Current Research in Structural Biology 3 (2021) 277–289

Contents lists available at ScienceDirect

Current Research in Structural Biology

journal homepage: www.journals.elsevier.com/current-research-in-structural-biology

Role of actin cytoskeleton in the organization and function of ionotropic glutamate receptors

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ARTICLE INFO

Handling editor: Gabrielle Rudenko

Keywords:
Actin
Actin-binding proteins
Glutamate receptors
Synapse
Neurons

ABSTRACT

Neural networks with precise connection are compulsory for learning and memory. Various cellular events occur during the genesis of dendritic spines to their maturation, synapse formation, stabilization of the synapse, and proper signal transmission. The cortical actin cytoskeleton and its multiple regulatory proteins are crucial for the above cellular events. The different types of ionotropic glutamate receptors (iGluRs) present on the postsynaptic density (PSD) are also essential for learning and memory. Interaction of the iGluRs in association of their auxiliary proteins with actin cytoskeleton regulated by actin-binding proteins (ABPs) are required for precise long-term potentiation (LTP) and long-term depression (LTD). There has been a quest to understand the mechanistic detail of synapse function involving these receptors with dynamic actin cytoskeleton. A major, emerging area of investigation is the relationship between ABPs and iGluRs in synapse development. In this review we have summarized the current understanding of iGluRs functioning with respect to the actin cytoskeleton, scaffolding proteins, and their regulators. The AMPA, NMDA, Delta and Kainate receptors need the stable underlying actin cytoskeleton to anchor through synaptic proteins for precise synapse formation. The different types of ABPs present in neurons play a critical role in dynamizing/stabilizing the actin cytoskeleton needed for iGluRs function.

1. Introduction

Accurate connectivity of neurons is indispensable for learning, memory formation, and development of higher-order cognitive-behavioural capabilities of an individual (Kempermann, 2010; Bisaz et al., 2014). During memory formation the synaptic activity involves a series of tightly regulated cellular and sub-cellular events. These events ultimately lead to the synapse formation by associating the pre-and post-synaptic partners at the specific neuro-spatial coordinate (Colón-Ramos, 2009; Cooper, 2013; Kimberley, 2007). An aberrant synaptic connection is associated with learning and memory disorders, neuropsychiatric and neurodevelopmental disorders. They are also closely related to the disorder in the functioning of many genes such as *SHANK3, LIMK1, SYNGAP1,* etc. These genes regulate the upstream signalling events to induce cytoskeletal dynamics in dendritic spines and modulate the spine structure, function, pre-and postsynaptic complexes (Comery et al., 1997; Biederer and Stagi, 2008; Yan et al., 2016; Firth and Wright, 2011). The postsynaptic conductance of each synapse is controlling the balance with other synapses to encode information while maintaining the effective network stability. Various types of iGluRs solely carry out postsynaptic excitatory transmission in the mammalian nervous system. The iGluRs are mainly anchored to the cortical actin cytoskeleton at the synapse. Actin cytoskeleton and its regulatory proteins are important for targeting and precise functioning of iGluRs (Cingolani and Goda, 2008; Kalinowska et al., 2015; Reshetniak and Rizzoli, 2019).

The literature suggests that learning and memory formation is tightly associated with the neuronal cytoskeleton. Cytoskeleton plays a pivotal role in multiple aspects of neuronal development and homeostasis maintenance (Lamprecht, 2016; Basu and Lamprecht, 2018; Bosch et al., 2014a,b). In the past 30 years, various studies in the field have uncovered that the actin cytoskeleton is the primary determinant of cell morphology, motility, and vesicle trafficking (Lee and Dominguez, 2010; Alberts et al., 2002). At steady state F-actin grows at the barbed end by adding adenosine triphosphate (ATP)-bound G-actin monomers and shrink at the pointed end by releasing adenosine diphosphate (ADP)--bound actin monomers through the process of treadmilling which generate forces for the movement of the cell [Fig. 1]. The G-actin/F-actin ratio influences various types of dendritic spine morphology (Lodish

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https://doi.org/10.1016/j.crstbi.2021.10.001
Received 27 March 2021; Received in revised form 4 September 2021; Accepted 9 October 2021

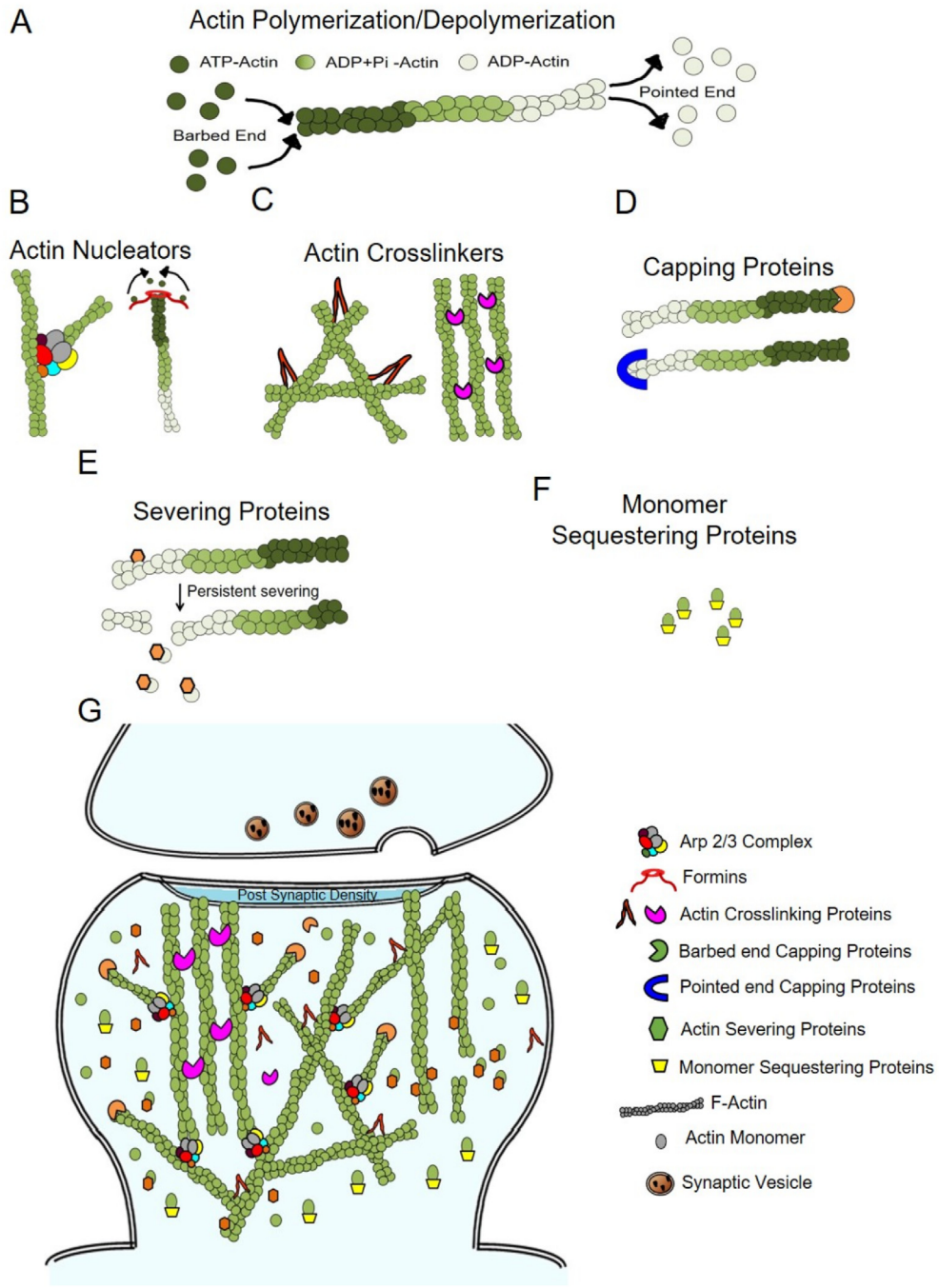

Fig. 1. Schematic representation of actin dynamics regulation and organization in dendritic spines. (A) Actin polymerization at barbed end by adding ATP-actin monomers and depolymerization at pointed end by releasing ADP-actin monomers. (B) Actin nucleation by Arp2/3 complex and formins. (C) Actin crosslinker (α-actinin and fascin) to crosslink F-actin. (D) Barbed end and pointed end actin Capping proteins. (E) Actin severing protein. (F) Monomer sequestering proteins. (G) Actin dynamics in the dendritic spines.

et al., 2000; Korn et al., 1987; Bárány et al., 2001a). Dynamic F-actin structures such as lamellipodia, filopodia, stress fibres are crucial for perfect spine functioning, vesicle biogenesis, endocytosis, repair, and regeneration (Svitkina, 2018; Letort, et al., 2015). The F-actin may exist as bundles or meshwork of branched and linear filaments in the dendritic filopodia (Fiala et al., 1998; Hotulainen and Hoogenraad, 2010; Miermans et al., 2017; Korobova and Svitkina, 2010). Actin structures regulate stabilization of dendritic spines critical to spine establishment and maturation, spine plasticity, and synapse functions (Svitkina, 2018; Kanjhan et al., 2016) [Fig. 1]. The actin enriched dendritic spines comprise both dynamic and stable actin structures shown using the photoactivatable form of green fluorescent protein (GFP) fused to actin (Honkura et al., 2008; Halpain, 2000). When the photoactivatable form of GFP-actin is activated in dendritic spines, fluorescence decays from the activated molecules are noticed in two phases with time constants. It indicates two pools of F-actin are present in the spine: a dynamic one with a fast-treadmilling rate and a stable one with a slower treadmilling rate. The dynamic F-actin is in the spine periphery, and the stable one restricts mainly to the base of the spine head. Multiple ABPs are present in dendritic spines, control the actin dynamics at a different pace according to their necessities inside the cells. These proteins are tightly governed in time and space by many signalling and scaffolding proteins through multiple regulatory pathways (Hotulainen and Hoogenraad, 2010) [Fig. 1]. Multiple ABPs like ADF/Cofilin, tropomyosin, actin nucleators (Arp2/3 and formins), profilin, and WASP family proteins participate in the actin dynamics (Pollard, 2016; Maiti and Bamburg, 2013). The actin nucleators like formins polymerize F-actin to create linear F-actin cables, whereas the Arp2/3 complex nucleate F-actin from the side of the existing filament creating a branched network (Xu et al., 2004; Pollard and Borisy, 2003). Barbed end capping proteins e.g., CapZ

prevent the addition of ATP-actin subunits, thereby decreasing the overall length of the F-actin (Winder and Ayscough, 2005). The well-characterized ADF/Cofilin family proteins severe F-actin from the pointed end and plays a significant role in actin turnover (Winder and Ayscough, 2005). Several other ABPs, e.g., α-catenin, Calponin, Spinophilin, Tropomodulin, Esp8, Cdc42, and cell adhesion molecules (CAMs) like cadherins, selectins, neuroligins are essential for proper recruitment of glutamate receptors and formation of intact synaptic arrangement (Brandt and Grosse, 2007).

The iGluRs are abundant among all the neurotransmitter receptors in the central nervous system (CNS). They are present in both the presynaptic axon terminal and postsynaptic compartment of dendritic spines (Reiner and Levitz, 2018). The binding of L-glutamate to iGluRs is usually responsible for basal synaptic transmission and many forms of synaptic plasticity, which affects the learning and memory of an organism (Andreas and Joshua, 2018; Platt, 2007). In mammals, most of the iGluRs are expressed from the early embryonic stage. The expression of iGluRs increases with their age (Behuet et al., 2019; Breese and Leonard, 1993; Tadros et al., 2007). Structurally iGluRs have four subunits, but the domain arrangement of these subunits differs from one receptor to the other receptor (Dingledine et al., 1999). The C-terminal cytoplasmic domain (CTDs) of iGluRs have variable length and different protein sequence compositions. The variable length of CTDs in iGluRs have numerous protein-protein interactions and post-translational modifications. This in turn modulate channel function, trafficking, localization and subsequent signalling outcome from the receptors. Huttlin et al., paper discusses the various post translational modifications present in CTDs of mouse iGluRs (Huttlin et al., 2010). In this review we have highlighted the different phosphorylation sites present on the CTDs of human iGluRs [Fig. 2] (Table 1). The accurate behaviour of iGluRs is determined by the receptor subunit composition and length of the CTDs (Warnet et al., 2020; Lundby et al., 2012; Howard, 2005).

Precise regulation of actin cytoskeleton and iGluRs set up the arena for synaptic plasticity of neural circuits (Kennedy, 2016; Lamprecht, 2016; Basu and Lamprecht, 2018). Although much progress has been made, but exact signalling pathways underlying learning and memory need to be further elucidated. Studying the detailed molecular interaction of cytoskeletal proteins with iGluRs is required to understand synaptic plasticity (Traynelis et al., 2010; Van Spronsen and Hoogenraad, 2010; Vyas and Montgomery, 2016). This review will focus on the

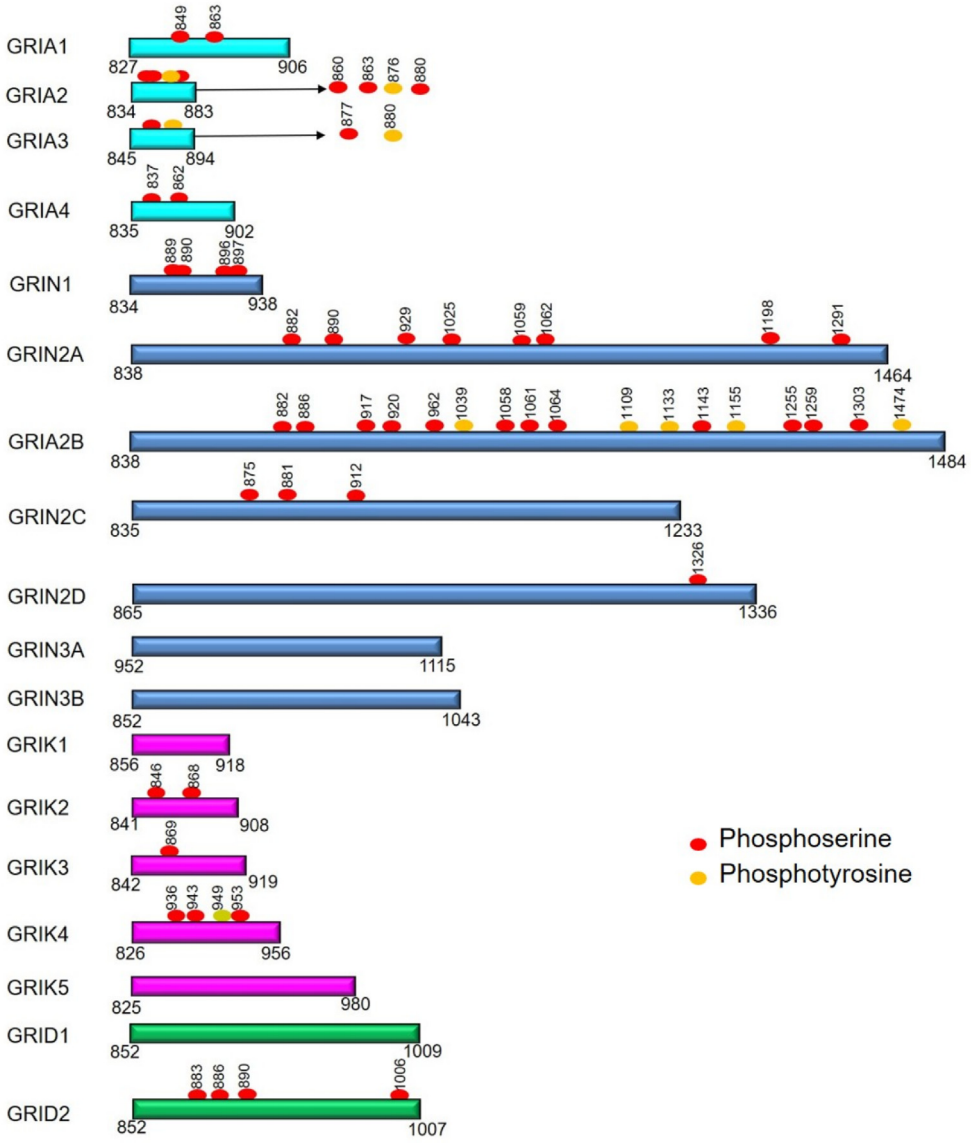

Fig. 2. Phosphorylation sites present on CTDs of iGluRs were mapped in this figure. Phosphoserine sites are marked in red and phosphotyrosine sites are marked in yellow. This figure uses the proteomic pattern identified in human iGluRs reported in the UNIPROT database.

Table 1
The list of ionotropic glutamate receptors present in human. Various post-translational modifications (PTMs) reported in the Uniprot Database from various literature are tabulated in the table. These PTMs affect the trafficking, localization and behaviour of the receptors.

Type of Glutamate Receptor	Subtype	Gene Name and Position	PTMs affecting the activity of the receptor	References
AMPA	GluA1	GRIA1 5q33.2	Phosphorylation, Glycosylation, Depalmitoylation, Lipidation	https://doi.org/10.1073/pnas.92.5.1376 https://doi.org/10.1074/jbc.272.51.32528 https://doi.org/10.1016/j.neuron.2007.09.016 DOI: 10.1016/0168-0102(95)00977-9
	GluA2	GRIA2 4q32.1	Phosphorylation, Glycosylation, Lipidation, Depalmitoylation	doi:10.1016/s0896-62730300722-0) https://doi.org/10.1016/j.neuron.2005.06.035 DOI: 10.1523/JNEUROSCI.0799-04.2004 https://doi.org/10.1046/j.1471-4159.1999. 731765.x
	GluA3	GRIA3 Xq25	Depalmitoylation, Glycosylation, Lipidation	https://doi.org/10.1021/pr0701254 https://doi.org/10.1016/j.neuron.2005.06.035
	GluA4	GRIA4 11q22.3	Depalmitoylation, Lipidation, Phosphorylation, Glycosylation	https://doi.org/10.1074/jbc.M205587200
NMDA	GluN1	GRIN1 9q34.3	Phosphorylation, Glycosylation Dephosphorylation	https://doi.org/10.1038/364070a0
	GluN2A	GRIN2A 16p13.2	Phosphorylation, Glycosylation	https://doi.org/10.1038/ncomms1871
	GluN2B	GRIN2B 12p13.1	Glycosylation, Phosphorylation	https://doi.org/10.1016/j.cell.2010.12.001 https://doi.org/10.1016/j.cell.2009.12.055 https://doi.org/10.1073/pnas.91.9.3954
	GluN2C	GRIN2C 17q25.1	Glycosylation, Phosphorylation	https://doi.org/10.1016/j.cell.2010.12.001 https://doi.org/10.1038/ncomms1871
	GluN2D	GRIN2D 19q13.33	Glycosylation, Methylation, Phosphorylation	https://doi.org/10.1016/j.cell.2010.12.001
	GluN3A	GRIN3A 9q31.1	Glycosylation	By Sequence analysis
	GluN3B	GRIN3B 19p13.3	Glycosylation	By Sequence analysis
Kainate	GluR5	GRIK1 21q21.3	Glycosylation, Phosphorylation	By Sequence analysis
	GluR6	GRIK2 6q16.3	Glycosylation, Phosphorylation	https://doi.org/10.4161/cib.19195
	GluR7	GRIK3 1p34.3	Glycosylation, Phosphorylation	https://doi.org/10.4161/cib.19195
	Grik	GRIK4 11q	Glycosylation	By Sequence Analysis
	Grik2	GRIK5 19q13.2	Glycosylation, Phosphorylation	https://doi.org/10.4161/cib.19195
Delta	KIAA1220	GRID1 10q23.1-q2.2	Glycosylation	By Sequence Analysis
	GluRD2	GRID2 4q22.1-q22.2	Glycosylation, Phosphorylation	https://doi.org/10.1016/j.cell.2010.12.001 https://doi.org/10.1038/ncomms1871

various types of iGluRs (Table 2) present in mammals and their crosstalk with different actin-binding proteins occurring in the synapses. Also, in this review, we will give an overview of the complex network of interactions that occurs in the CNS, focusing on the significance of actin cytoskeleton and iGluRs function in the context of synapse function.

2. AMPA receptors interaction with actin cytoskeleton

Alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors are ionotropic excitatory glutamate receptors activated by the binding of glutamate (Balasuriya et al., 2013). The AMPA receptors (AMPARs) are expressed in various regions of the CNS. The four AMPA (GluA 1–4) receptor subunits mostly gather as hetero-tetramers and rarely as homo-tetramers depending upon the synapse activity (Rossmann et al., 2011; Herguedas et al., 2016). The expression of these receptors in the CNS increases from the neonatal stage to adulthood (Pandey et al., 2015). The localization, mobility, and conductance of the highly dynamic tightly regulated AMPARs is fundamentally important for learning and memory formation. These receptors do not bind directly to the actin cytoskeleton. However, a highly remodelled actin cytoskeleton is critical for the accurate functioning of AMPARs, indicating linker or adapter proteins mediated interactions of AMPARs with actin cytoskeleton (Stefen et al., 2016; Hanley, 2014). The exact localization and trafficking of AMPARs are controlled by activity of actin cytoskeleton regulatory proteins (Hanley, 2014; Henley JM, 2013; Gu et al., 2010; Baines et al., 2014; Schulz et al., 2004; Kneussel, 2013).

2.1. Actin depolymerizing protein family

Actin-depolymerization factor (ADF)/cofilin family of actin-binding proteins are pivotal for the assembly/disassembly of actin inside the cell in response to any stimuli (Pollard and Borisy, 2003; Maiti and Bamburg, 2013; Kanellos and Frame, 2016; Ben Zablah et al., 2020). The ADF/Cofilin phosphorylation and dephosphorylation at Ser3 is crucial for the regulation of ADF/Cofilin activity in response to multiple intrinsic and extrinsic factors (Bamburg JR., 1999). ADF/Cofilin phosphorylation prevents its function to regulate actin dynamics and dephosphorylation facilitates actin binding. The ADF/Cofilin Ser3 phosphorylation is aided by the LIMK and TESK class of serine/threonine kinases (Arber et al., 1998). LIMKs are extensively studied kinases, whose activities are finally modulated by Rho GTPases, the central players of actin reorganization in response to signalling cues (Yang et al., 1998; Toshima et al., 2001). The significance of ADF/cofilin phosphorylation by LIMK1 and its role in actin regulation is shown by diminished ADF/cofilin phosphorylation and modified F-actin in LIMK1 knockout (KO) mice (Meng et al., 2002, 2004). ADF/Cofilin dephosphorylation at Ser3 by two phosphatases: chronophin and slingshot activate cofilin to govern the actin reorganization within the cell (Gohla et al., 2005; Niwa et al., 2002).

ADF/Cofilin is not only prerequisite for spine morphology and but also needed for spine changes during synapse plasticity (Borovac et al., 2018). In general, dendritic spine enlargement is associated with cofilin inactivation and actin assembly whereas spine shrinkage is linked to cofilin activation and actin disassembly (Ben Zablah et al., 2020). Overexpression studies of constitutively active/unphosphorylated cofilin(S3A) in neurons show decreased spine size and immature spine architecture (Shi et al., 2009). On the other hand, constitutively inactive/phospohomimetic cofilin (S3D) restores spine functions (Shi et al., 2009). It is also observed using immunoelectron microscopy that cofilin-1 is accumulated at the shell of spines abundant with dynamic actin and also at the PSD in the stratum radiatum of rat hippocampus (Racz and Weinberg, 2006). Overexpression of chronophin (ADF/Cofilin phosphatase) in mice hippocampal neurons result in spine shrinkage and

Table 2
This table had summarized the list of proteins which interact with the ionotropic glutamate receptors and actin cytoskeleton. These interacting proteins were reported in the Uniprot Database from multiple literature. These proteins modulate the receptor activity, their expression and actin dynamics in neurons to facilitate proper synapse formation.

Type of Glutamate Receptor	Subtype	Amino acid length (aa)	Proteins interact with the receptor and actin cytoskeleton	References
AMPA	GluA1	906	DLG1, CACNG2, SXN27	https://doi.org/10.1073/pnas.1011706107 DOI: 10.1038/nm.3117 https://doi.org/10.1074/jbc.273.31.19518
	GluA2	883	SNX27, PICK1	https://doi.org/10.1038/nm.3117 DOI: 10.1523/JNEUROSCI.0799-04.2004
	GluA3	894	Not yet known	–
	GluA4	902	EPB41L1/4.1N, CACNG5, and PRKCG	https://doi.org/10.1016/j.neuron.2008.07.034 https://doi.org/10.1038/nn.2266
NMDA	GluN1	938	SNX27, DLG4, LRFN1, and LRFN2	https://doi.org/10.1038/nm.3117 https://doi.org/10.1016/j.neuron.2004.08.003 DOI: 10.1523/JNEUROSCI.3799-05.2006
	GluN2A	1464	SNX27, AIP1, LRFN2, HIP1	DOI: 10.1523/JNEUROSCI.5175-06.2007 https://doi.org/10.1038/nm.3117 https://doi.org/10.1074/jbc.273.33.21105
	GluN2B	1484	HIP1, DLG3, DLG4, ARC, CAMK2A, PRR7	https://doi.org/10.15252/embj.201593070 DOI: 10.1523/JNEUROSCI.5175-06.2007 https://doi.org/10.1016/j.str.2019.04.001
	GluN2C	1233	SNX27, DLG4	https://doi.org/10.1126/science.7569905 DOI: 10.1128/MCB.01044-10
	GluN2D	1336	DLG4	By sequence similarity
	GluN3A	1115	Not yet known	–
	GluN3B	1043	Not yet known	–
Kainate	GluR5	918	KLHL 17, DLG4	By sequence similarity
	GluR6	908	KLHL 17, DLG4	By sequence similarity
	GluR7	919	PRKCABP, NETO2	By sequence similarity
	Grik	956	Not yet known	–
	Grik2	980	DLG4, NCALD	By sequence similarity
Delta	KIAA1220	1009	CBLN1, CBLN2	https://doi.org/10.1111/j.1471-4159.2012.07648.x
	GluRD2	1007	Delphilin, nPIST, PTPN4, BECN1, Shank	DOI: 10.1016/s0896-6273(02)00861-9 https://doi.org/10.1016/j.bbrc.2006.09.109 https://doi.org/10.1016/j.mcn.2004.02.007

knocking out causes gigantic spines (Kim et al., 2016). Although function of cofilin in dendritic spines was studied, precise regulation of spine morphology by ADF/cofilin and its phosphorylated state remains unclear. (Ben Zablah et al., 2020; Bosch et al., 2014a,b; Bisaria et al., 2020). Using live imaging it is discovered that enhanced ADF/cofilin activity levels notably increase the surface expression of AMPARs after LTP induction and inhibition of cofilin expression reduce AMPARs addition (Gu et al., 2010). The role of ADF/cofilin in trafficking of AMPRs during LTP is distinct from its function in changing the spine morphology (Gu et al., 2010). The spine enlargement triggered by chemical induction of LTP is temporally lagged behind the AMPAR insertion. Tight regulation of ADF/cofilin dephosphorylation and phosphorylation controls the AMPAR insertion and spine enlargement, respectively (Gu et al., 2010). However, detail molecular mechanism by which ADF/cofilin activity regulate AMPARs trafficking needed to be studied further.

2.2. Protein 4.1 family

Protein 4.1 family members are identified as actin interacting proteins, expressed in erythrocytes and neurons. Studies have shown that neuronal homologues 4.1N and 4.1G act as vital linker between the AMPARs and the actin cytoskeleton. They act as an anchor of the receptors to the plasma membrane (Hanley, 2014). The C-terminal of GluA1 subunit of AMPAR directly interacts with the F-actin binding protein 4.1N and 4.1G (Shen et al., 2000). Using yeast two hybrid system and a heterologous cell system, it was shown that the C-terminal of 4.1N/G binding to AMPAR is necessary for the GluA1 receptor's stabilized surface expression (Shen et al., 2000; Baines et al., 2014). Knockdown of 4.1N expression using small hairpin RNA (shRNA) reduced the insertion of GluA1 receptor at extrasynaptic sites (Lin et al., 2009). Studies are required to understand the molecular mechanism involved in 4.1 mediated actin cytoskeleton function linking LTP formation. Wonzy et al., mention that synaptic transmission and LTP is unaffected and Lin et al., demonstrate a decay in LTP due to 4.1 knockdown (Wozny et al., 2009; Lin et al., 2009). The precise molecular mechanism is unclear and further studies are required to understand the role of 4.1-mediated actin cytoskeleton function linking LTP formation. However, the experimental data from yeast two-hybrid assays have shown that in *Drosophila*, the actin cytoskeleton, coracle (*Drosophila* version of Protein 4.1) and DLG are necessary but not sufficient for the localization of glutamate receptors (Chen et al., 2005).

2.3. Drebrin

Drebrin, an F-actin binding protein is present in two isoforms: drebrin-A and drebrin-E. Drebrin-A is highly abundant in neurons and mainly expressed in PSD (Mizui et al., 2009). Drebrin-E is diffusely distributed in neurons. Drebrin-A contains neuron specific sequence (Ins2), which is absent in drebrin-E. Drebrin overexpression increases the length of the dendritic spines. In hippocampal neurons drebrin stimulates actin assembly and accumulation of PSD-95 in the PSD. AMPARs activity modulates the concentration of drebrin present in dendritic spines and its function. In cultured hippocampal neurons, pharmacological blockade of AMPARs by CNQX (cyanquixaline [6-cyano-7-nitroquinoxaline-2, 3-dione]) and GYKI (2,3-benzodiazepine) reduces drebrin levels. Philanthotoxin blocks only a subset of AMPARs that were Ca^{2+}-permeable. Therefore, drebrin accumulation in dendritic spines was uninfluenced by philanthotoxin (Takahashi et al., 2009). The blockade of other glutamate receptors does not affect the drebrin density in dendritic spines. During LTP, Ca^{+2} influx induced by *N*-methyl-D-aspartate receptor (also known as the NMDA receptor or NMDAR) activation reduces to the resting level and AMPARs density increases in dendritic spines. This leads to an increase in drebrin-A at postsynaptic sites. Moreover, chelating the intracellular Ca^{+2} concentrations cause a remarkable increase of drebrin expression in dendritic spines. These results further demonstrated that drebrin-A activity was dependent on the regulation of AMPAR function and intracellular Ca^{+2} concentration (Sekino et al., 2017; Lynch, 2004). It promotes drebrin-A decorated stable F-actin formation. Along with other postsynaptic proteins, drebrin-F-actin complex set up the stage for synaptic plasticity. In future it will be interesting to delineate the AMPAR dependent difference in drebrin isoform function.

2.4. RIL (reversion-induced LIM domain protein)

RIL is actin cytoskeleton associated protein containing PDZ domain in the N-terminal and (1–3) LIM domain in the C-terminal (Bach, 2000; Klaavuniemi et al., 2004). RIL stabilizes F-actin to maintain the structure of Z-disc and muscle fibers integrity (Klaavuniemi et al., 2004). The binding of RIL with α-actinin increases the affinity of α-actinin to F-actin, causing pronounced F-actin reorganization (Vallenius et al., 2004). Additionally, PSD fraction of rat forebrain is enriched of RIL. The RIL/α-actinin protein complex was interacting with AMPARs in the forebrain synaptosome (Schulz et al., 2004). In COS1 cells, it was observed that RIL acts as a bridge between the AMPARs and α-actinin/actin cytoskeleton (Schulz et al., 2004). The PDZ domain of RIL binds to α-actinin and LIM domain interacts with the AMPAR (Bach, 2000). Overexpression of RIL in cultured neurons increases AMPARs accumulation in dendritic spines as well as at the synaptic surface (Schulz et al., 2004). RIL is mediating the engagement of extrasynaptic receptors to dendritic spines or hindering the exit of receptors undergoing endosomal synaptic recycling. RIL maintains this interaction through α-actinin/actin-based regulation of transport/recycling AMPARs in dendritic spines (Schulz et al., 2004).

2.5. Rho GTPases

The role of Rho GTPases to reorganize F-actin structures are well-characterized (Hall, 1998). Rho GTPases are activated by GTPase activating protein in response to external stimuli. The already activated Rho GTPases bind to numerous downstream effector molecules like kinases and several ABPs to modulate the actin dynamics inside the cell (Sit and Manser, 2011). It is well-known that the release of glutamate triggers a change in the internal calcium levels in the spine head which increases the GTPase activity of RhoA (Borovac et al., 2018). This response, in turn, causes phosphorylation of ADF/Cofilin and activates other actin reorganizing proteins to modulate the underlying actin cytoskeleton (Borovac et al., 2018). The stimulation signal by AMPARs determines the Rho-GTPases activity. Highly active AMPARs lead to less active Rho-GTPases, increase actin cytoskeleton dynamics to remodel spine structures and shapes. Less active AMPARs result in precise activity of Rho-GTPases leading to less dynamic F-actin. Therefore, the RhoA GTPase activity level is dependent upon AMPAR signalling (Korkotian and Segal, 1999; Schubert et al., 2006). Such machinery acts as a safeguard mechanism to guarantee a certain level of synaptic activity at a particular synapse (Schubert et al., 2006). The mechanistic details of the signalling pathways responsible for glutamate receptor activation to Rho GTPases function is unexplored (Rocca and Hanley, 2015). Future functional studies detailing the role of Rho GTPases and their upstream/-downstream signalling proteins will shed light on the mechanism of synapse formation and function.

2.6. Actin binding drugs

Actin binding drugs are small molecules that interact with actin. These drugs modulate the actin dynamics by influencing actin polymerization/depolymerization. Earlier studies have shown that AMPARs localization and mobility are hampered when cultured neurons are treated with Latrunculin A (Lat A: F-actin destabilizing drug) (Zhou and Xiao MY, 2001). The dynamic pool of F-actin is necessary for AMPAR trafficking during LTP and LTD. F-actin stabilizing drugs such as Jasplakinolide inhibits the internalization of AMPARs from the synaptic plasma membrane by deregulating the F-actin depolymerization (Hanley, 2014). Nevertheless, more definitive studies are needed to understand the signalling cascade occurring in the dendritic spines which ultimately influence the memory formation.

Overall, precise functioning of AMPARs is governed by the accurate functioning of multiple cytoskeleton regulatory proteins that directly or indirectly modulate the AMPARs activity during synapse formation.

3. NMDA receptors and actin cytoskeleton

The NMDAR is another class of iGluRs profoundly expressed in the CNS, are essential for synapse functions in the brain. NMDARs are heteromeric assemblies of GluN1, GluN2 and GluN3 subunits. Depending upon the subunit composition, the NMDARs are activated by binding of glutamate and glycine (or D-serine). The binding of glutamate to the NMDARs modulates the calcium influx and subsequent signalling cascade, which is crucial for the proper development and function of brain (Guo et al., 2017).

Constant remodelling of the actin cytoskeleton generates higher-order actin networks, which provide structural stability to NMDARs (Pelucchi et al., 2020). In turn strong activation of NMDAR can change actin cytoskeleton's integrity (Lei, 2001). Multiple actin cytoskeleton modulators e.g., ADF/cofilin, Spectrin, drebrin are present in the CNS are tightly linked to the functioning of NMDAR. They cater a potential biochemical relationship between the NMDARs activity and the cytoskeleton dynamics.

3.1. GTPases

The regulation of actin dynamics by GTPases is well-established phenomena (Hall, 1998). The NMDARs regulate the spine morphological functions through the GTPases, e.g., the Rho, Cdc 42 and Rac family of proteins (Tada and Sheng, 2006). RhoA and RhoB are expressed in the hippocampal neurons (O'Kane et al., 2003). The electrophysiology studies in the field have shown that these GTPases respond to the glutamate levels present in the postsynaptic neurons (Kim et al., 2003). RhoB activation occurs downstream of NMDARs stimulation. A few studies revealed that RhoA activated through these receptors, in turn, activates ROCK kinase and profilin IIa. The enhanced profilin activity modulates the F-actin treadmilling process to regulate the size of the dendritic spines (Silva, 2003; Michaelsen et al., 2010; Bennett et al., 2011; Stefen et al., 2016). Another study using immunoprecipitation, demonstrated direct interaction of GluN1 with Rac-GTPase (Tejada-Simon et al., 2006). After NMDAR activation, Rac is likely to translocate to the receptor proximity through protein-protein interaction resulting in dendritic growth which needs to be examined further (Tejada-Simon et al., 2006). The necessity of simultaneous activity of NMDARs and GTPases for spine morphological plasticity needs to be characterized in detail in the future.

3.2. Actin interacting proteins and NMDARs

The F-actin present in the PSD, linked to NMDARs through cytoskeleton regulatory proteins expressing in the PSD e.g., PSD-95. Co-immunoprecipitation studies in the literature have illustrated the direct interaction of α-actinin with PSD-95 and NMDAR subunits signifying the role of α-actinin in localization of NMDARs (Wyszynski et al., 1997). Influx of Ca^{+2} through NMDARs leads to activation of Ca^{+2}/calmodulin kinase. Subsequently, calmodulin-dependent kinase is phosphorylated and activated to induce the inactivation of NMDARs. It blocks the binding of α-actinin to NMDARs (Rycroft and Gibb, 2004; Wang et al., 2014; Oswald, 2017). Parallel observation by Ehler et al., demonstrates the direct binding of calmodulin with GluN1 subunit inactivates the NMDARs (Ehlers et al., 1996). NMDAR activity regulate the ADF/Cofilin function in the dendritic spines during LTP and LTD. As mentioned earlier, NMDAR stimulation leads to activation of downstream Rho GTPases which in turn modulates the ADF/cofilin phosphorylation causing inactivation of ADF/cofilin, promoting actin assembly and spine enlargement (Meng et al., 2004) [Fig. 3]. On the other hand, NMDAR activation and influx of Ca^{+2} induce phosphatases to activate ADF/cofilin causing spine shrinkage during LTD. NMDAR-mediated Ca^{+2} influx also induces the removal of Drebrin-A to facilitate the polymerization of F-actin and association of F-actin with other spine resident actin-binding proteins to enlarge the spine head (Shirao et al., 2017; Yasuda et al.,

2018). Similar studies have reported that NMDAR trafficking requires dynamic actin regulation during synaptic plasticity (Stefen et al., 2016). Cytoskeletal interacting protein spectrin, plays a crucial role in activation of NMDARs through its direct interaction with the C-terminal cytoplasmic domains of GluN2A and GluN2B (Hardingham, 2019; Wechsler and Teichberg, 1998). Post-translational modifications on spectrin and NMDARs modulate their interaction which is critical for synapse activity (Wechsler and Teichberg, 1998). Other actin regulating proteins like Eps8 (Epidermal growth factor receptor pathway substrate 8); controls various cellular protrusions by F-actin binding. Esp8 has barbed-end actin filament capping and actin-bundling activities which is essential for the synaptic balance of NMDAR subunits GluN2A and GluN2B (Morini et al., 2018). Eps8, which is part of the NMDARs complex, is also required for spine growth and LTP (Menna et al., 2013; Stamatakou et al., 2013). Neurons from Eps8 KO mice display altered expression and subunit composition of NMDARs (increased expression of GluN2B and decreased GluN2A). Also, the mice lacking Eps8 display immature filopodia on neurons and impaired cognitive functions. In the Eps8 KO mice, the functional maturation of the postsynaptic compartments is also affected (Morini et al., 2018). Another scaffolding protein Shank is present in the synaptic region associate themselves with various classes of ABPs. It is evident from the literature that the deletion of the Shank gene from mice reduces the synaptic F-actin leading to suppression of NMDAR localization (Yan et al., 2016). Later on, inhibition of cofilin activity enhances the stabilization of F-actin levels and ultimately normalizes the NMDAR function in Shank deleted mice (Cho et al., 2013).

The NMDARs interact with actin cytoskeleton through scaffolding proteins present in the post-synapse. The receptors' activity during synaptic transmission controls the functioning of many actin cytoskeleton regulators. In turn, they actively moderate the cytoskeleton's dynamicity for proper learning and memory formation. The delicate balance between NMDAR activity and actin dynamics regulation by ABPs is mandatory for normal spine dynamics.

4. Membrane associated guanylate kinases (MAGUKs) and cell adhesion molecules with AMPAR and NMDAR

MAGUKs can be classified into several different subfamilies: the DLGs, CASK, the palmitoylated membrane proteins (MPPs), the Zonula occludens (ZO) proteins, the caspase activation and recruitment domain (CARD)-containing MAGUK proteins (CARMAs) and the MAGUKs with inverted orientation PDZ (MAGI) subfamily proteins (Zhu et al., 2016; De Mendoza et al., 2010). The MAGUKs are made up of several PDZ domains, an SH3/WW domain, and an inactive guanylate kinase (GK) domain. These domains are necessary to assemble cell adhesion molecules, cytoskeletal proteins, receptors, ion channels and the downstream signalling components at the plasma membrane (De Mendoza et al., 2010; Zhu et al., 2016). The MAGUK family proteins interact with guanylate kinase-associated protein (GKAP), via the GK domain, and GKAPs bind to Shank and Homer (Hayashi et al., 2010) [Fig. 3]. It is well known that Shank interacts with ABPs to link the core PSD structure to the actin cytoskeleton in dendritic spines (Qualmann et al., 2004; Macgillavry et al., 2016). Interaction of GKAP with Shank is essential for its synaptic localization and stabilization (Hayashi et al., 2010). In fact, PSD-95, GKAP, Shank, and Homer are tightly associated to a stable structure, which is resistant to actin depolymerization (Hayashi et al., 2010; Romorini et al., 2004).

The recycling and redistribution of AMPARs depend upon the certain members of MAGUKs family and cell adhesion molecules. MAGUKs family proteins and cell adhesion molecules viz., PSD-95, SAP-97, neuroligin-1, N-cadherin regulate both AMPARs and actin cytoskeleton functions (Keith and Husseini, 2008; Sheng, 2011; Schapitz et al., 2010).

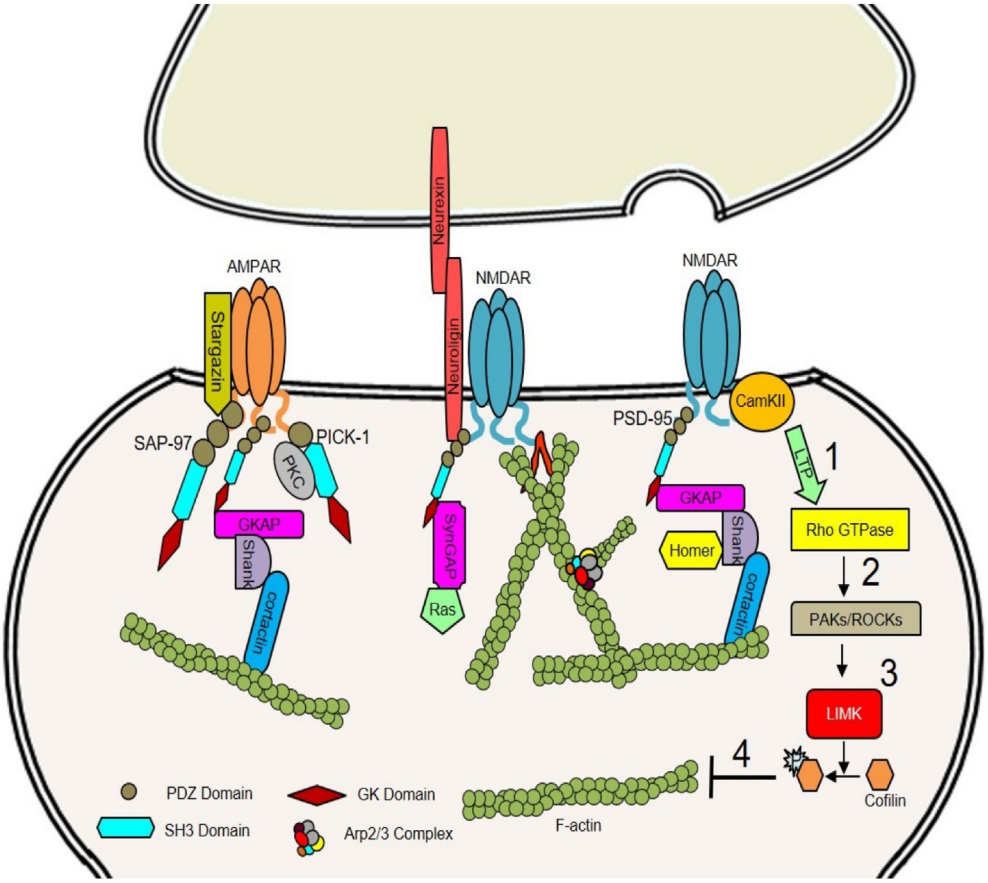

Fig. 3. Schematic representation of iGluRs-associated proteins at the postsynaptic density. AMPARs and NMDARs are linked to a wide array of proteins and regulators via PDZ scaffolding proteins. AMPARs interact with PDZ-containing proteins including PSD-95, PICK-1, SAP-97, which is necessary for membrane targeting and linking the receptor to intracellular enzymes. NMDARs are clustered within the PSD by binding to scaffolding proteins PSD-95 members, α-actinin, SAP-97 which in turn bind effector molecules and cytoskeletal proteins. PSD-95 interacts with a number of intracellular proteins, e.g., the cell-adhesion molecule neuroligin, SynGAP (synaptic Ras-GTPase-activating protein), and GKAP (guanylate kinase-associated protein). (1) During LTP, activation of NMDARs causes increased intracellular calcium which activates CamKII. CamKII in turn activates small Rho GTPases. (2) These small GTPases bind to and activate PAKs and ROCKs. (3) This directly phosphorylates and activates LIMK1 which in turn phosphorylates and inactivates cofilin. (4) Inactivated cofilin cannot sever F-actin.

Germline knockdown of PSD-95 in mice results in lack of functional AMPARs on PSD (Béïque et al., 2006). Using light and electron microscopy techniques it was confirmed that the expression of PSD-95 on the membrane acts as hot spot for accumulation of AMPARs (MacGillavry et al., 2013; Nair et al., 2013). It is well-characterized that knockdown and over expression of α-actinin (actin cross-linker) alter the spine density and structure (Hodges et al., 2014). Recently it is demonstrated through biochemical, cell biological and electrophysiological experiments that α-actinin binds to N-terminus of PSD-95 thereby it ensures the tethering of PSD95-AMPARs complex to PSD (Matt et al., 2018). Another interacting partner of AMPARs is SAP-97, whose overexpression in cultured mouse hippocampal slices of CA1 neurons exhibited proper trafficking of the AMPAR to the synapses that uncovered a direct interaction of SAP-97 with the GluA1 subunit. Also, the experiments carried out in CACO-2 cells showed that SAP-97 interacts with the cortical actin cytoskeleton. Together, these data suggest that SAP-97 is crucial for clustering the receptors on the membrane and attached to the cortical actin cytoskeleton for even distribution of the receptors on the membrane (Hanley, 2014; Howard et al., 2010; Baucum, 2017). Apart from these members, SAP-102 also plays crucial role in F-actin reorganization and localization of AMPARs on PSD through Ephrin B and PAK signalling. Knockdown of SAP-102 using shRNA caused increased number of dendritic filopodia (Murata and Constantine-Paton, 2013).

Cadherins and their associated catenin are expressed in the pre-and postsynaptic compartment of the CNS (Salinas and Price, 2005; Bamji, 2005). At later stages of brain development N-cadherin accumulates at the excitatory synapse and along with β-catenin modulates the morphogenesis of dendritic spines and functioning of the synapses (Benson and Tanaka, 1998). Cadherins interaction with ABPs like cortactin, Arp2/3, formin-1 and Rho family of GTPases are well-established to impact the spine formation and stability (Takeichi and Abe, 2005). Another study reported that N-cadherin directly interacts with GluR2 to regulate the synapse morphology and strength (Saglietti et al., 2007).

Cell adhesion molecules like Neuroligins are present at the postsynaptic transmembrane region, required for accurate synapse activity, but the underlying mechanisms remain unexplored (Liu et al., 2016). The crosstalk between Neuroligin-1 and neurexins cause clustering of PSD-95 and functional AMPARs to the PSD (Mondin et al., 2011). Neuroligin-neurexin mediated pre-and postsynaptic alignment is important for synaptic efficacy (Haas et al., 2018). The immunofluorescence and electrophysiology studies using hippocampal neurons exhibit that point mutation (Y782) on Neuroligin-1 mimics the phosphorylated condition, which recruits functional AMPARs and PSD-95 to the membrane (Letellier et al., 2018). Another study in the field uncovers the regulation of synapse development by Neuroligin-1 through the interaction of LIMK/cofilin mediated actin reorganization (Liu et al., 2016). Electrophysiological studies have demonstrated that expression of both Neuroligin-1 and N-Cadherin are prerequisite for an increase in AMPARs mediated mEPSC frequency in cultured neurons (Stan et al., 2010).

Disc-Large (Dlg) family members e.g., PSD-95 (DLG-4), SAP-102 (DLG-3) and SAP-97 (DLG-1) were first identified to interact with NMDARs (Bissen et al., 2019). PDZ domain of PSD-95/SAP-90 bind to a conserved motif at the extreme C-terminal region of GluN2 subunits of NMDARs (Kornau et al., 1995; Niethammer et al., 1996). GluN2A or GluN2B directly interact with SAP-102 for synaptic clustering of NMDA receptor subunits. SAP-97 binds directly to the C-terminus of GluA1 subunit forming a part of the macromolecular complexes at the PSD (Bissen et al., 2019). SAP-102 interacts with AMPARs at the synapses (Elias et al., 2008). The interaction of SAP-102 with GluN2B in the secretory pathway supports the efficient delivery of the NMDAR to the synaptic sites (Vieira et al., 2020; Sans et al., 2000, 2003). Also, SAP-102 interaction with Rho-GEF Kalirin-7 is required for actin reorganization, synaptogenesis and AMPAR trafficking (Murata and Constantine-Paton, 2013; Bissen et al., 2019). It has been shown that SAP-97 bind to PKA anchoring molecule (AKAP), actin and GluR1 binding protein 4.1 (Colledge et al., 2000; Lue et al., 1994; Rumbaugh et al., 2003). Similarly, PSD-95 can also interact with neuroligin via its PDZ3 (Dakoji et al., 2003).

5. Myosin motors with AMPARs and NMDARs

Myosin superfamily motor proteins hydrolyse ATP and generate force on actin filaments. Various myosin isoforms are crucial for AMPARs trafficking; Myosin-V (plus end directed) and Myosin-VI (minus end directed) are well-characterized among all others (Hanley, 2014). The activity of myosin Va and Vb is important for neuronal functions. Unbiased biochemical studies have revealed the direct interaction between AMPAR subunit and Myosin-Va C-terminal tail. Electrophysiological experiments revealed that Myosin-Va couples with small GTPase Rab11 for short range transport of AMPARs from dendritic shaft to spine head. Myosin-Va is not required for long range trafficking of AMPARs along dendrites and constitutive entry of AMPARs into dendritic spines (Correia et al., 2008). The recycling endosomes containing AMPARs are actively translocated along actin filaments to the plasma membrane using myosin-Vb. These studies demonstrate the crucial role of myosin-V in AMPAR trafficking, though which form of myosin-V is more important in regulating AMPAR recycling, needs to be explored further (Rudolf et al., 2011). Biochemical studies exhibited that myosin-VI is linked to AMPARs through SAP-97 which in turn directly binds to PSD-95. Also, AMPAR internalization is hampered in myosin-VI knockout mice (Osterweil et al., 2005). In a contradictory study it was shown that myosin-VI has a role in trafficking of AMPAR towards plasma membrane (Nash et al., 2010). Understanding the detailed mechanism of AMPAR trafficking by myosin motor isoforms need to be elucidated in the future.

NMDARs linked to multiple proteins in the PSD. The proper functioning of the myosin motors is necessary at the postsynaptic sites for the accurate trafficking of the NMDARs to their relevant place (Bu et al., 2015). It was observed that the activity of myosin-V was also controlled by Ca^{+2} influx due to activation of NMDARs (Wang et al., 2008). In cultured hippocampal neurons, it was observed that constitutively active myosin light chain kinase (MLCK) modulate the NMDAR mediated synaptic currents, whereas inhibitors of MLCK dampen the current. Immunofluorescence data revealed that MLCK and NMDAR did not colocalize with each other. But the effect of MLCK to NMDARs is mediated through the actomyosin complex which increase membrane tension on NMDARs (Lei 1 et al., 2001). Recently a study revealed that besides MLCK, myosin-IIb is involved in NMDARs trafficking (Bu et al., 2015). However, there is no evidence for their direct interaction and the underlying mechanism is unclear.

6. Delta receptors and actin cytoskeleton

The delta receptor family (GluD1 and GluD2) are regarded as subfamily of iGluRs because of amino-acid sequence homology. GluD1 was discovered from the cDNA library by molecular cloning (Burada et al., 2020; Yamazaki et al., 1992). These receptors are atypical because they do not exhibit functional agonist-induced ion channel currents when expressed either alone or with other iGluRs, in transfected cells, nor do they bind to any glutamate analog (Burada et al., 2020; Kakegawa et al., 2007). GluD1 and GluD2 receptors are expressed in the various regions of the brain like the cortex, hippocampal region, and the cerebellar interneurons (Konno et al., 2014). The expression level of these receptors is upregulated during postnatal development (Hepp et al., 2015). It is already known that GluD1 is highly expressed in the forebrain and low in the hindbrain, whereas GluD2 is predominantly present in the Purkinje cells of the cerebellum (Kohda et al., 2016; Nakamoto et al., 2020). However, ligands like D-serine and glycine bind to these receptors' ligand-binding domain and induce a conformational change in them (Naur et al., 2007). Recent advancements in the field have demonstrated the crucial role of delta receptors in synaptogenesis, learning, and memory formation. C-terminal tail domain deletion of GluD1 completely abolishes the receptor's synaptic functioning, while surface expression

was not hampered (Tao et al., 2019; Fossati et al., 2019). The studies on GluD1 knockout mice have shown that this receptor is essential for normal synapse formation and maintenance of spine dynamics (Khan, 2017). Deletion of this receptor cause abnormality in the LIMK1-cofilin signalling pathway that regulates the actin dynamics through Cofilin-1 activity. Subsequently, it affects learning and memory functions (Gupta et al., 2015). It is mentioned in the earlier section that the signalling cascade of LIM kinases and cofilin controls the NMDAR activity. The study has shown that the subunit expression ratio of the NMDAR (GluN2A/GluN2B) is impaired in the GluD1 knockout mice. Future studies are required to understand the detailed molecular mechanistic function of the glutamate delta receptor family influencing the functioning of NMDAR via LIM kinases and cofilin (Khan, 2017).

GluD2 is predominantly present in the postsynaptic density of excitatory synapses and plays an essential role in synaptic functions (Yuzaki, 2003). Studies have shown that GluD2 is mainly localized in the parallel fibers of Purkinje cells (PF-PC) in dendritic spines and did not localize in dendritic spines lacking synaptic contacts with parallel fibers (Hirano, 2012; Ichikawa et al., 2016). GluD2 is essential for the proper alignment of pre-and postsynaptic elements on PF-PC. They have a critical role in synapse formation, motor learning, motor coordination, and induction of long-term depression (LTD). The complete C-terminal cytoplasmic domain (CTD) of GluD2 is indispensable for the proper functioning of this receptor and LTD formation (Burada et al., 2020; Elegheert et al., 2016; Yuzaki and Aricescu, 2017). This CTD of GluD2 interacts with a large number of scaffolding and signalling proteins and binds a large number of PDZ proteins like PDS-93, PTPMEG, SSCAM, Shank, n-PIST, Delphilin, Spectrin. Most of these PDZ proteins like Spectrin, Delphilin, n-PIST, Shank are actin cytoskeleton interacting proteins (Mandolesi et al., 2009; Das et al., 2018; Dutta et al., 2017). It is already known that Spectrin aids in the anchoring of GluD2 to the cytoskeleton and this interaction is also modulated by calcium. Elevation in the intercellular calcium level causes delta receptors' de-clustering by dissociating these receptors from Spectrin (Hirai and Matsuda, 1999). The actin cytoskeleton plays a pivotal role in the clustering of GluD2 in the postsynaptic density membrane (PSD membrane). Also, cytoskeleton disrupting agents like Cytochalasin D (inhibit actin polymerization by binding to F-actin) and Latrunculin A disrupt the clustering of GluD2 at the PSD membrane. The removal of the GluD2 cluster by Latrunculin A was re-established 24 h after removing the drug (Hirai, 2000). It suggests that morphological changes in the actin cytoskeleton modulate the delta receptors clustering on the dendritic spines and their effect on synaptic efficacy and plasticity need to be elaborated in the future.

Earlier studies have shown that PDZ domain of Delphilin binds to the C-terminus of GluD2. Surface plasmon resonance revealed that phosphorylation of C-terminal tail of GluD2 by protein kinase A inhibit the interaction of Delphilin PDZ domain and GluD2 C-terminal (Miyagi et al., 2002; Sonoda et al., 2006). Delphilin stabilizes the actin cytoskeleton by the FH2 domain (Dutta et al., 2017; Silkworth et al., 2018). Similarly, other proteins viz., nPIST, Spectrin also bind to the actin cytoskeleton, support these receptors to anchor the actin cytoskeleton (Das et al., 2018). Deletion of Delphilin affects the GluD2 receptors' localization. The regulation of delta receptor's activity mediated by different actin-binding proteins is needed to be elucidated in the future.

In conclusion, the functional activity of the delta receptors depends on the actin cytoskeleton and its regulatory proteins, which modulate the cytoskeleton function through various signalling pathways.

7. Kainate receptors and actin cytoskeleton

Kainate receptors or kainic acid receptors (KARs) are present on both pre-and postsynaptic regions. However, their expression is less compared to AMPARs and NMDARs in the brain (Dingledine et al., 1999). The activation of postsynaptic kainate receptors has a minor role in synaptic plasticity. However, when the presynaptic kainate receptors are activated, it results in facilitation or suppression of the neurotransmitter release. There are five types of kainate receptor subunits, of which only GluK1 and GluK2 form functional tetrameric receptor along with other subunits (Graham et al., 2009). Similar to other families of glutamate receptors, they do not bind or modulate the synaptic actin pool directly. The crosstalk between Kainate receptors and cytoskeleton regulatory proteins are not well-characterized.

Recent studies in the field have shown that the GluK1 and GluK2 interact with spectrin-actin binding scaffolding protein 4.1N through the proximal domain present in the C-terminal tail (Dingledine et al., 1999; Copits and Swanson, 2013). This communication is necessary for the correct distribution, trafficking, and endocytosis of the GluK2 receptors on the neuronal plasma membrane. The interaction between GluK2 with protein 4.1N happens through phosphorylation by protein kinase C and the receptor's palmitoylation. Palmitoylation deficient GluK2 receptors exhibit reduced surface expression and compromised endocytosis. Actinfilin, an actin-binding protein expressed in the synapse. It binds to GluK2 for targeting the degradation. Actinfilin acts as a substrate adaptor protein, binds to Cullin-3 for linking GluK2 with E3 ubiquitin-ligase complex (Salinas et al., 2006). Actinfilin expression in the synapse is important for trafficking of GluK2 receptors even though the function of actinfilin in the synapse is unclear. Post-translation modification of kainate receptors play a pivotal role in synaptic plasticity and trafficking of these receptors. A crucial aspect of future research will involve underscoring the detailed molecular kainate receptor function with respect to the actin-binding proteins.

8. Auxiliary proteins and cytoplasmic interactors that bridge iGluRs and the cytoskeleton

The iGluRs with their the auxiliary or accessory proteins remain an integral part of the receptor complexes on the cell surface. They influence receptor localization, trafficking, gating, and function which is fundamental to synaptic plasticity, learning, and memory (Payne, 2008; Coombs and Cull-Candy, 2009). The auxiliary proteins of iGluRs play a significant role in AMPAR biogenesis in the plasma membrane.

Protein interacting with C-kinase 1(PICK1) was discovered as an interacting partner of protein kinase-C (Staudinger et al., 1995). PICK1 is a PDZ and BAR domain containing protein, which binds to the GluA2/3 subunit via PDZ domain (Hanley, 2008). The N-terminal acidic region of PICK1 binds to Ca^{2+} to regulate interaction with AMPARs (Lu et al., 2014). The C- terminal acidic region regulate the BAR domain that interacts with activated CamKII and endophilins. Neurexin induces clustering of PICK1 at the post synapses. Studies have shown that PICK1 directly binds to Arp2/3 complex and inhibit actin polymerization leading to spine shrinkage during LTD (Rocca et al., 2008; Rocca et al., 2013). Recently, it was uncovered that PICK1 binds to Rho GTPases like Rac and Cdc42. In general, Cdc42 regulate dendritic spine morphogenesis via small effector molecule N-WASP. N-WASP promotes actin polymerization through activation of Arp2/3 complex (Rocca and Hanley, 2015). While binding to Cdc42, PICK1 is upstream of Cdc42 and binding to Arp2/3, PICK1 is downstream of effector molecule (Rocca and Hanley, 2015). Hence, PICK1 can modulate the actin dynamics in multiple pathways. Another pathway to facilitate LTD may involve PICK1 binding to AMPARs. The complex interacts with Arc/Arg3.1, a protein that has been found to associate with cytoskeletal matrix (Goo et al., 2018). This may engage dynamins and endophilins to selectively reduce AMPAR surface expression at post-synapse. Presynaptic plasticity mediated by AMPARs involves interaction with PICK1 (Haglerød et al., 2017). Neuroligin interacts with PICK1 which interacts with GluK1 and GluK2 which may lead to its control on the PSD. KARs are also known to bind to both GRIP and PICK1 but with differential regulation. As discussed earlier that the detailed signalling pathways that transduce from glutamate receptor activation to Rho-GTPases activity are unclear. In future, it will be worth to explore the precise function of PICK1 to control actin dynamics in neurons.

Recent studies on TARPs (Transmembrane AMPAR regulatory proteins) revealed that TARPs associated with AMPAR plays a crucial role in AMPAR maturation and trafficking (Chen L, 2000; Nicoll et al., 2006).

Schnell et al. had shown the direct interaction of PSD-95 with Stargazin (TARP member) was sufficient and necessary for localization of AMPAR. PSD-95 interacts with TARPγ8, γ4 and γ3 (Schnell et al., 2002). The C-terminal tail of TARPγ4 also interacts with multiple other MAGUKs like PSD-93, SAP-97 and SAP-102. TARPγ3 interacts with PSD-93 and PSD-95 in vivo but not SAP-102 or SAP-97. The interaction between TARPs and PSD95 is also regulated by phosphorylation of multiple serines at the C-terminus of TARPs by CAMKII and PKC involved in NMDA induced LTP or LTD (Tomita et al., 2005; Park et al., 2016).

9. Conclusion

In this review, we have discussed the significance of actin cytoskeleton and its regulatory proteins for proper functioning of iGluRs. Also, we have pointed how the field is trying to understand the crosstalk of actin cytoskeleton scaffolding proteins with iGluRs in the context of receptor activity and their trafficking. Advancement in the last ten years uncovered the expression of ABPs and scaffolding proteins in the dendritic spines. These proteins associate with the iGluRs and auxiliary proteins to regulate iGluRs behaviour and localization. To comprehend the synapse activity, it is important to understand the spatio-temporal regulation of actin dynamics with various types of iGluRs.

Although numerous studies were going on to understand the role of ABPs in spine morphogenesis and their interaction with various iGluRs to modulate receptor trafficking and function. However, the complete mechanistic biochemical role of these ABPs in synapse formation is unclear. In the future, multiple outstanding challenges e.g., the detailed function of Rho-GTPases with AMPAR and NMDAR, Delphilin with GluD2, NMDAR and AMPAR activity with respect to Drebrin and many more similar questions are required to investigate. Future experiments using advanced biochemical and cell biological tools are necessary to elaborate the role of cortical actin cytoskeleton in iGluRs function for synapse formation. In the future, in vivo studies will also aid in understanding the receptor biology involving actin cytoskeleton.

CRediT authorship contribution statement

Priyanka Dutta: Conceptualization, Writing – original draft, Formal analysis. **Pratibha Bharti:** Conceptualization, Writing – original draft, Formal analysis, The manuscript was conceptualized, designed, and written by PD, JK and SM. PD and PB analysed and wrote the draft. **Janesh Kumar:** Conceptualization, Writing – original draft, Formal analysis. **Sankar Maiti:** Conceptualization, Writing – original draft, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors thank Dr. Radha Chauhan for critical reading the manuscript and insightful inputs. This work is supported by DST Inspire Faculty Fellowship Award [grant number: DST/INSPIRE/04/2017/001906] awarded to PD. SM is thankful to SERB (CRG/2019/001727) and IISER-Kolkata for providing the funding and facility.

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