, synaptic plasticity, or both. The regulation of p250GAP activity is unknown, but it is possible that it could be clustered with NR2B to specifically regulate pools of Rac activated by NMDAR-associated Kalirin-7. Finally, it should be noted that p250GAP has recently been identified as a risk loci for schizophrenia-

associated disorders (Ohi et al. 2012). This is interesting given the evidence linking NMDAR hypofunction to schizophrenia (Coyle et al. 2003; Snyder and Gao 2013), yet additional work with larger cohorts will be required to determine its possible importance.

17.2.3 Interplay Between AMPA Receptors and RhoA Activity via GEFs and GAPs

While Rac regulators are linked to NMDARs, it is intriguing that RhoA regulators have been found in a complex with AMPARs. In a screen for AMPAR-binding proteins, Kang et al identified the RhoA-specific GEF GEF-H1/Lfc as a component of the AMPAR complex in the brain (Kang et al. 2009). This interaction was found to be important for AMPAR activity-dependent regulation of spine development (Kang et al. 2009). Previous studies had implicated AMPAR activity in the stabilization of dendritic spines, with inhibition of AMPAR activity significantly reducing spine density (McKinney et al. 1999; Fischer et al. 2000). The underlying signaling mechanisms remained however elusive. Kang et al. demonstrated that the decrease in spine density caused by blocking AMPAR activity was associated with an increase in RhoA activity. Even more importantly Kang el al. showed that knockdown of GEF-H1 expression was able to eliminate both the decrease in spine density and increase in RhoA activity. Thus, an increase in AMPAR activity is likely to trigger the inactivation of GEF-H1 and consequently RhoA activity, thereby stabilizing spine structure. How AMPAR activity influences GEF-H1/Lfc function remains currently unknown. Notably, in spines GEF-H1/Lfc also forms a complex with Spinophilin and Neurabin, two actin interacting proteins. Association between GEF-H1/Lfc and these proteins was reported to modulate the actin cytoskeleton in a Rho-dependent manner, thereby contributing to spine development (Ryan et al. 2005).

The Rho-GAP OPHN1 was also found to form a complex with AMPARs (Nadif Kasri et al. 2009). OPHN1, however, does not seem to be regulated by AMPAR activity, but instead OPHN1 regulates the stabilization of synaptic AMPARs. In particular, NMDAR activation was shown to drive OPHN1 into dendritic spines, where it then forms a complex with AMPAR. In turn, OPHN1 signaling regulates activity-dependent AMPAR stabilization, as well as maintenance of spine structure, thereby permitting synaptic maturation and plasticity. The mechanism by which OPHN1 controls these events involves its Rho-GAP activity and a RhoA/Rho-kinase signaling pathway (Nadif Kasri et al. 2009; Govek et al. 2004). A likely scenario is that spine enriched OPHN1 contributes to the stabilization of AMPARs by locally inactivating RhoA/Rho-kinase activities and modulating actin dynamics (i.e., in the proximity of AMPARs). Consequently, decreased or defective OPHN1 signaling results in destabilization of synaptic AMPARs, leading to impairment in synapse maturation and plasticity and eventually loss of spines. This is of particular

relevance, as *OPHN1* mutations have been identified in families with mental retardation associated with cerebellar hypoplasia and lateral ventricle enlargement (Billuart et al. 1998; Bergmann et al. 2003; Philip et al. 2003; des Portes et al. 2004; Zanni et al. 2005). Thus, glutamatergic dysfunction and defects in early circuitry development caused by OPHN1 mutations could be an important contributory factor to the cognitive deficits observed in *OPHN1* patients. Noteworthy, OPHN1 has also been implicated in another form of plasticity, namely mGluR-LTD that relies on the activation of group I metabotropic glutamate receptors (mGluRs) and occurs at later developmental stages (Nadif Kasri et al. 2011). In this case, however, OPHN1, whose expression is rapidly induced by mGluR activation, exerts its effects via interaction with members of the endophilin-A family, endophilin A2 and A3 (Endo 2/3), which mediate the downregulation of surface AMPARs during mGluR-LTD (Nadif Kasri et al. 2011). Thus, OPHN1 likely operates during adulthood to weaken synapses in response to behaviorally relevant stimuli. In light of the previously reported role for LTD in behavioral flexibility and novelty detection (Kemp and Manahan-Vaughan 2007; Luscher and Huber 2010), the requirement of OPHN1 in mGluR-LTD could offer an intriguing potential explanation for some of the behavioral deficits exhibited by *OPHN1* patients.

17.2.4 Specification of Inhibitory Synapses by a Neuroligin 2 and Collybistin Interaction

Although excitatory synapses receive a disproportionate amount of attention, it should be emphasized that Rho-family GTPase signaling is likely to be important for inhibitory synapse formation as well. Collybistin, a Cdc42 GEF, is mutated in human disorders of epilepsy/hyperekplexia and intellectual disability (Shimojima et al. 2011; Lesca et al. 2011; Kalscheuer et al. 2009; Marco et al. 2008; Harvey et al. 2004). One such mutation that is associated with epilepsy is a missense mutation of a critical residue within the SH3 domain of collybistin (Harvey et al. 2004). Recently it was discovered that this SH3 domain is selective for binding to neuroligin 2, an organizer of nascent inhibitory synapses that mediates trans-synaptic neuroligin/neurexin interactions (Poulopoulos et al. 2009). It was previously shown that collybistin facilitates the membrane targeting of gephryin, the primary scaffolding protein of inhibitory synapses, but that the SH3 domain of collybistin inhibits this function (Harvey et al. 2004; Kins et al. 2000; Papadopoulos et al. 2007). Gephyrin interacts with a conserved 15 amino acid region that is present in all neuroligins (Poulopoulos et al. 2009). This suggested that there must be a molecular mechanism to specify gephryin clustering at developing neuroligin 2 inhibitory synapses, but not at developing excitatory synapses organized by neuroligin 1. Thus, the specific interaction between collybistin and neuroligin 2 appears to explain how specific clustering of gephyrin can occur at inhibitory synapses. Importantly, collybistin knockout mice exhibit a striking loss of

inhibitory synapses, which is accompanied by significant changes in hippocampal plasticity. These effects are associated with increased levels of anxiety and impaired spatial learning (Papadopoulos et al. 2007). As yet, it is still not clear what the exact role of the GEF domain is for collybistin during inhibitory synapse development or maintenance (Papadopoulos and Soykan 2011). Collybistin is a Cdc42 GEF, but it remains to be seen whether Cdc42 regulates inhibitory synapse formation or maintenance (Tyagarajan et al. 2011; Reddy-Alla et al. 2010). It is possible that future work will identify additional Rho-family GTPases that are activated by collybistin that regulate inhibitory synapses. It should be noted that the Rac GAPs, srGAP2 and WRP/srGAP3, also interact directly with gephryin and appear to facilitate inhibitory synapse formation (Okada et al. 2011). Indeed, loss of WRP in mice results in reduced densities of gephyrin and GABA-A receptor clusters in the hippocampal formation. Thus, inhibitory synapse function is likely to be fine-tuned by coordinated action of GEFs and GAPs organized by a neuroligin 2/gephryin complex, yet the relevant GTPases remain to be clarified.

17.3 Scaffolding and Linker Proteins Focus Rho GTPase Signaling

Transfer of information from one enzyme to the next in cell signaling cascades is often organized around protein scaffolds. These platforms for signaling allow for increased signal efficiency, signaling precision, and can also facilitate the diversity of cellular functions a given enzyme can regulate (Pawson and Scott 2010). Given that a single Rho-family GTPase can regulate multiple different cellular processes, this has emerged as an important mechanism for specifying the whens and wheres of a Rho-family GTPase action (Fig. 17.1b).

17.3.1 A GIT1 and Rac Signaling Scaffold Involved in Synaptogenesis and Attention Deficit Hyperactivity Disorder

GIT1 (G-protein-coupled receptor kinase-interacting protein 1) is a multifunctional scaffolding and adaptor protein composed of multiple domains (Hoefen and Berk 2006). This includes a GAP domain for Arf GTPases as well as a Spa Homology Domain that binds to the Rac and Cdc42 GEFs α-PIX and β-PIX. The interaction between GIT1 and β-PIX is of high affinity, in the nanomolar range, and may be organized in a heteropentameric structure containing a GIT1 dimer and β-PIX trimer (Schlenker and Rittinger 2009). The functional implications of this higher order structure are unknown, but may facilitate the coordinated binding of multiple signaling molecules with β-PIX. β-PIX GEF activity is enhanced within the context

of GIT1 by the ability of GIT1 to also scaffold the CaMKKβ and CaMKI kinases (Saneyoshi et al. 2008). Kinases often interact with scaffolding proteins in order to preferentially target their activity towards substrates. Indeed, CaMKKβ phosphorylation of CaMKI is induced by NMDA-mediated calcium influx, activating the CaMKI-mediated phosphorylation of β-PIX at serine 516. This potently stimulates its GEF activity towards Rac and is required for excitatory synapse development. Interestingly, β-PIX also binds to PAK (p21 activated kinase) via an N-terminal SH3 domain (Mott et al. 2005), suggesting that the GIT1/β-PIX/PAK complex can organize and regulate β-PIX GEF activity and the Rac-mediated activation of PAK. Loss of GIT1 in mice results in reduced dendritic arborization and spine density and in multiple Attention Deficit Hyperactivity Disorder (ADHD)-like behaviors (Won et al. 2011; Menon et al. 2010; Schmalzigaug et al. 2009). Importantly, GIT1 SNPs (single nucleotide polymorphisms) that reduce GIT1 expression are associated with human ADHD (Won et al. 2011). In mice, GIT1 loss specifically reduces Rac1 activation, but does not alter the active levels of the Arf GTPase Arf6, supporting a key role of GIT1 in Rac signaling (Won et al. 2011). Surprisingly GIT1 knockout mice also have specific impairments in pre-synaptic inhibitory input, indicating that GIT1 additionally regulates presynaptic organization and actin dynamics. This is supported by other studies reporting that β-PIX regulates actin polymerization required for synaptic vesicle recruitment during initial axonal bouton formation (Sun and Bamji 2011).

17.3.2 Keeping Rac Activation in Check by a Disc-1/PSD95/Kalirin-7 Complex

While the GIT1 signalosome serves to cluster β-PIX and downstream effectors of Rac, it is also important to insure that Rac is held inactive until the appropriate moment. Recent work identified the Rac GEF Kalirin-7 in a complex with Disc-1 and PSD-95 that limits Rac activation (Hayashi-Takagi et al. 2010). Disc-1 is a schizophrenia susceptibility gene originally identified as a causal mutation in a Scottish family with significant psychosis (Millar et al. 2000; St Clair et al. 1990). PSD-95 is the major structural protein of the excitatory post-synaptic density that links multiple signaling proteins to receptors at the postsynaptic membrane (Kim and Sheng 2004). Disc-1 binding to Kalirin-7 inhibits its ability to bind to and promote Rac activation (Hayashi-Takagi et al. 2010). Importantly, the complex between Disc-1, Kalirin-7, and PSD95 is rapidly disassembled in response to synaptic activity and NMDA activation. The release of Kalirin-7 from the inhibitory complex corresponds with a rapid activation of synaptic Rac. Although the effect of PSD95 on Kalirin-7 may be to enhance its localization to the PSD, its dissociation in response to synaptic activity may also facilitate Rac activation. For example, PSD95 interacts with the Rac GAPs BCR as well as with ABR that could further oppose Rac activation (Oh et al. 2010). The long-term consequences of

overactive Rac signaling or the loss of Disc-1 were also assessed, as glutamatergic synapse dysfunction is implicated in schizophrenia (Hayashi-Takagi et al. 2010). Interestingly, it was found that over time active Rac, or the loss of Disc-1, significantly decreased spine size, which might be related to spine abnormalities observed in postmortem schizophrenia samples. These results, in combination with the GIT1 studies, reveal how scaffolding proteins can bidirectionally modulate Rac signaling in space and time and indicate that the loss of this regulation may be associated with neuropsychiatric disorders.

17.3.3 Tuning p190-RhoGAP Function by PAR-6 and Arg to Control RhoA Activity in Spine and Dendrite Stabilization

As mentioned above, in addition to Rac, the spatial-temporal control of RhoA levels/activity is also critical for the proper formation and stabilization of dendritic spines. While it is known that RhoA levels during synaptogenesis are regulated by Ube3a-mediated ubiquitination and degradation of the Rho GEF ephexin-5, the regulation of RhoA levels/activity in maturing spines to govern their maintenance/stabilization is an enduring question. One key emerging player in the stabilization of spines as well as dendritic branches is the p190A-RhoGAP (p190), which is expressed at high levels in the adolescent/mature brain (Lamprecht et al. 2002; Settleman 2003). Somewhat unexpectedly, the polarity protein PAR-6 in a complex with atypical PKC (aPKC), but independent of its interaction with PAR-3, was found to contribute to spine maintenance, by reducing the activity of RhoA in spines in a p190-dependent manner (Zhang and Macara 2008). Indeed, evidence was presented that PAR-6, via its N-terminal PB1 domain, binds to and recruits aPKC to spines. Spine localized aPKC in turn either directly or indirectly triggers the phosphorylation of p190, thereby locally inactivating RhoA activity and contributing to the stabilization of spines (Zhang and Macara 2008). The upstream input(s) that regulate PAR-6 in neurons still remain(s) unknown. While in other systems, this involves the binding of PAR-6 via its CRIB domain to Cdc42-GTP; this does not seem to be the case in neurons (Zhang and Macara 2008). A possible scenario could be that the PAR-6/aPKC complex is coupled to AMPARs, as described above for the Rho GEF GEF-H1/Lfc.

Additionally, p190 was found to be phosphorylated in neurons by Arg (Abl-related gene), a member of the Abl non-receptor tyrosine kinase family (Hernandez et al. 2004; Sfakianos et al. 2007). Neurons in mice that lack Arg develop normally through postnatal day P21 (P21); however by P42 these mice lose dendritic spines and synapses and display reductions in dendritic arbor size complexity. Notably, these deficits are coincident with the impairment in memory tasks by the loss of Arg in mice (Sfakianos et al. 2007; Kerrisk and Koleske 2013). Arg promotes phosphorylation of p190, which then can bind to two SH2 domains in

p120RasGAP (p120). p190 is recruited to the plasma membrane by the PH and CalB domains of p120 GAP, where it then diminishes RhoA activity (Bradley et al. 2006). Intriguingly, the Arg/p190-mediated reduction in RhoA activity, while critical for dendrite arbor stability, does not appear to be involved in spine stabilization (Lin et al. 2013). Indeed, reducing RhoA activity in Arg knockdown neurons blocked dendrite loss, but did not rescue the spine/synapse loss observed in these neurons. Instead, spine destabilization in Arg knockdown neurons was prevented by blocking NMDAR-dependent relocalization of cortactin from spines or by forcing cortactin into spines via fusion to an actin-binding region of Arg (Lin et al. 2013). Thus, the Arg-p190 axis preserves dendrite structure in early adulthood by attenuating Rho activity, while Arg interacts with the NMDAR and cortactin to control spine stabilization. Together with the PAR6 studies, these results indicate that dependent on what protein complex p190 is in, it dampens RhoA activity to control either spine or dendrite stabilization.

17.3.4 Anchoring Rac by IP3K-A to Actin During Synaptic Plasticity

Although the primary mechanism to regulate Rho-family GTPase signaling is by the focal targeting of their regulators, the targeting of Rho-family GTPases themselves by scaffolding proteins can also occur. Perhaps the best example of this is IP3K-A, an F-actin-binding lipid kinase (Schell et al. 2001). Prior work had established that IP3K-A is highly expressed in neurons and phosphorylates inositol 1,4,5-trisphosphate (IP3) to generate inositol(1,3,4,5)tetra-kisphosphate (IP4). Thus it modulates intracellular calcium release mediated by IP3 (Choi et al. 1990; Irvine et al. 1986). Surprisingly, it was found that IP3K-A directly modulates actin polymerization in cells, independent of its kinase activity (Windhorst et al. 2008; Kim et al. 2009). IP3K-A is recruited to spines by synaptic activity via its F-actin-binding domain and was found to bind selectively to activated Rac (Kim et al. 2009). Importantly, the binding of active Rac to IP3K-A did not occlude the ability of downstream effectors such as PAK to simultaneously bind Rac, suggesting that IP3K-A could scaffold activated Rac to F-actin in a way that potentiated its ability to further stimulate actin remodeling. The role of IP3K-A in regulating Rac activity and targeting is likely to be important, as IP3K-A knockout mice exhibit profound deficits in synaptic plasticity as well as learning and memory paradigms (Kim et al. 2009).

17.4 Effector Clustering: Linking GAPs and GEFs to Downstream Rho GTPase Targets

In order to influence cellular physiology, Rho-family GTPases must bind to and regulate protein effectors. Rho effector proteins have evolved several domains, which can function as specific docking sites for GTP-bound Rho GTPases. Canonical activity-dependent GTPase-binding domains include the Cdc42/Rac Interactive Binding (CRIB) domain from the PAK kinases; the Protein kinase C-related homology region 1 (HR1) domain typified by Rho-associated kinase, PKN, and Rhotekin kinase; and the GTPase Binding Domains (GBD) of formins (Burbelo et al. 1995; Shibata et al. 1996; Flynn et al. 1998; Rose et al. 2005). One of the most efficient mechanisms to regulate how Rho-family GTPase signaling can shape cellular responses is to physically couple the regulators of their activation to downstream effectors (Fig. 17.1C). In this way, effectors can be selectivity tuned to the action of specific Rho-family GTPases. Additionally, this type of interaction allows for bidirectional coordination of signaling events, with effectors sometimes influencing the activity of GEFs and GAPs upon binding. Alternatively, GAP or GEF binding may directly influence effector activity in addition to modulating their activation by Rho-family GTPases. Although this is a relatively newer concept for Rho-family signal integration, several important examples have emerged which are discussed below.

17.4.1 Enhancing Cdc42 Signaling by an Intersectin-l and N-WASP Complex

One of the earliest examples of this type of signaling cascade organization came from the observation that the long splice variant of the endocytic protein, Intersectin-l, contains an additional DH-PH domain specific for Cdc42 activation that is not found in the short splice variant (Intersectin-s) (Hussain et al. 2001; Thomas et al. 2009; Pucharcos et al. 1999). While Intersectin-s is widely expressed in many cell types, Intersectin-l is almost exclusively neuronal. Surprisingly, it was found that although the DH domain of Intersectin-l could specifically bind to and activate Cdc42, full-length Intersectin-l does not, suggesting that Intersectin-l exists in an autoinhibited state (Hussain et al. 2001). Furthermore, the ability of Intersectin-l to stimulate actin dynamics in cells is blocked by inhibitory N-WASP activity (a Cdc42 effector that activates Arp2/3-dependent actin polymerization), suggesting a link between Intersectin-l, Cdc42, and N-WASP (Hussain et al. 2001). Activation of Intersectin-l is mediated by binding to N-WASP via the SH3 domain(s) of Intersectin-l with the proline-rich domain of N-WASP. The release of Intersectin-l inhibition is likely mediated by an N-WASP interaction with the fifth SH3 domain (SH3E) of Intersectin-l (Zamanian and Kelly 2003). Surprisingly, the mechanism of Intersectin-l inhibition is probably distinct from

other SH3-inhibited GEFs, since mutation of the proline-binding groove of SH3E does not alter its inhibition, suggesting that inhibition and its release are not via a direct competition for SH3 domain ligand binding. Consistent with this, recent crystal structures have suggested that the Intersectin-l SH3E domain uses an interface distinct from proline ligand binding to interact with the DH domain, which may occlude GTPase binding (Ahmad and Lim 2010). As discussed above, the Intersectin-l and N-WASP interaction is important for EphB regulation of synaptogenesis and spine maturation. Recent work also supports a role for Intersectin-l and N-WASP in facilitating somato-dendritic endocytosis, which may involve actin-mediated pushing of clathrin-coated vesicles into cells during scission (Thomas et al. 2009; Merrifield et al. 2004; Benesch et al. 2005).

17.4.2 GAP-Mediated Control of Rac1 Signaling to WAVE1

Like N-WASP, WAVE1 is a Rho-family GTPase effector protein, expressed throughout the CNS and whose function is to activate Arp2/3 complex-mediated branched actin filament polymerization (Padrick and Rosen 2010; Pollitt and Insall 2009). Instead of functioning downstream of Cdc42, WAVE1 senses Rac activation to regulate spine morphogenesis and activity-dependent synaptic plasticity such as LTP and LTD (Soderling et al. 2007). Analysis of WAVE1-deficient mice indicates it is critical for many behaviors, including anxiety, sensorimotor function, and learning and memory (Soderling et al. 2003). Mass spectrometry analysis of WAVE1-associated proteins led to the identification of the mechanism by which WAVE1 senses Rac activation and how this activation is tuned by negative feedback (Eden et al. 2002). Active Rac binds to the Rac effector CYFIP1 (also known as SRA-1) and induces the dissociation of CYFIP1 and several associated inhibitory proteins (Abi-1/2 and Nap1), allowing WAVE1 to interact with and stimulate Arp2/3-dependent actin polymerization. Interestingly, analysis of the WAVE1 complex of proteins also identified a neuronal Rac GAP protein, WRP (also known as srGAP3) (Soderling et al. 2002). WRP contains a carboxyl-terminal SH3 domain that binds directly to WAVE1 within the poly-proline-rich region, analogous to the Intersectin-l and N-WASP complex. Notably, WAVE1 mice mutants for the WRP-binding site display abnormal dendritic spines, altered plasticity, and subtle deficits in memory, indicating that the regulation of Rac activity within the WAVE1 complex is a crucial feature of the signaling pathway (Soderling et al. 2007). Moreover, WRP is also likely to regulate WAVE1-mediated actin dynamics in specific spatial contexts, as it contains a unique N-terminal inverse F-BAR domain that senses and induces dendritic filopodial formation during the earliest stages of spine formation (Carlson et al. 2011). WRP has been implicated in several human neuropsychiatric and developmental disorders, including intellectual disability associated with 3p-syndrome and schizophrenia (Endris et al. 2002; Addington and Rapoport 2009; Wilson et al. 2011). Consistent with a role of

WRP in contributing to these syndromes, multiple aspects of these disorders are modeled in mice lacking WRP (Carlson et al. 2011; Waltereit et al. 2012).

17.4.3 Regulation of Formin-Mediated Actin Remodeling by SrGAP2

In addition to the regulation of N-WASP and WAVE1, Rho GTPases also potently stimulate actin remodeling through the regulation of the Diaphanous-related formins. Formins form a large family of proteins (15 in mammalians) whose actin regulatory properties are kept in check by an autoinhibition mechanism (Chesarone et al. 2010). Rho GTPases physically disrupt this autoinhibition by binding within a GTPase-binding domain (Rose et al. 2005; Otomo et al. 2005). Relieving this autoinhibiton through GTP-dependent binding unmasks formin activity, resulting in either actin polymerization of linear filaments or actin filament severing, depending on the type of formin. Recently it was discovered that the Rac GAP srGAP2, a close homolog of WRP, binds the formin FMNL1 through its SH3 domain, analogous to the association of WRP with WAVE1 (Mason et al. 2011). srGAP2 is implicated in neocortical development by facilitating the formation of leading edge processes of migrating newborn neurons that are necessary to effectively migrate to the correct laminar position within the cortical plate as well as dendritic spine maturation (Guerrier et al. 2009; Charrier et al. 2012). Of note, srGAP2 has two main duplicates in humans (SRGAP2B and SRGAP2C), which encode a truncated F-BAR domain that interacts with ancestral SRGAP2 to inhibit its function. Interestingly, expression of the SRGAP2C paralog in mouse cortical neurons in vivo phenocopies srGAP2 deficiency, leading to the emergence of human-specific features, including neoteny during spine maturation and increased density of longer spines (Charrier et al. 2012; Dennis et al. 2012). The interaction of srGAP2 with FMNL1 does not occur until after Rac has activated the formin, meaning the formation of the complex is temporally regulated by an activity-dependent conformational change (Mason et al. 2011). srGAP2 binds to a critical region of the formin that appears to be required for FMNL1 activity, which is to sever actin filaments in response to active Rac. The in vivo role of actin severing is still unclear, but is likely to result in remodeling of existing actin networks into newly polymerized filaments by exposing barbed ends of actin that are competent for additional actin subunit assembly. Remarkably, reconstitution of the complex using purified components showed that the srGAP2 SH3 domain potently inhibits the FMNL1 actin severing activity (Mason et al. 2011). Together these data indicate that upon activation, srGAP2 binds FMNL1 and shuts off both the upstream activation signal Rac and the functional output of severing actin filaments. In this way the srGAP2 and FMNL1 complex may function as a timing mechanism to limit the extent of actin severing in vivo.

17.5 Future Directions

The sophistication and nuances of Rho-family GTPase signaling are only matched by the diversity of the neurophysiologic processes they regulate. The above studies have begun to illuminate the molecular mechanisms through which they achieve these important functions and how the dysfunction of their regulation ultimately leads to neurodevelopmental and neuropsychiatric disorders. Proteomic analysis of GTPase regulators suggests that their incorporation into molecular complexes is likely to be a common and important theme (Okada et al. 2011). Beyond identifying and characterizing the complexes, however, new technologies and concepts will be required to decode the importance of the spatial and temporal regulation of Rho-family signaling. Recent advances in super-resolution imaging, including PALM, SIM, STORM, and array tomography promise to help reveal where these complexes exist in synaptic space, leading to new insights into their possible functions (Schermelleh et al. 2010; Ahmed 2011; Triller and Choquet 2008). Additionally the ability to monitor the dynamics of sub-synaptic pools of actin using these techniques will likely be paired with the genetic disruption of specific complexes, allowing the field to delve more deeply into not only cataloging the nanometer scale location of these complexes but also their functional relevance at high resolution. 2-photon FLIM imaging of the spatial and temporal activity of Rho GTPases promises to reveal new insights into how these pathways are orchestrated at submicron and millisecond timescales. For example, recent work has demonstrated that the induction of spine-specific LTP leads to activation of Rho and Cdc42 activation, but with differing spatial profiles (Murakoshi et al. 2011). These approaches may also be combined with disruptions of specific GEF and GAP complexes, using high resolution imaging of activity reporters to reveal their importance in space and in time. New advances in light-gated regulation of Rho-GTPase activity using genetically encoded photo-switches, such as the LOV (light, oxygen, voltage) domain, also promises new avenues to investigate how GTPase activity modulates specific neuronal functions with the spatial resolution of light diffraction (Wu et al. 2009). As recently demonstrated for the role of Rac in addiction, when combined with technology for optogenetics, it promises to reveal the importance of GTPase signaling in specific brain regions under behavioral paradigms (Dietz et al. 2012). Most of these new imaging advances, however, will need to be paired with a deeper understanding of the biochemical nature of how GTPase signaling complexes are physically put together in order to manipulate their activity in a spatial manner. Caution must also be exerted when overexpressing proteins to understand their functions, particularly the GTPases. For example it has recently been shown that the Rho-family GDIs are limiting, and that the overexpression of one GTPase may alter the activity and localization of other endogenous GTPases by outcompeting the limiting pool of GDI (Boulter et al. 2010). Thus, a combinatorial approach, using biochemical, genetic, and new imaging approaches to dissect and understand how GTPase signaling is organized in space and time, will likely be required. Yet the rewards for such approaches will

be great as it is already clear that Rho GTPases govern the whens and wheres of neuronal development and synaptic responses.

Acknowledgments We thank Jim Duffy for his help with the graphic art of Fig. 17.1. We apologize to colleagues we did not cite due to space limitations. L.V.A. is supported by grants from the NIH (R01 MH082808 and R01 NS082266) and S.H.S by NIH (2R56NS059957-06).

The authors declare that they have no conflict of interest and that there are no competing financial interests.

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