Review

The roles of cyclin-dependent kinase 5 in dendrite and synapse development

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Since the isolation of cyclin-dependent kinase 5 (Cdk5), this proline-directed serine/threonine kinase has been demonstrated as an important regulator of neuronal migration, neuronal survival and synaptic functions. Recently, a number of players implicated in dendrite and synapse development have been identified as Cdk5 substrates. Neurite extension, synapse and spine maturation are all modulated by a myriad of extracellular guidance cues or trophic factors. Cdk5 was recently demonstrated to regulate signaling downstream of some of these extracellular factors, in addition to modulating Rho GTPase activity, which regulates cytoskeletal dynamics. In this communication, we summarize our existing knowledge on the pathways and mechanisms through which Cdk5 affects dendrite, synapse and spine development.

Keywords: Dendritic spines · Eph receptors · Neurite outgrowth · Rho GTPases · Trk receptors

1 Cdk5 – a unique cyclin-dependent kinase

Cyclin-dependent kinases (Cdks), named for their requirement of cyclins for activation, were initially identified and characterized for their involvement in cell cycle progression. Cdk5, a member of the Cdk family, was later discovered based on sequence homology with the other Cdks [1]. Similar to all Cdks, Cdk5 phosphorylates proline-directed serine and threonine residues, and show preference for the sequence S/TPXK/H/R with a basic residue in the fourth position [2]. Although Cdk5 similarly associates with several cyclins including cyclin D and E, its activation is dependent on two neural-specific, non-cyclin activators p35 and p39. Due to the predominant expression of p35 and p39 in the nervous system, Cdk5 activity is largely restricted to the nervous system despite the ubiquitous expression of Cdk5. Since p35 exhibits a myristoylation signal, binding of Cdk5 to p35 leads to membrane-associated Cdk5 activity. Upon association, Cdk5 phosphorylates p35 and induces proteasome-dependent degradation of p35 [3]. p35-mediated activation of Cdk5 is therefore usually transient. Nonetheless, Cdk5 can also be activated by a cleaved fragment of p35 known as p25, which is generated under pathological conditions when calpain is activated. Since p25 lacks the myristoylation signal, and exhibits a longer half-life compared to p35, activation of Cdk5 by p25 results in prolonged activation of Cdk5 in the cytosol [2]. Aside from association with different activators, Cdk5 activity is also regulated by phosphorylation whereby phosphorylation at Tyr15 enhances Cdk5 activity [4].

Functionally, Cdk5 is unique among Cdks in that it plays little role in cell cycle regulation. Rather, generation of Cdk5-knockout mice revealed that Cdk5 is implicated in the regulation of neuronal migration. Mice deficient in Cdk5 are characterized by perinatal death and aberrant lamination of the cortex [5]. In accordance with the dependence of Cdk5 activity on p35 and p39, mice lacking both p35 and p39 exhibit a phenotype that is essentially...
indistinguishable from that observed in Cdk5-deficient mice [6]. Further studies aimed at identifying additional Cdk5 substrates implicate Cdk5 in a vast array of biological processes, including the regulation of neuronal survival, axonal transport and synaptic transmission [2, 7, 8].

The involvement of Cdk5 in the regulation of neuronal survival was initially suggested by the presence of swollen cell soma and nuclear margination in the brain stem and spiral cord neurons in Cdk5-deficient mice, indicating a potential pro-survival role of Cdk5 in these neuronal populations [5]. Indeed, recent studies show that Cdk5 may favor neuronal survival by counteracting pro-apoptotic signaling via inhibition of JNK activation following apoptotic stimulus [9]. Nonetheless, deregulated Cdk5 activity was also associated with various models of neurodegenerative diseases, including Alzheimer’s disease and Parkinson’s disease. Neuronal death characterized by enhanced Cdk5 activity is often associated with generation of p25 [3]. Although the mechanisms by which Cdk5/p25 exacerbates neuronal death are barely beginning to be unraveled, Cdk5 has been observed to inhibit the pro-survival effect of transcription factor MEF2 [10]. In addition, Cdk5/p25-mediated phosphorylation of NMDA receptor is required for ischemia-induced cell death in hippocampal neurons [11]. These observations suggest that precise regulation of Cdk5 activity is crucial for ensuring neuronal survival [8], and reveals the important role of Cdk5 in the life and death decision of a neuron.

Recently, Cdk5 has been implicated in the regulation of synaptic transmission [7], and has been demonstrated to play a central role in the regulation of dopamine signaling through the phosphorylation of DARPP-32. In addition, Cdk5 has been reported to regulate neurotransmitter release, such as through modulating synaptic vesicles recycling [7]. Interestingly, recent evidence indicates that Cdk5 also takes part in the regulation of neurite outgrowth and synapse development. Here we review the emerging roles of Cdk5 in dendrite and synapse development.

2 Regulation of dendrite development by Cdk5

Precise regulation of neurite outgrowth and formation of synaptic contacts are crucial for the proper development and functioning of the nervous system. During the early stages of development, migration of the newly generated neurons to their final destination is followed by neuronal differentiation characterized by the outgrowth of neuronal processes. Axon and dendrite extension are guided by a number of chemoattractants and chemorepellants that are usually present in a gradient. Examples of these extracellular guidance cues include ephrins, semaphorins and neurotrophins. Binding of these factors to their receptors often results in the modulation of the cytoskeleton such as actin filament and microtubules, thereby leading to changes in growth cone morphology or neurite extension/retraction. A family of small GTPases known as Rho GTPase serves as important regulators of actin dynamics, and are thus key mediators in the regulation of growth cone dynamics and neurite growth in response to extra-cellular cues.

It was demonstrated soon after the isolation of Cdk5 that inhibition of Cdk5 activity attenuated neurite outgrowth in developing cortical neurons [12], although the mechanisms implicated are only beginning to be unraveled in the past few years. Indeed, Cdk5 and its activator p35 and p39 are all expressed at growth cones [13, 14], indicating their potential involvement in neurite growth and extension. Since then, Cdk5 has been observed to modulate dendrite outgrowth and extension by affecting both guidance cue signaling and Rho GTPase activity, indicating that regulation of dendrite growth by Cdk5 occurs at multiple levels. Figure 1 summarizes the roles of Cdk5 in the regulation of neurite outgrowth.

2.1 Cdk5 as an important mediator of semaphorin 3A signaling

Semaphorin 3A is a diffusible factor that is secreted by the cortical plate during development. It was initially observed to act as a chemorepellent for extending axons, thereby directing axon growth towards the white matter [15]. Unexpectedly, semaphorin 3A was later identified as a chemoattractant for dendrites. The differential effect of semaphorin 3A on axons and dendrites was attributed to the asymmetric localization of soluble guanylate cyclase, localizing to apical dendrites of cortical neurons [16]. Downstream effect of semaphorin 3A signaling is mediated by a receptor complex composed of neuropilins-1/2 and plexin-As. Binding of semaphorin 3A to plexin/neuropilin complex results in the recruitment of several proteins such as Rho GTPase Rac, Rho GTPase effector LIM-kinase and collapsing response mediator protein (CRMP) to affect growth cone morphology.

Recently, Cdk5 was identified as an important mediator of semaphorin 3A signaling. Cdk5 and a Src kinase Fyn were found to be required for the induction of axon growth cone collapse in dorsal root ganglion neurons. Activated Fyn binds to Cdk5 and leads to Cdk5 recruitment to Plexin-A2 and phosphorylation of Cdk5 at Tyr15, which is required for semaphorin 3A-induced growth cone collapse [17]. Furthermore, Cdk5 and Fyn were also observed to mediate semaphorin 3A-triggered local protein synthesis at growth cones through the activation of translation initiation factor eIF-4E [18]. Interestingly, Cdk5 has also been observed to modulate semaphorin 3A signaling through phosphorylation of CRMP2, the intracellular signal required for semaphorin 3A-induced growth cone collapse. Phosphorylation of CRMP2 by Cdk5 primes CRMP2 for GSK3β phosphorylation, which then results in the dissociation of CRMP2 from tubulin. More importantly, dual phosphorylation of CRMP2 by Cdk5 and GSK3β was
found to be required for semaphorin 3A-induced growth cone collapse [19, 20], revealing the importance of these kinases in the regulation of semaphorin 3A functions.

Since the studies focusing on semaphorin 3A-induced growth cone collapse were essentially carried out in axon growth cones, it is unclear if similar signaling events occur in dendritic growth cones. Nonetheless, a recent paper reveals that semaphorin 3A-Fyn signaling can induce neurite outgrowth and dendritic branching in cortical neurons [21]. Although the potential involvement of Cdk5 in the semaphorin 3A-induced neurite outgrowth and dendrite branching was not examined in this study, it is clear that semaphorin 3A signaling is active in dendrites, and thus Cdk5 may also play a role in dendrite outgrowth and guidance through modulation of semaphorin 3A signaling.

2.2 Regulation of neurotrophin-mediated neurite growth by Cdk5

Neurotrophins comprise another family of secreted factors that have been demonstrated to act as guidance cues for developing axons and dendrites. Members of the neurotrophin family include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and NT-4/5. Actions of the neurotrophins are mediated by Trk receptors, a family of receptor tyrosine kinases, and the low-affinity neurotrophin receptor p75. While all neurotrophins bind to p75 with comparable affinity, rather remarkable selectivity was observed for the association of neurotrophins with the Trk receptors. NGF binds preferentially to TrkA, while BDNF and NT-4/5 bind preferentially to TrkB. NT-3 associates with TrkC with high affini-
ty, but also binds weakly to TrkA and TrkB [22]. Neurotrophins have been observed to increase dendrite growth and branching in cortical and hippocampal neurons. In particular, neurotrophins were demonstrated to associate with a number of Rho guanine nucleotide exchange factors (GEFs), resulting in activation of Rho GTPase and neurite outgrowth [15].

Several studies reveal that stimulation with neurotrophins, such as NGF and BDNF, can lead to enhanced Cdk5 activity [23–25]. In particular, it was demonstrated that NGF treatment of PC12 cells leads to elevation of p35 expression and Cdk5 activity through the induction of transcription factor Egr-1 by sustained Erk activation. Reversing this increase in Cdk5 activity inhibits NGF-induced neurite outgrowth, indicating that Cdk5 is required for the induction of neuronal differentiation by NGF [25]. Moreover, it was recently demonstrated that NGF-induced activation of Cdk5 in PC12 cells leads to phosphorylation of protein phosphatase 1 (PP1), which also contributes to NGF-triggered neurite outgrowth [26]. NGF treatment also results in the activation of another transcription factor STAT3 in PC12 cells, where inhibition of neurotrophin-induced STAT3 activation attenuates neurite outgrowth [27]. Since STAT3 was recently identified as a Cdk5 substrate [28], it will be interesting to examine if the involvement of STAT3 in neurotrophin-induced neurite outgrowth requires phosphorylation by Cdk5. Taken together, these observations collectively reveal the importance of Cdk5 in the induction of neuronal differentiation downstream of NGF stimulation.

While the involvement of Cdk5 in NGF-induced neurite outgrowth has been demonstrated, its precise involvement in dendrite growth in primary neurons, in particular downstream of neurotrophin stimulation, remains enigmatic. A search for Cdk5 consensus sites on Trk receptors reveals that TrkB and TrkC contain potential Cdk5 phosphorylation sites, therefore prompting us to examine if Trk receptors serve as Cdk5 substrates. Interestingly, Cdk5 was found to phosphorylate TrkB and TrkC, but not TrkA. More importantly, inhibition of TrkB phosphorylation by Cdk5 essentially abolishes BDNF-triggered increase in primary dendrites in hippocampal neurons, thus revealing an important role of Cdk5 in the regulation of dendrite development downstream of BDNF stimulation. Furthermore, inhibition of Cdk5 was found to attenuate activation of Rho GTPase Cdc42 following BDNF treatment, indicating that Cdk5 may also modulate Rho GTPase activity [24]. Indeed, as reviewed in the next section, a number of proteins involved in the regulation of Rho GTPase activity have been identified as Cdk5 substrates.

### 2.3 Modulation of Rho GTPase downstream responses

Rho GTPases are a family of small GTPase that serves as key regulator of actin dynamics. Members of the Rho GTPase family include Rac1, RhoA and Cdc42. Similar to other GTPases, activation of Rho GTPase involves binding to GTP, followed by translocation to the membrane. Catalysis of GTP to GDP renders the Rho GTPases inactive. Activity of Rho GTPase is regulated by GEFs and GT-Pase-activating proteins (GAPs). GEFs favor the exchange of GDP for a GTP, thereby promoting activation of the Rho GTPase. GAPs, on the other hand, facilitate catalysis of GTP to GDP, thereby leading to a more rapid inactivation of the Rho GTPase. Activated Rho GTPases such as Rac1 and RhoA subsequently recruit their respective downstream effectors including PAK1 and ROCK, which then directly modulate actin dynamics. Among the Rho GTPases, RhoA is frequently associated with growth cone collapse and neurite retraction, while Rac1 and Cdc42 are usually involved in neurite extension. Interestingly, there is certain selectivity in the GEFs, GAPs and effectors that are recruited by different Rho GTPases. For example, GEF Tiam 1 is specific for Rac1, while Dbs is specific for Cdc42. Effector Pak1 is activated downstream of Rac1 and Cdc42 activation, but not RhoA [29].

Cdk5 has been observed to phosphorylate a number of GEFs and effectors of Rac1, Cdc42 and RhoA (see Table 1, [30–34]). Aside from phosphorylation, Cdk5 has also been observed to interact with α-chimaerin, a GAP for Rac1 and Cdc42 [19, 35]. Interestingly, Cdk5-mediated phosphorylation mostly inhibits the activity of various Rho GTPases, with ephexin1 being the only exception. Although direct phosphorylation of GEFs or effectors of different Rho GTPases by Cdk5 has not been demonstrated to affect neurite outgrowth, these observations indicate that Cdk5 plays a major role in modulating the activity of these Rho GTPases. Given the pivotal role of Rho GTPases in the regulation of actin dynamics, it can be anticipated that Cdk5 may directly affect dendrite growth and development through regulating Rho GTPase activity.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Functional type</th>
<th>Effect of Cdk5 phosphorylation</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Ephexin 1</td>
<td>GEF</td>
<td>Enhances ephexin1-mediated RhoA activity</td>
<td>[30]</td>
</tr>
<tr>
<td>RasGRF1</td>
<td>GEF</td>
<td>Leads to the degradation of RasGRF1 by calpain</td>
<td>[31]</td>
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<tr>
<td>RasGRF2</td>
<td>GEF</td>
<td>Reduces RasGRF2-mediated Rac activity</td>
<td>[32]</td>
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<tr>
<td>WAVE1</td>
<td>Effector</td>
<td>Inhibits WAVE 1-mediated actin polymerization</td>
<td>[33]</td>
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<tr>
<td>Pak1</td>
<td>Effector</td>
<td>Cdk5/p35 inhibits Pak1 activity, but not via direct phosphorylation of Cdk5</td>
<td>[34, 36]</td>
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2.4 Phosphorylation of other cytoskeletal components by Cdk5

Aside from modulating actin dynamics, regulation of cytoskeletal components such as microtubules and neurofilaments also contribute to neurite outgrowth. Cdk5 has been observed to phosphorylate neurofilament heavy chain and a number of microtubule-binding proteins such as Tau [36]. In accordance with the phosphorylation of Tau by Cdk5, hyperphosphorylated Tau was observed in a transgenic mice overexpressing p25 [37]. Furthermore, Cdk5 phosphorylates several microtubule-associated proteins including MAP2 and MAP1b [38, 39]. Inhibition of Cdk5 activity concurrently inhibits laminin-induced axonal growth and phosphorylation of MAP1b in cerebellar macroneurons [40], suggesting that MAP1b phosphorylation by Cdk5 may affect axonal growth. Cdk5 activity is also implicated in the regulation of MAP1b distribution through phosphorylation of Rho GEF RasGRF2 [32]. In addition to phosphorylating microtubule proteins, Cdk5 also phosphorylates the heavy chain of neurofilament [41]. Although the precise involvement of Cdk5-mediated phosphorylation of these cytoskeletal proteins in dendrite growth remains to be determined, given their important role in neurite outgrowth and extension, it is plausible that Cdk5 may affect dendrite development through affecting microtubule and neurofilament dynamics.

3 The role of Cdk5 in synapse formation

Transmission of information in the nervous system relies on the precise formation of synaptic contact between neurons. Synapse formation occurs when the extending axons of the pre-synaptic neurons come into contact with the cell bodies or the dendrites of the post-synaptic neurons. The formation of synaptic connections can lead to the development of protrusions on the dendrites known as spines, which is usually associated with excitatory synapses. Unlike neurite outgrowth, which takes days to modulate, spine morphology is highly plastic, with changes occasionally observed in seconds to minutes. The contact site between the pre- and post-synaptic neurons then further develop, which is characterized by changes in the receptors expressed in the pre- and post-synaptic regions, and changes in the expression of scaffold proteins. Clustering of the receptors on the pre-synaptic organization is also regulated to modulate synaptic strength. Since Cdk5 and its activators are expressed in synapses [42, 43], it was long speculated that Cdk5 could affect synapse development and functions. Regulation of synapse and spine development by Cdk5 is summarized in Fig. 2.

3.1 Regulation of neurotransmitter receptor expression by Cdk5

The involvement of Cdk5 in synapse formation was initially observed in the neuromuscular junction (NMJ) [42]. Due to its large size, the NMJ serves as an excellent model for elucidating the pathways involved in the regulation of post-synaptic organization during synapse formation and maturation. Although p35 is expressed predominantly in the nervous system, it was found that p35 is also expressed in muscle concentrated at the NMJ [42]. Expression of acetylcholine receptors at the NMJ is regulated by neuregulin (NRG), which triggers expression of acetylcholine receptor in cultured myotubes. Interestingly, NRG receptor ErbB was identified as a Cdk5 substrate. Phosphorylation of ErbB receptor by Cdk5 is required for the initiation of NRG downstream signaling and the induction of acetylcholine receptor expression by NRG, revealing an unexpected role of Cdk5 in the regulation of neurotransmitter receptor in muscle [42]. Cdk5 activity was later observed to also be required for the expression of GABA_\text{\textsubscript{A}} receptors in the central nervous system (CNS) downstream of NRG stimulation [44], indicating that Cdk5 is important in NRG-mediated regulation of neurotransmitter receptors at both central and peripheral synapses.

A recent study indicates that the mechanism by which Cdk5 mediates NRG-induced gene transcription involves the transcription factor STAT3 [28]. We have recently identified Cdk5 as a serine kinase for STAT3. Inhibition of Cdk5 activity attenuated activation of STAT3 following NRG stimulation and transcription of target genes such as c-fos, indicating that Cdk5 activity is required for NRG-induced STAT3-mediated gene transcription [28]. Aside from STAT3, Cdk5 has also been observed to modulate the activity of another transcription factor MEF2. Phosphorylation of MEF2 by Cdk5 inhibits its transcriptional activity, in addition to augmenting degradation of the transcription factor [10, 45]. Although the regulation of MEF2 by Cdk5 has not been directly observed to affect synaptic organization, a recent study indicates that activity-dependent regulation of MEF2 levels affects the number of excitatory synapses [46]. These observations indicate that Cdk5 may also affect transcription of neurotransmitter receptor through the modulation of MEF2 activity. Further study will be required to verify this possibility.

Recent identification of novel Cdk5 substrates revealed that Cdk5 may also exhibit a more universal role on gene transcription through the modulation of histone acetylation. Structural remodeling of the chromatin, such as acetylation or deacetylation of histones, has been demonstrated to lead to activation and silencing of gene expression, respectively. Histone deacetylation and the subsequent repression of gene transcription is mediated by histone deacetylase (HDAC), which is a complex
whose activity is regulated by post-translational modification such as phosphorylation of proteins in the complex. Recently, we have identified mSds3, an essential component of the HDAC1 corepressor complex, as a novel substrate of Cdk5. We found that in the presence of Cdk5 activity, acetylation of histones is reduced. More importantly, increasing Cdk5 activity enhances mSds3-mediated transcriptional repression [47]. Although whether HDAC1 activity contributes to gene transcription at the synapse remains to be investigated, our observation suggests that Cdk5 may take part in the regulation of neurotransmitter receptor expression through multiple pathways.

3.2 Modulation of neurotransmitter receptor clusters

In addition to the regulation of neurotransmitter receptor expression, Cdk5 is also implicated in the regulation of neurotransmitter receptor clustering. Examination of the NMJ phenotype of Cdk5-knockout mice revealed that acetylcholine receptor endplate is significantly broader in Cdk5–/– diaphragm. Furthermore, treatment of Cdk5−/− myotubes with agrin, which induces acetylcholine receptor clustering, results in a marked enlargement in acetylcholine receptor clusters when compared with that observed in wild-type cultures [48, 49]. These findings indicate that Cdk5 plays an important role in the regulation of acetylcholine receptor clustering during synapse formation.

Although the mechanisms implicated in the regulation of neurotransmitter receptor clustering by Cdk5 remained largely unknown, PSD-95, a scaffold protein important for the clustering of receptors at the post-synaptic density, was recently identified as a Cdk5 substrate. Phosphorylation of PSD-95 by Cdk5 suppresses multimerization of PSD-95 in CNS synapses and reduces PSD-95-mediated clustering of NMDA receptor subunit NR1 [50]. Furthermore, reduction in PSD-95 levels in Aβ-treated cortical neurons was observed to require Cdk5 activity, suggesting that Cdk5 may contribute to PSD-95 degradation in pathological conditions [51]. Since PSD-95 is an essential regulator of the post-synaptic density composition, modulation of PSD-95 levels and clustering by Cdk5...
will likely serve important roles in shaping the postsynaptic density.

4 Cdk5 as a modulator of spine morphogenesis

Regulation of spine morphogenesis is not only important during development, but also contributes to synaptic plasticity in the adult brain. Spine formation starts with the extension of a filopodia from the dendritic shaft, which eventually transforms to a more stubby mushroom shape as spines mature. Similar to the regulation of neurite outgrowth and extension, spine morphogenesis requires the coordinated modulation of actin and microtubules. In accordance with the important roles of Rho GTPase in the regulation of actin dynamics, regulation of spine development was also observed to involve Rho GTPases. As mentioned in the previous section, Cdk5 was observed to phosphorylate a number of Rho GTPase effectors (Table 1), suggesting that Cdk5 may play a role in the regulation of spine morphogenesis. Indeed, dendritic spine density was enhanced in a transgenic mouse overexpressing Cdk5 activator p25 [52], suggesting that Cdk5 may contribute to spine morphogenesis.

Among the GEFs phosphorylated by Cdk5, phosphorylation of ephexin1 was recently associated with the regulation of spine morphogenesis. Treatment of hippocampal neurons with ephrins, a family of repulsive axon guidance cues, was observed to result in spine retraction [53]. We recently demonstrated that ephrin-induced spine retraction requires Cdk5-mediated phosphorylation of ephexin1 [30]. Stimulation of ephrin receptor EphA4 leads to RhoA activation. We found that ephrin-induced RhoA activation requires Cdk5 activity. Activation of EphA4 results in phosphorylation of Cdk5 at Tyr15, thereby enhancing its activity. Importantly, inhibition of Cdk5 markedly reduces ephrin-A1-induced spine retraction. Further studies on the underlying mechanisms revealed that Cdk5 regulates RhoA activity through phosphorylation of Rho GEF ephexin1. Inhibiting Cdk5-mediated phosphorylation of ephexin1 attenuates RhoA activity and ephrin-A1-triggered spine retraction [30]. Our observations indicate that phosphorylation of ephexin1 and subsequent regulation of RhoA activity by Cdk5 contributes to the regulation of spine morphogenesis.

Phosphorylation of WAVE1 by Cdk5 is also associated with spine morphogenesis. Cdk5-mediated phosphorylation of WAVE1 inhibits WAVE1 activity, resulting in reduced actin polymerization. Knockdown of WAVE1 is associated with enhanced filopodia but reduced stubby-shaped spines. In addition, cAMP-dependent dephosphorylation of WAVE1 at the Cdk5 site enhances spine density [33]. Although the precise involvement of Cdk5 in the WAVE1-dependent regulation of spine morphogenesis requires further investigation, this study suggests that Cdk5 may modulate spine density and maturation through regulation of WAVE1 activity.

It should be noted that synaptic activity has also been observed to regulate spine morphology. In particular, induction of long-term potentiation (LTP) is associated with the enlargement and splitting of spines, while long-term depression (LTD) is associated with spine regression [29]. Cdk5 activity has been implicated in modulating LTP and LTD in learning paradigms. For example, Cdk5 activity increases during associative learning and fear conditioning, and is required for effective associative learning [54]. In addition, spatial learning and LTD are impaired in p35-deficient mice [55]. On the other hand, LTP is enhanced in a transgenic mouse overexpressing p25 [52]. These observations underscore the importance of Cdk5 in LTP and LTD, and suggest that Cdk5 may also modulate spine morphogenesis through the regulation of synaptic plasticity.

5 Conclusion

Since the identification of Cdk5, this kinase has been implicated in almost all aspects of neuronal development. Although an increasing number of studies support the emerging role of Cdk5 in the regulation of dendrite and synapse development, our understanding of the mechanisms implicated is far from clear. Nonetheless, existing findings provided some interesting hints. First of all, Cdk5 activity has been observed to underlie the action of extracellular cues on the regulation of dendrite and synapse development. Cdk5 activity was required for the downstream functions of receptor tyrosine kinases including ErbB, Trk and Eph receptors, in addition to acting as an important mediator for semaphorin signaling. Furthermore, modulation of Rho GTPase activity by Cdk5 will likely emerge as an essential mechanism for the regulation of dendrite and spine motility. Finally, Cdk5 has long been demonstrated as a kinase for a number of microtubule-binding proteins such as Tau, MAP2 and MAP1b [2], but how these phosphorylation events affect microtubule dynamic during dendrite growth and synapse development remains enigmatic. Further elucidation on the regulation of actin and microtubule dynamics by Cdk5 will enhance our understanding of the role of Cdk5 in synapse and dendrite development.

Although existing studies have focused mainly on the developmental role of Cdk5 in synapse formation and neurite extension, it would be interesting to examine if Cdk5 also affects synaptic plasticity in adults through similar mechanisms. Indeed, as mentioned previously, Cdk5 was observed to affect LTP and LTD in adult animals [52, 55]. Explicating the involvement of different guidance cues and the role of Rho GTPase in Cdk5-mediated spine motility and synapse modulation in adults, and how these pathways contribute to learning and memory formation will help to consolidate the involvement of Cdk5 in adult
synaptic plasticity. Furthermore, recent studies indicate that in neurodegenerative diseases such as Alzheimer’s disease, deficits in synaptic functions occur prior to actual neuron loss. Given the involvement of deregulated Cdk5 activity in these neurodegenerative disorders, it is plausible that Cdk5 may affect synapse functions in addition to modulating neuronal survival as the disease progresses. Understanding the role of Cdk5 in the modulation of synaptic functions in different neurodegenerative disease may provide new insights on the therapeutic treatment for these disorders.

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