Review

Cell PRESS

Dendritic spine dynamics – a key role for kalirin-7

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Changes in the structure and function of dendritic spines contribute to numerous physiological processes such as synaptic transmission and plasticity, as well as behavior, including learning and memory. Moreover, altered dendritic spine morphogenesis and plasticity is an endophenotype of many neurodevelopmental and neuropsychiatric disorders. Hence, the molecular mechanisms that control spine plasticity and pathology have been under intense investigation over the past few years. A series of recent studies has improved our understanding of spine dynamics by establishing kalirin-7 as an important regulator of dendritic spine development as well as structural and functional plasticity, providing a model for the molecular control of structural plasticity and implicating kalirin-7 in synaptic pathology in several disorders including schizophrenia and Alzheimer's disease.

Dendritic spine plasticity mechanisms

In the mammalian forebrain, most excitatory synapses are located on dendritic spines, mushroom-shaped protrusions of dendrites [1]. Spine morphology modulates synaptic properties, including strength, stability, calcium dynamics, receptor content and the ability to undergo plasticity [2,3]. In the young brain, dendritic filopodia and spines are very dynamic, actively participating in synapse formation and elimination [4]. Spine plasticity driven by changes in synaptic activity contributes to the remodeling of neural circuits during postnatal development and critical periods, and their experience-dependent plasticity throughout life [3,5].

The degree of spine dynamics is reduced during adulthood as spines stabilize and spine elimination decreases, but changes in spine size, and to a lesser extent in spine numbers, occur spontaneously, and in association with physiological and pathological conditions [3,6]. Rapid spine enlargement parallels various forms of potentiation including long-term potentiation (LTP), whereas long-term depression (LTD) seems associated with spine shrinkage [7]. In mature neurons the majority of spines are stable [8]; however, in some physiological and pathological conditions this stability is altered, indicating that steady-state morphology of spines is tightly regulated and that these mechanisms can be impaired in diseases. Accordingly, spines can undergo morphological changes in live animals during changes in sensory input, social interactions, stress, environmental enrichment, learning and other behavioral conditions [3], and a large number of disorders of the central nervous system are associated with altered spine numbers and morphology. These include neurodevelopmental disorders such as fragile X, syndromic and non-syndromic mental retardation, Down's syndrome and autism spectrum disorders [9–12]. Aberrant spine morphology also occurs in psychiatric disorders [13] and drug addiction [14], as well as in neurodegenerative disorders, including Alzheimer's disease (AD) [15], Huntington's disease (HD) [16] and Parkinson's disease [17]. Thus, uncovering the molecular mechanisms of dendritic spine structural plasticity will provide crucial insight into normal brain development and function, and will facilitate the understanding and treatment of several human disorders.

Spine morphogenesis and plasticity rely on dynamic remodeling of the actin cytoskeleton within spines [18,19]. Actin rearrangements are regulated by Rho-like small GTPases (Rac, RhoA and Cdc42), molecular switches that control dendrite and spine morphology [20]. Specifically, active Rac1 and Cdc42 promote spine formation, enlargement and maintenance, whereas RhoA has opposite effects on spine density and stability [20]. A key role for Rho GTPase signaling in human cognitive development is demonstrated by the association of many proteins in the Rho GTPase pathway with human X-linked mental retardation, in which altered spine morphology is the most evident anatomical alteration [20,21]. Rho GTPases are activated by guanine-nucleotide exchange factors (GEFs) and are deactivated by GTPase activating proteins (GAPs). Importantly, recent studies have shown that several Rho GEFs and GAPs that localize to dendritic spines play important roles in dendritic spine morphogenesis by modulating the activity of Rho GTPases. These include the Rho-GAPs oligophrenin and α-1-chimerin, and the Rho-GEFs intersectin, Tiam1, α-PIX, β-PIX and kalirin-7 [22–28]. Understanding the differential roles of these GEFs and GAPs at different stages of development, in different regions of the brain and for different subtypes of neurons will be necessary to provide a more complete mechanism for the regulation of spine dynamics by actin cytoskeletal rearrangement.

The postsynaptic Rac1-GEF kalirin-7 (Figure 1a,b) is emerging as a key regulator of spine plasticity (Figure 1c) [1]. Kalirin-7 is the most abundant isoform of kalirin proteins in adult brain [29,30]. Its expression is undetectable at birth and increases thereafter in parallel with synaptogenesis [28]. Its neuron-specific expression is mainly restricted to the hippocampus and cerebral cortex

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0166-2236/$ – see front matter doi:10.1016/j.tins.2008.06.001 Available online xxxxx

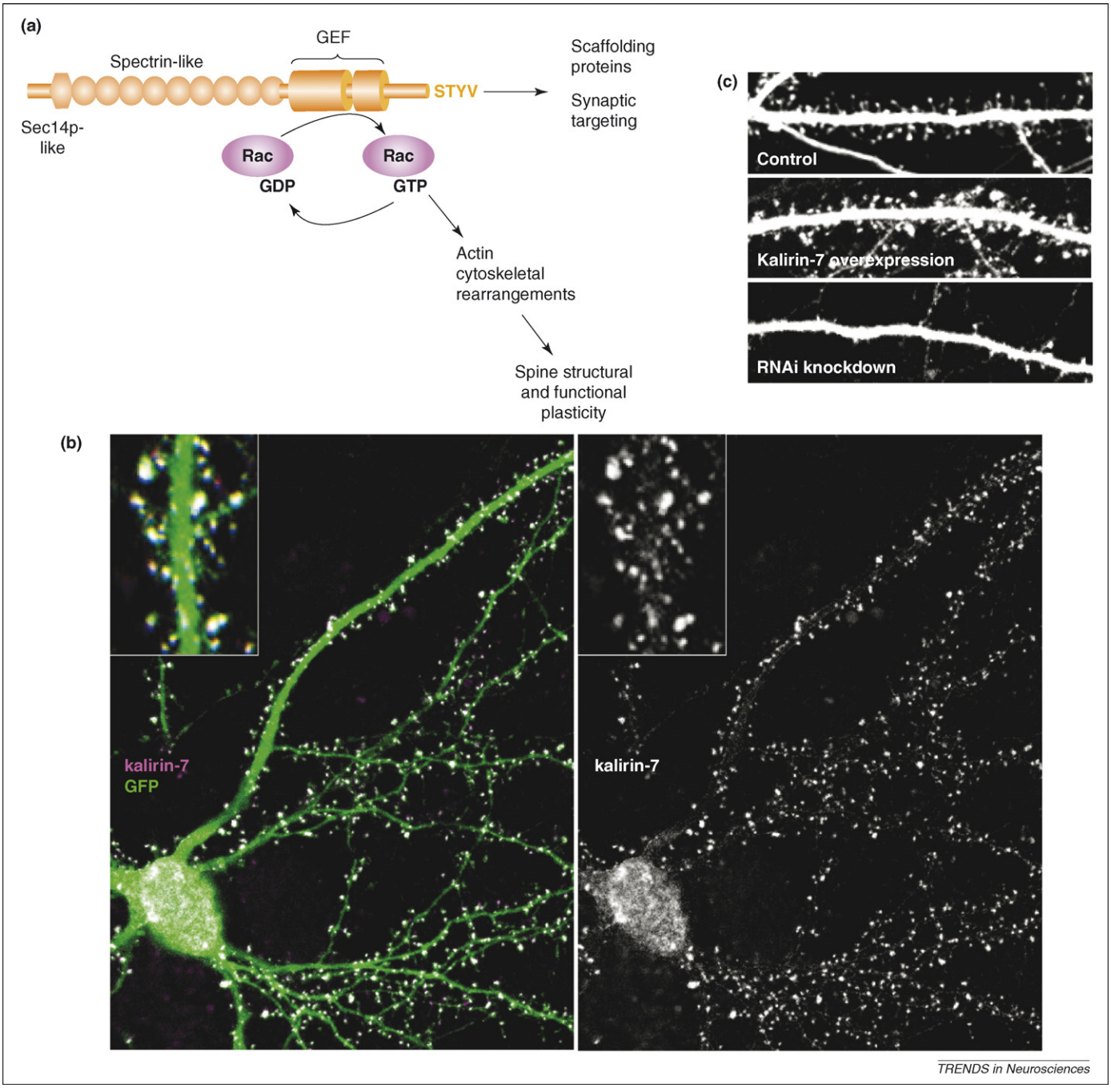

Figure 1. Kalirin-7 is a postsynaptic regulator of spine morphogenesis. **(a)** Domain structure of kalirin-7; the Dbl-homology (DH) and pleckstrin homology (PH) domains provide the GEF activity; at its C terminus, kalirin-7 contains a unique 20 amino acid sequence ending in a PDZ domain-binding motif (STYV). The GEF domain activates Rac1, and controls spine remodeling by modulating actin cytoskeletal rearrangements. **(b)** In pyramidal neurons, kalirin-7 is targeted to dendritic spines. Images show GFP-filled neurons cotransfected with other constructs. **(c)** Kalirin-7 regulates dendritic spine morphogenesis and maintenance in pyramidal neurons: its overexpression promotes spine formation and enlargement; its RNAi-mediated knockdown causes spine shrinkage and loss.

[31], suggesting that kalirin-7 might be an important player in the regulation of structural plasticity that underlies learning and memory. A series of recent studies has begun to uncover the precise functions of kalirin-7 in the control of dendritic spine morphogenesis and its relevance to development, plasticity and synaptic pathology. Here we will discuss its integrative role in spines as a potential model for other signaling mechanisms that might regulate dendritic spine morphogenesis in response to multiple cellular inputs.

Spine maturation: a role for EphB/kalirin-7/PAK signaling

Dendritic spine morphogenesis is a vital part of the process of synapse formation and maturation during CNS development, and it is highly regulated by several important signaling pathways. B-type ephrins and their EphB receptors are a family of intercellular adhesion-like molecules that control multiple aspects of neuronal development, including synapse formation and maturation, as well as synaptic structural and functional plasticity [32]. Acti-

vation of EphB receptors in neurons induces the rapid formation and enlargement of dendritic spines, as well as rapid synapse maturation [32], and several downstream effectors of EphB signaling modulate dendritic spine morphogenesis, including Tiam1, intersectin and kalirin-7 [33]. In young hippocampal neurons, kalirin-7 plays an important role in the maturation of spiny synapses induced by trans-synaptic ephrinB/EphB signaling (Figure 2a) [34]. EphB2 activates kalirin-7, leading to the recruitment of kalirin-7 to synapses [34]. EphrinB1-induced spine morphogenesis requires EphB receptor kinase activity, kalirin-7 RacGEF activity, Rac1 activation and p21-activated kinase (PAK) phosphorylation. These findings demonstrate that in young hippocampal pyramidal neurons, kalirin-7 links trans-synaptic signaling through ephrinB and EphB receptors to spine formation and maturation. However, the roles of this pathway in mature neurons, other brain regions and other types of neurons remain to be elucidated.

Activity-dependent spine structural and functional plasticity: a role for kalirin-7

Structural modification of the excitatory synapse in response to neuronal activity is a key component of experience-dependent development and plasticity in the developing and adult mammalian brain. Dendritic spine morphogenesis and synaptic function are strongly correlated in plasticity models such as sensory deprivation and environmental enrichment [3], and synaptic AMPA receptor (AMPAR) content is also influenced by spine size [2]. In pyramidal neurons, various forms of activity-dependent plasticity are associated with the rapid enlargement of spine heads, which occur in parallel with the delivery of AMPAR into spines [1,5,35,36]. AMPARs, particularly those containing GluR1, are essential for basal excitatory transmission and are required for synapse potentiation [37]. Whereas NMDA receptor (NMDAR)-dependent activation of calcium/calmodulin-dependent protein kinase II (CaMKII) is important for the early stages of synaptic structural and functional plasticity, and for learning and memory [38], the mechanisms that link the structural and functional components of synaptic plasticity are not well understood. Xie, Srivastava and colleagues have recently shown that kalirin-7 is rapidly phosphorylated by CaMKII in response to NMDAR stimulation, a modification that enhances kalirin-7's GEF activity (Figure 2b) [28]. Activated kalirin-7 is essential for NMDAR-dependent Rac1 activation and resulting spine enlargement and maintenance, increased GluR1 content in spines and enhanced AMPAR-mediated synaptic transmission. These effects are consistent with a previous study linking Rac1 activation with AMPAR clustering during synapse maturation [39] and depend on actin polymerization, indicating that kalirin-7 might regulate AMPAR maintenance in spines by regulating the actin cytoskeleton to which AMPARs are anchored [19]. It is also possible that kalirin-7 signaling might influence the targeting of AMPAR through interactions with molecules such as stargazin, a transmembrane AMPAR regulatory protein (TARP) that is crucial for AMPAR assembly and trafficking [40], and PSD-95, a common binding partner for both stargazin and kalirin-7.

These studies demonstrate that in mature cortical pyramidal neurons, kalirin-7 might be a central player in the transmission of the signal from NMDAR to the actin cytoskeletal rearrangement and AMPAR trafficking that underlie synaptic structural and functional plasticity.

Adhesion signaling and spine stability: a role for kalirin-7

In addition to its roles in ephrin- and activity-dependent dendritic spine remodeling, kalirin-7 is also crucial for the modulation of spine morphology by another class of trans-synaptic adhesion molecules, N-cadherins. Signaling by N-cadherins modulates synaptic plasticity, as well as spine morphology and stability [32,36,41]. Xie and colleagues found that upon engagement of N-cadherin in cortical pyramidal neurons, kalirin-7 is recruited into complexes with N-cadherin-associated proteins through the interaction of its C tail with the PDZ domain of AF-6/afadin (Figure 2c) [42]. AF-6 is an actin-binding scaffolding protein enriched in adhesion junctions, which is also regulated by the GTPase Rap [43]. This adhesion-induced spine enlargement also involves Rac1 and PAK. By providing adhesion molecules the ability to actively regulate postsynaptic actin rearrangements, this pathway might underlie the rapid coordination of synaptic adhesion with spine remodeling during synapse maturation and plasticity, but might also assure spine stability in mature neurons.

Protein signaling networks regulating spine dynamics

Numerous multidomain proteins with enzymatic activity have been found to participate in an ever-growing signaling pathway network in dendritic spines that regulates synaptic structure and function [44,45]. As the complexity of the signaling network governing dendritic spine dynamics increases, it is becoming clear that crosstalk between pathways is crucial for the convergence of signaling and appropriate structural or functional modification of the synapse. We discuss kalirin-7 as a model of a point of convergence of several key pathways that have been implicated in dendritic spine morphogenesis, including PDZ interactions and regulation by other small GTPases.

Kalirin-7 is concentrated in dendritic spines of forebrain pyramidal neurons (Figure 1b) and interacts with a large number of proteins (Figure 3), several of which regulate its localization and GEF activity, and hence modulate its signaling [46]. Kalirin-7 is highly enriched in postsynaptic densities (PSD), and its C terminus interacted in a yeast two-hybrid screen with 16 PDZ domain-containing proteins (Figure 3). These proteins interact with receptors and other signaling proteins and might therefore link kalirin-7 with multiple receptor-associated pathways. Most of them are abundant in the PSD; several (PSD-95, SAP102, SAP97, Chapsyn-110, S-SCAM, PICK-1) function in trafficking glutamate receptors or in the assembly of glutamate receptor-associated signaling complexes. Of these, PSD-95 might link kalirin-7 with NMDAR and AMPAR [28,46]. Others (AF-6, SAP97, ZO-1, MAGI-1, MAGI-2, MUPP1, spinophilin) mediate adhesion signaling. Kalirin-7 interactors also include several

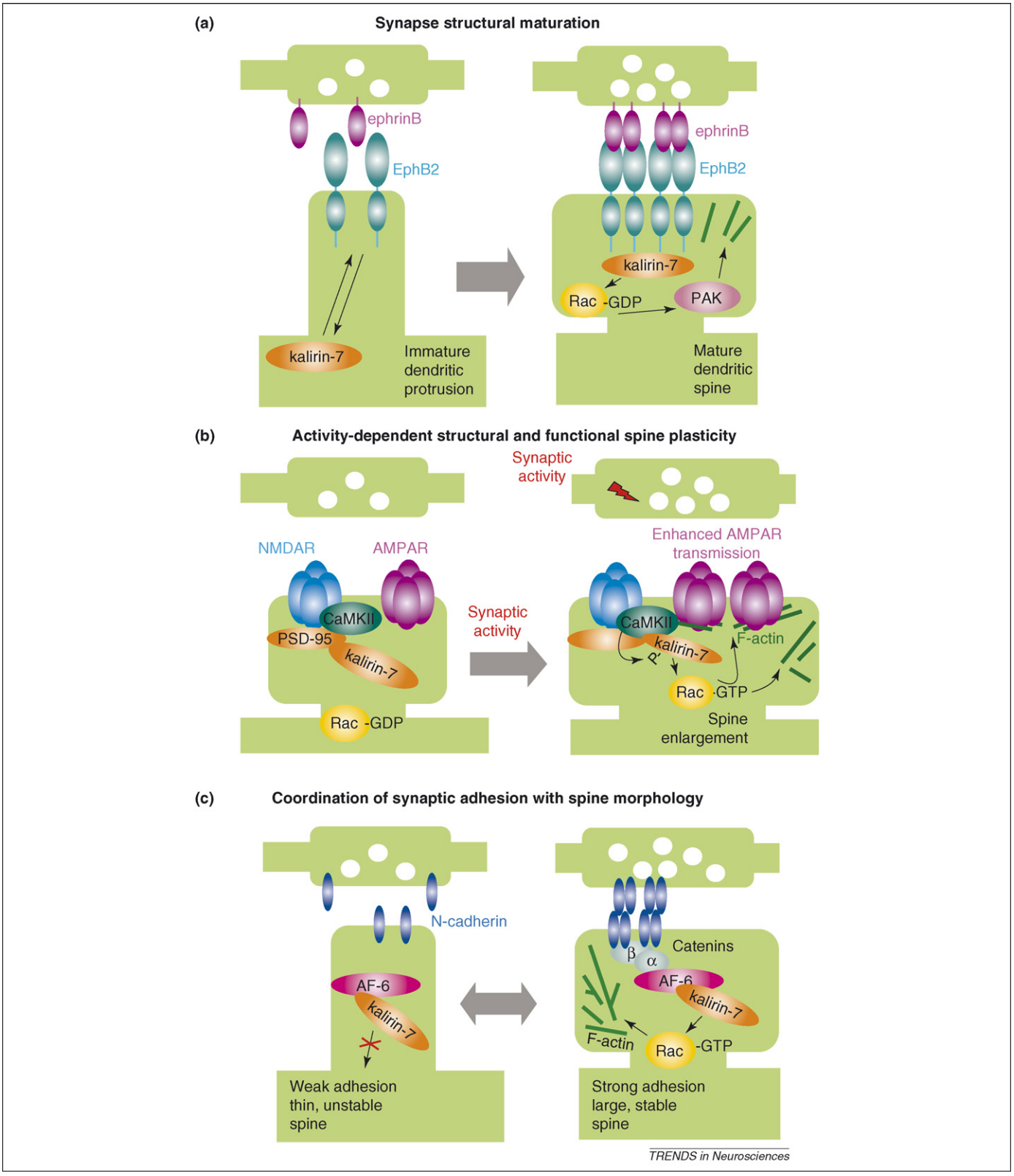

Figure 2. Mechanisms of spine development, plasticity and stability: control by kalirin-7. **(a)** In young hippocampal pyramidal neurons, kalirin-7 controls rapid spiny synapse maturation induced by ephrinB/EphB trans-synaptic signaling. **(b)** In mature cortical pyramidal neurons, kalirin-7 mediates activity-dependent spine plasticity. **(c)** In cortical pyramidal neurons, kalirin-7 mediates coordination of synaptic adhesion with spine morphology downstream of N-cadherin.

actin-binding proteins. Spinophilin and neurabin are particularly interesting because they modulate dopamine receptor signaling [47] and regulate spine morphogenesis [48]. The physiological significance of many of these interactions awaits investigation.

Recent studies indicate that kalirin-7 might be regulated by the small GTPase Arf6 (Figure 3) [49], which, together with its activator EFA6, regulates the conversion of filopodia to spines and the stability of early and mature spines, potentially through Rac1-dependent signaling [50].

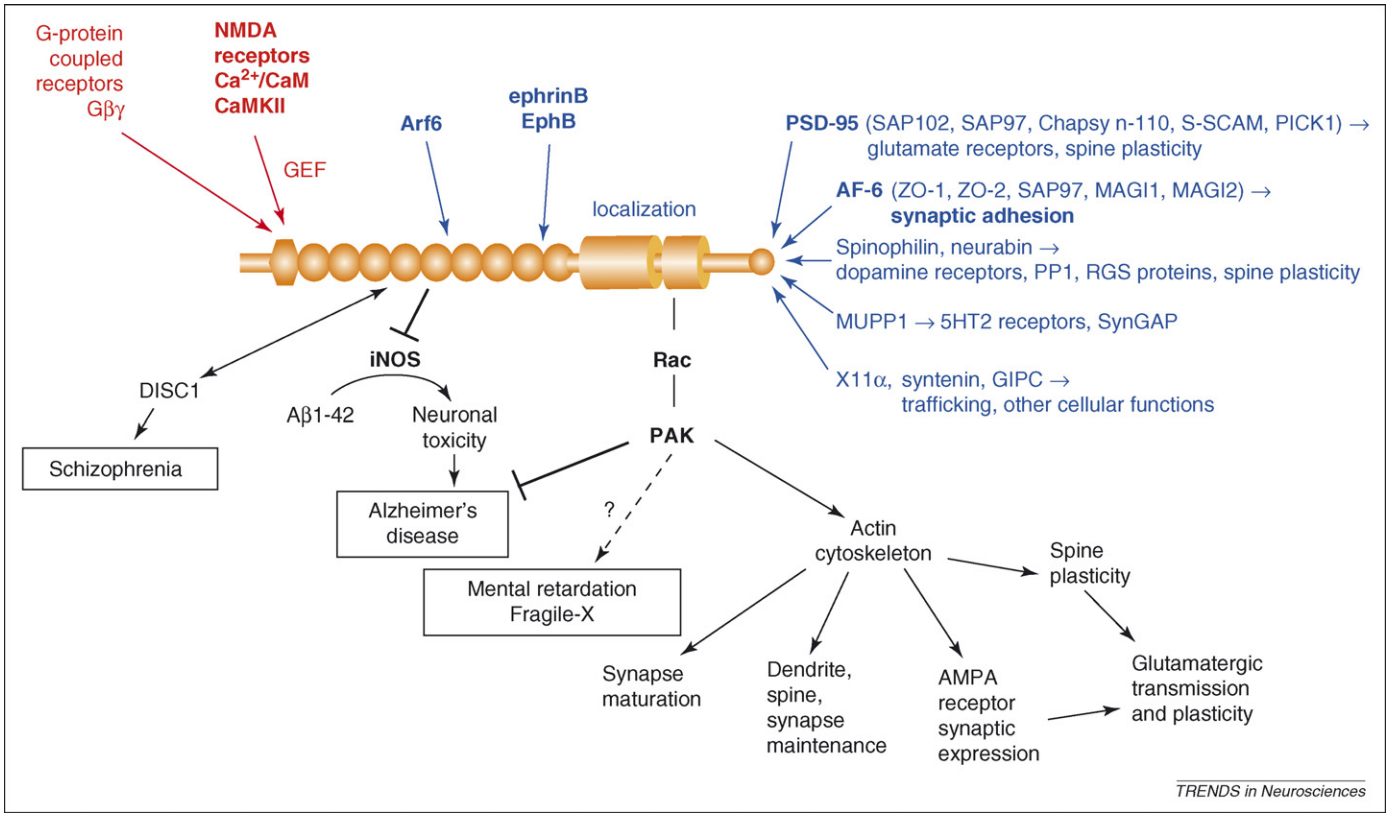

Figure 3. Synaptic signaling networks: regulators and targets of kalirin-7. Signaling by NMDAR and G-protein-coupled receptors modulates kalirin-7 GEF activity (red). Interactions with EphB, Arf6 and PDZ domain-containing proteins control kalirin-7 localization. The major signaling output (black) of kalirin-7 is through Rac1 and PAK; however, it also interacts with and modulates other proteins, including iNOS and DISC1. Hence, kalirin-7 signaling controls multiple aspects of spine plasticity and might be involved in spine pathology associated with CNS disorders. Proteins in bold letters are discussed in the text.

In nonneuronal cells, Arf6 recruits kalirin-7 to the plasma membrane and enhances kalirin-induced membrane ruffling, an indicator of Rac1 activation, suggesting that kalirin-7 has the potential to mediate EFA6/Arf6-dependent spine remodeling in neurons [49].

This multitude of functional interactions indicates that kalirin-7 might function as a hub for multiple signaling pathways that control diverse aspects of spine plasticity (Figure 3). Kalirin-7 might fulfill several unique functions in the propagation of signals from receptors at the synaptic membrane to actin (Figure 4). As each kalirin-7 molecule activates several Rac1 molecules, kalirin-7 provides an amplification step in these signaling cascades (Figure 4a). Multiprotein complexes, such as those containing NMDAR/CaMKII/kalirin-7 or N-cadherin/AF-6/kalirin-7, provide signal channeling through spatial localization of the signaling cascades, resulting in higher signaling specificity and temporal efficiency (Figure 4b). Because kalirin-7 is regulated by ephrinB/EphB, NMDAR, cadherins, Arf6 and potentially others, it could integrate multiple signaling inputs, resulting in a higher degree of control than separate pathways would (Figure 4c). In addition, by regulating spine structure and AMPAR synaptic expression, kalirin-7 coordinates synapse structure and function (Figure 4d).

Regulation of synapse structure in interneurons

Recent studies reveal that regulators of dendritic spine dynamics in pyramidal neurons can also play a role in aspiny synapse formation and maintenance in interneurons. The AMPAR subunit GluR2 [51] and the scaffolding protein Shank3 [52] have both been shown to induce spine formation in aspiny interneurons or cerebellar granule cells, but much less is known about the structural regulation of these aspiny synapses. An interesting recent finding is that kalirin-7 is also important for the maintenance of the dendritic arbor and of excitatory synapses in inhibitory neurons [53]. Kalirin-7 has lower but still detectable expression levels in hippocampal interneurons, and it is postsynaptically concentrated in excitatory synapses made onto dendritic shafts of these neurons. Kalirin-7 overexpression increases dendritic branching and induces formation of spine-like structures, whereas its knockdown causes a reduction in dendritic length and branching and in the number of excitatory (but not GABAergic) synapses made onto them. Correct regulation of the balance of inhibition and excitation is crucial for normal brain circuit development and function to allow plasticity while avoiding excitotoxicity [54]. Conversely, abnormal GABAergic interneuron development and function, leading to abnormal excitatory and inhibitory synapse balance, is thought to contribute to several CNS disorders, including autism, schizophrenia, bipolar disorder, epilepsy and Alzheimer's disease [55]. Kalirin-7 might therefore play an important role in inhibitory neuron development, function and pathology, and contribute to disorders associated with abnormal inhibitory neuron function.

Synaptic pathology: a role for kalirin-7

Aberrant spine morphology is a hallmark of many neurodevelopmental, neuropsychiatric and neurodegenerative

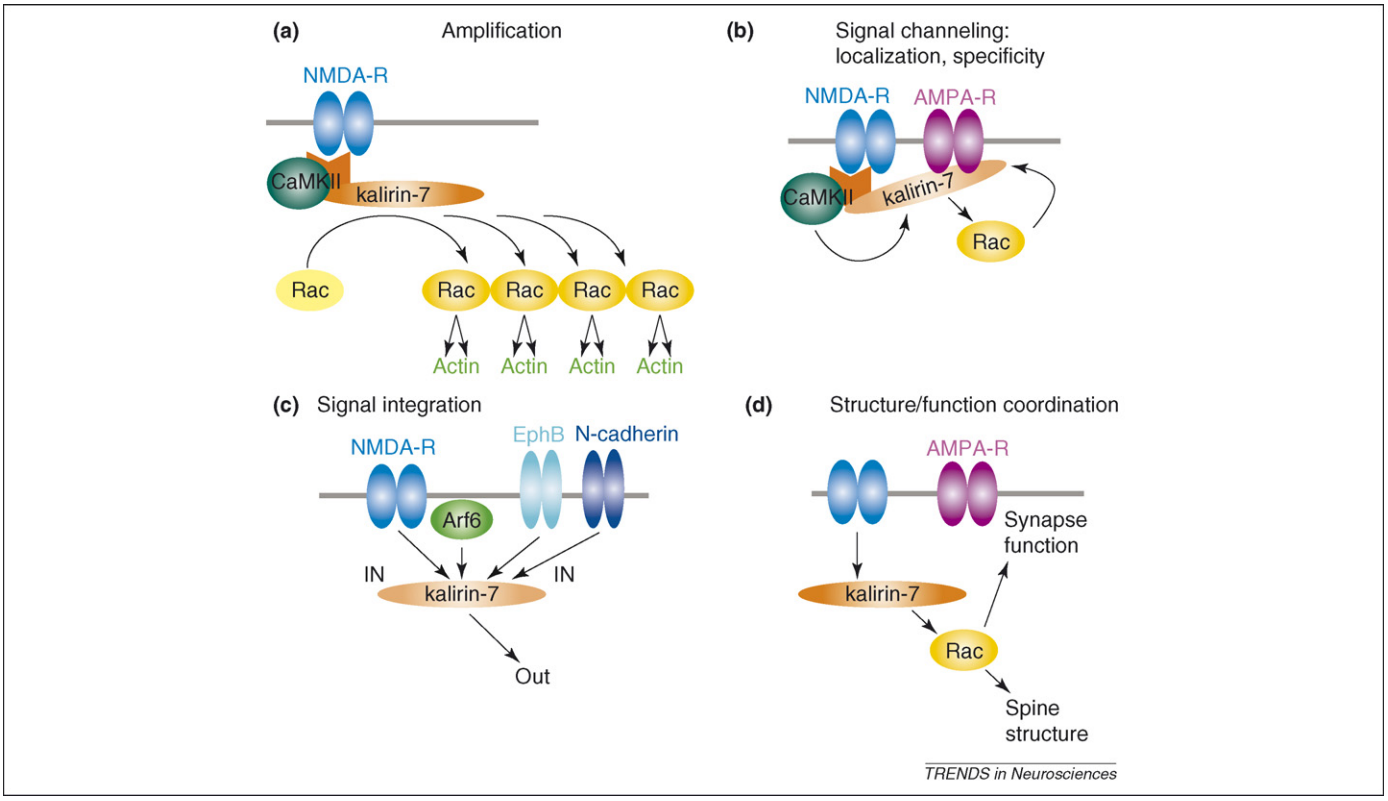

Figure 4. Roles of kalirin-7 in postsynaptic signaling. **(a)** Signal amplification by kalirin-7: each kalirin-7 molecule activates several Rac1 molecules. **(b)** Signal channeling through spatial localization and proximity of the signaling proteins, facilitated by the direct interactions of the components. **(c)** Integration of multiple signaling inputs onto kalirin-7. **(d)** Coordinated regulation of spine structure and synaptic function. Each signaling aspect is shown individually.

disorders, including autism spectrum disorders [9], Rett syndrome [10], fragile X syndrome [12], schizophrenia [13], mood disorders [56], stress [56], drug addiction [14], Alzheimer's disease [15], Parkinson's disease [17] and Huntington's disease [16]. The close relationship of synapse structure and function implicates spine dysgenesis in many of these diseases and, indeed, many of the susceptibility genes associated with these disorders encode proteins that regulate synaptic structure and/or function. Although many protein signaling pathways in spines have been identified as contributors to synaptic pathology, a comprehensive hypothesis for the molecular basis of dendritic spine dysgenesis in disease remains elusive. Recent studies suggest a potential role for kalirin-7 and its signaling and interacting partners in several neuropsychiatric disorders. Thus, unraveling the role of spine signal integrators such as kalirin-7 in synaptic disease might provide a more complete picture of synaptic pathologies and suggest possible novel approaches to treatment of these diseases.

Schizophrenia

Reduced dendritic spine numbers on pyramidal neurons in cortical regions is a consistent anatomical finding in schizophrenia, particularly in regions implicated in the pathophysiology of schizophrenic symptoms, such as layer 3 dorsolateral prefrontal cortex [57]. Moreover, several of the strongest candidates for schizophrenia susceptibility genes produce proteins that are important determinants of synaptic plasticity and cortical network development and modulation [58], and several antipsychotic drugs alter spine density [59], suggesting that modulating dendritic spine morphology might be an important therapeutic target in the treatment of schizophrenia. The molecular mechanism by which dendritic spine morphogenesis contributes to schizophrenia is still in early stages of investigation, but several lines of evidence suggest that a role for modulators of dendritic spine morphology such as kalirin-7 might be important. First, Lewis and colleagues found that the mRNA expression level of kalirin-7 (also called Duo in humans) was significantly reduced in unmedicated subjects with schizophrenia, and that spine density was strongly correlated with the expression levels of kalirin-7 and with Cdc42 [60]. Second, kalirin-7 (also called HAPIP) directly interacted with DISC1 (Disrupted-in-Schizophrenia-1), the product of a prominent schizophrenia susceptibility gene, in a yeast two-hybrid screen [61]. Third, because glutamatergic mechanisms are thought to be central to schizophrenia pathophysiology and pharmacotherapy [57,62] and because kalirin-7 is important in NMDAR signaling and AMPAR trafficking [28], defective kalirin-7 signaling might contribute to the abnormal glutamatergic mechanisms that can underlie altered spine morphology and cognitive functions associated with schizophrenia. This possibility is also supported by the reduced expression of several kalirin-7-interacting proteins, including glutamate receptors, PSD-95 and spinophilin, in the brains of schizophrenic subjects [63,64]. Fourth, as kalirin-7 seems also important for interneuron dendrite and synapse maintenance [53] and as GABAergic systems are dysregulated in schizophrenia [57], kalirin-7 might also contribute to schizophrenia by affecting inhibitory neuron development and function. Taken together, these lines of evidence suggest that abnormal kalirin-7

signaling could contribute to the synaptic pathology associated with schizophrenia, potentially by interfering with spine formation, maintenance or activity-dependent plasticity, leading to the observed endophenotype of reduced dendritic spine density that might underlie schizophrenia-related cognitive dysfunction. Much work is still required to better establish kalirin-7's role in schizophrenia. Additionally, other signaling molecules that play a similar integrative role in dendritic spine dynamic regulation might contribute to schizophrenia pathogenesis.

Alzheimer's disease

Dendritic spine dysfunction and degeneration are thought to be among the earliest events in Alzheimer's disease (AD), occur in animal models of AD and correlate well with cognitive deficits in AD patients [15,65]. Soluble oligomers of β-amyloid (Aβ) are hypothesized to alter glutamatergic synaptic function and lead to synaptic alterations that contribute to the cognitive deficits associated with AD well before Aβ plaques form and induce neuronal toxicity. Although the molecular mechanisms underlying synaptic pathology in AD are still unclear, recent studies indicate that kalirin-7 might be an important player in AD synaptic pathophysiology. Analysis of *postmortem* brain tissue found that in human subjects with AD, kalirin-7 mRNA and protein were consistently underexpressed in the hippocampus, a brain region primarily affected in AD, but not in the cerebellum, a structure less affected by AD [66]. Furthermore, kalirin-7 interacts with inducible nitric oxide synthase (iNOS) and inhibits the increase in its activity induced by amyloid β1–42 (Aβ) peptide and lipopolysaccharide (LPS) treatment in cultured neuron-like cells [67]. Because kalirin-7 expression is reduced in the hippocampus in AD, the increase in iNOS activity often associated with AD might be the result of a decrease in kalirin-7-mediated inhibition [67], providing a potential biochemical mechanism for kalirin-7's contribution to the pathogenesis of the disease.

A role of kalirin-7 in AD-associated synaptic pathology is further suggested by its interaction with several proteins that are affected in AD and contribute to AD pathology, including PAK, X11α, PSD-95 and GluR1 [28,34,46,68–71]. The interaction with PAK is particularly interesting because levels and activities of PAK1 and 3 are reduced in brains of subjects with AD. PAK signaling is disrupted by Aβ oligomers, whose elevated levels in AD are thought to cause synaptic toxicity. Additionally, active PAK prevents Aβ oligomer-induced toxicity, whereas inhibition of PAK causes AD-like synaptic pathology [71]. Dysfunction of the kalirin-7/Rac1/PAK pathway might therefore mediate spine pathology in AD and might provide a target for future therapies. These studies provide evidence that abnormal kalirin-7 signaling could play a role in spine degeneration and synapse loss in AD and might contribute to cognitive impairment in early AD. Further studies are needed to understand the mechanistic links of AD with kalirin-7 and other key regulators of spine dynamics.

Other disorders

Preliminary lines of evidence suggest a possible role for kalirin-7 in other disorders that involve spine dysgenesis. Rho GTPases are heavily implicated in several forms of mental retardation [20,21], suggesting that modulation of this pathway by molecules such as kalirin-7 could contribute to these diseases. For example, PAK plays an important role in diseases that affect human cognition, as demonstrated by the association of the gene encoding PAK3 with X-linked mental retardation [20,21,72]. Interestingly, PAK inhibition reversed spine dysfunction and cognitive deficits in an animal model of fragile X syndrome [73], suggesting that modulation of this pathway, potentially by kalirin-7, might contribute to these disorders. Drug addiction is also associated with significant changes in spine number and morphology in several brain regions [14]. Kalirin levels in the nucleus accumbens and striatum were increased by chronic treatment of rats with cocaine, indicating a potential role in spine dynamics associated with addiction [74]. Finally, kalirin-7 also interacts with Huntingtin-associated protein 1 (HAP1) [75]. As morphological alterations of dendrites and spines occur in Huntington's disease (HD) and in animal models of HD [16,76], the potential role of kalirin-7 in HD pathophysiology requires further investigation. Taken together, it is clear that kalirin-7 has the potential to play a signaling role in several neurological disorders in which dendritic spine dynamics are altered, but much is still unknown about the specific mechanism by which kalirin-7, or other signaling hubs like it, results in human disease.

Conclusions and future directions

Answering several important remaining questions regarding the functions of kalirin-7 would significantly advance our understanding of the neurobiological implications of synaptic signaling and structural plasticity. It is hence of immediate interest to determine the role of kalirin-7 signaling in LTP or LTD in specific brain regions, such as the hippocampus, cortex, striatum or amygdala. Although genetic studies demonstrate a crucial role for regulators of Rho GTPase signaling in human cognitive development, very little is known about how these proteins control synapse development, function and behavior *in vivo*. It will also be important to dissect the roles of kalirin-7 relative to other synaptic Rho GEFs [1,5] and to provide a more complete model of the process of signal integration by the multiple pathways that have been shown to regulate kalirin-7's activity in neurons at different stages of development and in response to a variety of molecular and behavioral stimuli. Because knockdown studies demonstrate that normal expression levels of kalirin-7 are required for the maintenance of spines, synaptic AMPAR clusters and functional excitatory synapses in mature pyramidal neurons [28,77], knockout studies will also be of utmost importance in clarifying the degree to which kalirin-7 contributes to all of these processes *in vivo*. Finally, several recent studies suggest that kalirin-7 might contribute to the pathophysiology of psychiatric and neurodegenerative disorders. It is therefore of immediate importance to investigate the mechanisms underlying the role of kalirin-7 and other Rho GEFs in these disorders, to determine how kalirin might control specific disease endophenotypes, and to search for genetic associations of kalirin-7 with these disorders.

In conclusion, future studies on the molecular signaling controlling spine dynamics by signal integrators such as kalirin-7 promise to shed light on the neurobiological bases of learning and memory and might reveal new therapeutic avenues for the treatment of disorders such as mental retardation, schizophrenia and Alzheimer's disease.

Acknowledgements

We thank Robert Sweet (University of Pittsburgh) and Jaime Grutzendler (Northwestern University) for useful comments, Zhong Xie for images and Michael Cahill and Kathryn Schoedel for proofreading the manuscript. Research described in the text has been funded by grants from NIH-NIMH (MH071316–01A1), NARSAD and NAAR (to P.P.).

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