Review

Cdk5: a multifaceted kinase in neurodegenerative diseases

Zelda H. Cheung and Nancy Y. Ip

Division of Life Science, Molecular Neuroscience Center and State Key Laboratory of Molecular Neuroscience, The Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, China

Since the identification of cyclin-dependent kinase-5 (Cdk5) as a tau kinase and member of the Cdk family almost 20 years ago, deregulation of Cdk5 activity has been linked to an array of neurodegenerative diseases. As knowledge on the etiopathological mechanisms of these diseases evolved through the years, Cdk5 has also been implicated in additional cellular events that are affected under these pathological conditions. From the role of Cdk5 in the regulation of synaptic functions to its involvement in autophagy deregulation, significant insights have been obtained regarding the role of Cdk5 as a key regulator of neurodegeneration. Here, we summarize recent findings on the involvement of Cdk5 in the pathophysiological mechanisms underlying various neurodegenerative diseases.

Cdk5 in the control of neuronal survival: balance is the key

Cdk5 is a serine/threonine kinase that is activated upon association with its activator p35 or p39. A predominantly neural-specific kinase because of the restricted expression of its activators in the nervous system, Cdk5 is crucial for neuronal migration, neuronal differentiation, synapse development and synaptic functions [1]. Cdk5 is also implicated in the control of neuronal survival during development and in disease; either too much or too little Cdk5 activity impairs neuronal survival [2]. Recent advances in the field have provided additional mechanistic insights into the role of Cdk5 in the maintenance of neuronal survival. Identification of antiapoptotic protein Bcl-2 as a Cdk5 substrate revealed that Cdk5-mediated phosphorylation of Bcl-2 is crucial for its antiapoptotic function, which contributes to the maintenance of neuronal survival during development [3]. Furthermore, although Cdk5 has been termed an 'atypical cyclin-dependent kinase' for its assumed minimal role in cell cycle control, studies have revealed that nuclear Cdk5 is crucial for the suppression of cell cycle entry, which induces neuronal death [4]. Association with the cyclin-dependent kinase inhibitor p27 causes Cdk5 to localize to the nucleus, where it reduces expression of cell cycle genes by disrupting the association of transcription factor E2F1 with its activating cofactor DP1 [5,6]. These findings reveal that a certain level of Cdk5 activity is necessary for maintaining neuronal survival in postmitotic neurons.

By contrast, aberrant Cdk5 activation has long been associated with the pathophysiology of numerous neurodegenerative conditions. Excessive Cdk5 activity has been implicated in neuronal loss triggered by oxidative stress, excitotoxicity and ischemia, and in animal models of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases [2]. In particular, calpain-mediated cleavage of p35 into p25 has been suggested as the culprit for the pathological deregulation of Cdk5. Although Cdk5–p25 is not catalytically more active than Cdk5–p35 [7], the significantly longer half-life exhibited by p25 compared to p35 prolongs Cdk5 activation. In addition, the lack of a myristoylation signal on p25 may result in redistribution of Cdk5 activity, thereby contributing to neuronal loss. It has been postulated that nuclear Cdk5 may be selectively associated with Cdk5-mediated neuronal loss [8]. Of note, nonmyristoylated p35 and p39 are preferentially accumulated in the nucleus [9] and translocation of Cdk5–p25 into the nucleus has been observed in response to endoplasmic reticulum stress and DNA damage [8,10]. Nonetheless, further studies have revealed that cytoplasmic and nuclear Cdk5 can both mediate neuronal survival and death depending on the experimental paradigms adopted [5,11], suggesting that the regulation of neuronal survival by Cdk5 is context-dependent. In this review, we summarize recent literature on the role of Cdk5 in the pathophysiology of several neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's diseases. Although Cdk5 has been linked to different pathogenic mechanisms in different disorders, it is becoming increasingly clear that the action of Cdk5 in these cellular processes may be shared among the neurodegenerative diseases, further underscoring a pivotal regulatory role of Cdk5 in the pathology of these neurological disorders.

Alzheimer's disease

Significant progress has been made regarding the contribution of Cdk5 to the pathophysiology of Alzheimer's disease. Despite initial controversy concerning the detection of p25 and elevated Cdk5 activity in postmortem samples of Alzheimer's disease patients, subsequent studies using animal models of the disease largely confirm that Cdk5 deregulation contributes to neuronal loss in the disease [12]. Indeed, a recent study revealed that selective inhibition of Cdk5–p25 with a p5 fragment derived from p35 reduces amyloid beta (Aβ)-induced neuronal loss in cortical neurons [13]. Cdk5 is implicated not only in tau hyperphosphorylation but also in regulating the generation of Aβ.

Corresponding author: Ip, N.Y. (boip@ust.hk).

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More importantly, accumulating evidence indicates that Cdk5 deregulation also contributes to synaptic abnormality, which precede neuronal death in Alzheimer's disease (Figure 1).

Regulating Aβ generation

Aβ has long been postulated as the toxic instigator of the cascade of pathological events that eventually culminate in synaptic dysfunction and neuronal loss in Alzheimer's disease. Aβ is generated through sequential amyloidogenic cleavage of precursor protein APP by β-secretase BACE1 and γ-secretase, with the oligomeric form of Aβ suggested as the major mediator of its toxicity [14,15]. Cdk5 activation has been demonstrated to increase Aβ production and its accumulation in the cell body and neurites [16], and inhibition of Cdk5 activity attenuates Aβ production in transgenic mice overexpressing p25 [17]. Further studies revealed that Cdk5-mediated phosphorylation of STAT3, which enhances the transcriptional activity of STAT3 [18], results in elevated transcription of BACE1, thereby increasing generation of Aβ [19]. Indeed, levels of tyrosine-phosphorylated STAT3 are augmented by Aβ treatment in human Alzheimer's brain samples [20]. Cdk5 has also been linked to phosphorylation of tropomyosin-related kinase A (TrkA) and neuronal loss induced by NGF deprivation, an event that is blocked by anti-Aβ antibodies [21]. A previous study by the same group revealed that deprivation of trophic factors such as NGF and BDNF triggers Aβ generation by favoring the amyloidogenic pathway [22]. They further demonstrated that the cell loss triggered by NGF deprivation is accompanied by delayed phosphorylation of TrkA, which is dependent on Aβ generation and activity of β- and γ-secretase and Cdk5 [21]. Further investigation of the contribution of these signaling events to neuronal loss in Alzheimer's disease is warranted to characterize the precise involvement of Cdk5. In particular, because we have identified the BDNF receptor TrkB as a Cdk5 substrate [23], it is of interest to examine whether similar signaling events are induced by BDNF deprivation in neurons, and whether TrkB plays a role in disease pathophysiology.

Regulation of tau phosphorylation

Tau hyperphosphorylation and the presence of neurofibrillary tangle are among the major hallmarks of Alzheimer's disease. Phosphorylation of tau has been demonstrated to impair its microtubule binding, thereby destabilizing microtubules. In accordance with the identification of

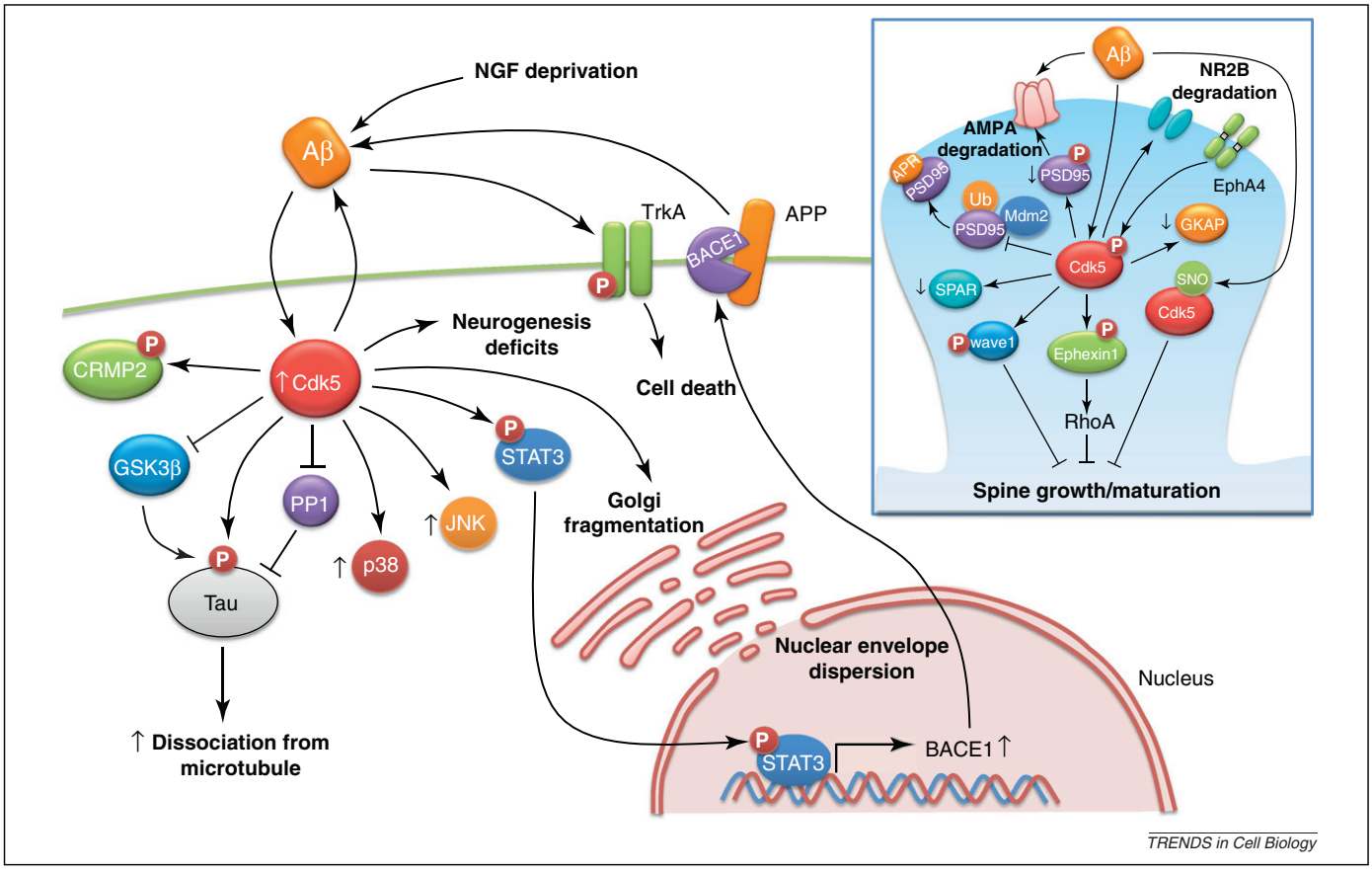

Figure 1. Cdk5 as a key regulator of Aβ generation and synaptic abnormality in models of Alzheimer's disease. Aβ stimulation increases Cdk5 activity, which in turn enhances Aβ generation by increasing transcription of BACE1. NGF deprivation, which leads to elevated Aβ production, results in delayed TrkA phosphorylation, which is dependent on Cdk5 activity and Aβ generation. Cdk5 also phosphorylates microtubule-binding proteins tau and CRMP2, and facilitates tau phosphorylation through inhibition of phosphatase PP1. Intriguingly, Cdk5-mediated phosphorylation of GSK3β, another tau kinase, reduces GSK3β activity. Additional studies will be required to clarify the role of Cdk5 in tau hyperphosphorylation. Cdk5 also mediates p38 MAPK activation, JNK activation, Golgi fragmentation, nuclear envelope dispersion and neurogenesis deficits in models of Alzheimer's disease. At the synapse (inset), Cdk5 phosphorylates several postsynaptic proteins including PSD95, GKAP and SPAR, resulting in increased degradation of these proteins. Cdk5 also inhibits ubiquitination of PSD95 by reducing its association with E3 ubiquitin ligase Mdm2, thereby limiting binding of endocytic adaptor complex AP2. Cdk5 also facilitates downregulation of AMPA in response to Aβ, and NR2B receptors at the synapse. Cdk5 is also implicated in spine morphogenesis through phosphorylation of ephexin1 downstream of EphA4 activation, and WAVE1. *S*-Nitrosylated Cdk5 (SNO-Cdk5) has recently been linked to Aβ-induced spine loss.

Cdk5 as a tau kinase, knockdown of Cdk5 expression reduces tau phosphorylation and neurofibrillary tangle in triple-transgenic Alzheimer's mice [24]. Furthermore, Aβ-induced activation of Cdk5 is suggested to mediate local phosphorylation of tau that is missorted to the somatodendritic compartment, which results in dissociation of tau from microtubules [25]. Cdk5 also facilitates tau phosphorylation by inhibiting phosphatase PP1 through phosphorylation of PP1 [26]. In addition, Cdk5-mediated phosphorylation of CRMP2, another microtubule binding protein that is hyperphosphorylated in patients with Alzheimer's disease, is particularly resistant to dephosphorylation [27]. These findings collectively suggest that Cdk5 may also enhance phosphorylation of microtubule binding proteins in Alzheimer's disease by interfering with their dephosphorylation.

Intriguingly, Cdk5 also inhibits the activity of GSK3β, another tau kinase [17,28]. In fact, GSK3β has been suggested as the major kinase that mediates tau hyperphosphorylation, with Cdk5 serving a modulatory role by regulating GSK3β activity [17,28]. Inhibition of Cdk5 activity increases tau phosphorylation by activating GSK3β in young p25-expressing transgenic animals [17]. By contrast, a study using a *Drosophila* model of tauopathy suggested that Cdk5 may not be implicated in tau toxicity [29]. It is therefore important to further decipher the precise roles of the various kinases in tau hyperphosphorylation, and their relative contributions to the pathophysiology of the disease.

Synaptic dysfunction

Earlier findings established Cdk5 as a key regulator of synaptic development and function. From regulating neurotransmitter release and controlling the expression and clustering of postsynaptic neurotransmitter receptors, to modulating spine morphogenesis, Cdk5 is implicated in every aspect of synaptic function [30]. A recent study confirmed the essential role of Cdk5 in neurotransmission by demonstrating that Cdk5 is an inhibitor of neurotransmitter exocytosis using an optical assay that allows unambiguous measurement of presynaptic function [31]. More importantly, Cdk5 also regulates synaptic plasticity and is involved in higher cognitive functions such as learning and memory, although its involvement appears to be complex [32]. Although earlier studies suggest that Cdk5 activity is required for associative learning and that long-term potentiation (LTP) is elevated by transient p25 activation in p25-expressing transgenic mice [33,34], Cdk5 conditional knockout animals also exhibit enhanced LTP and NMDA receptor-mediated excitatory current due to reduced calpain-dependent degradation of the NMDA receptor subunit NR2B [35]. In agreement with this finding, transgenic mice overexpressing the tau kinase tau-tubulin kinase-1 (TTBK1) also display elevated Cdk5 activity, calpain-mediated reduction of NR2B levels and learning deficits [36]. Cdk5 was previously implicated in the downregulation of surface AMPA receptors at the synapse triggered by Aβ treatment through facilitation of the degradation of PSD95 [37]. A recent study further demonstrated that reduced Cdk5 activity elevates ubiquitination of PSD95 by enhancing its association with E3 ubiquitin ligase Mdm2. This ubiquitination appears to facilitate binding with clathrin endocytic adaptor complex AP2, rather than triggering proteasome-dependent degradation of PSD95 [38]. Because ubiquitination of PSD95 may contribute to endocytosis of AMPA receptors [39], these findings suggest a novel mechanism by which Cdk5 may regulate AMPA trafficking. Interestingly, PSD95 is not the only postsynaptic scaffold protein that is regulated by Cdk5 activity. GKAP is another postsynaptic density scaffold protein that is degraded upon Aβ treatment [40], and was recently identified as a substrate of Cdk5. Phosphorylation of GKAP by Cdk5 triggers its ubiquitination and degradation. Inhibition of Cdk5 activity not only reverses Aβ-induced loss of GKAP at the synapse but also attenuates actin remodeling triggered by Aβ stimulation [40]. Collectively, these observations underscore the essential role of Cdk5 in regulating synaptic function and plasticity, which may contribute to synaptic abnormality in Alzheimer's disease. Cdk5 is also implicated in degradation of the PSD95-interacting protein SPAR [41], so it will be interesting to further examine whether SPAR degradation also plays a role in synaptic dysfunction in Alzheimer's disease.

In accordance with the essential involvement of Cdk5 in regulating synaptic plasticity, we have revealed a modulatory effect of Cdk5 on spine morphogenesis. EphA4-mediated spine retraction was found to require Cdk5 activity, which phosphorylates the RhoGEF ephexin 1 to facilitate activation of RhoA triggered by ephrinA1–EphA4 signaling [42]. In addition, Cdk5-mediated phosphorylation of WAVE1 inhibits WAVE1 activity and spine maturation [43]. *S*-Nitrosylation of Cdk5 is also implicated in spine loss triggered by Aβ and is elevated in postmortem brains of patients with Alzheimer's disease, and following Aβ stimulation [44]. Nonetheless, conflicting data have been reported regarding the effect of *S*-nitrosylation on Cdk5 activity [44,45]. Additional studies are therefore required to verify whether Cdk5 activity is elevated or diminished in response to *S*-nitrosylation. It will also be important to obtain additional mechanistic insights into the role of Cdk5 in spine abnormality in Alzheimer's disease.

Recent studies have revealed additional mechanisms by which Cdk5 contributes to the pathophysiology of Alzheimer's disease. Elevated Cdk5 activity was found to activate the JNK and p38 MAPK signaling pathways in response to Aβ stimulation [46,47]. Inhibition of Cdk5 also reverses Golgi fragmentation and nuclear envelope dispersion triggered by Aβ [48,49]. Cdk5 is also implicated in neurogenesis deficits observed in APP transgenic mice [50]. These studies further underscore the important role of Cdk5 in the pathogenesis of Alzheimer's disease. Finally, Aβ was recently demonstrated to impair trafficking of mitochondria and TrkA, with the defect reversed in tau knockout animals [51]. Because we have identified a Cdk5 substrate, endophilin B1, as a potential regulator of TrkA trafficking [52,53], it will be interesting to examine whether Cdk5 also plays a role in TrkA trafficking defects in Alzheimer's disease.

Taken together, these studies reveal abnormal elevation of Cdk5 activity as a key event that contributes to the pathology of Alzheimer's disease. Cdk5 deregulation is not

only associated with elevated Aβ generation but also contributes to synaptic malfunction observed in the brain in Alzheimer's disease. Although the precise involvement of Cdk5 in tau hyperphosphorylation requires further clarification, the development of drugs that selectively suppress the aberrant activation of Cdk5, without affecting basal Cdk5 activity, may prove beneficial in the treatment of Alzheimer's disease.

Parkinson's disease

Cdk5 deregulation was initially associated with neuronal loss in Parkinson's disease when inhibition of Cdk5 activity conferred neuroprotection in animal models of the disease [54]. MPTP injection or treatment with MPP^+ enhances p25 levels and Cdk5 activity [53–57], although MPP^+ treatment also triggers degradation of p35 via the proteasome pathway [58]. The mechanism by which Cdk5 mediates neuronal loss in Parkinson's disease is incompletely understood, but accumulating studies are beginning to reveal the role of Cdk5 in multiple pathological mechanisms of the disease (Figure 2).

Oxidative stress

Oxidative stress is one of the major pathogenic mechanisms of Parkinson's disease, as evidenced by the presence of DNA damage, protein oxidation and lipid peroxidation in the brains of patients [59]. Accumulating studies reveal that Cdk5 may contribute to Parkinson's disease pathology by impairing antioxidative cellular defenses. For example, Cdk5 phosphorylates the antioxidative peroxidase peroxiredoxin 2 (Prx2) at Thr89 to inhibit its activity in response to MPTP or MPP^+ treatment [56]. More importantly, overexpression of a Thr89 phosphomimetic mutant of Prx2 significantly attenuates the protective effect of Prx2 against MPP^+-induced cell death [56]. Cdk5 also exacerbates oxidative stress in $MPTP^-$ or MPP^+-treated cells by hindering DNA damage repair, which is often triggered by oxidative stress and can lead to cell death. Cdk5-mediated phosphorylation of DNA repair enzyme apurinic/apyrimidinic endonuclease 1 (Ape1) at Thr232 reduces its activity and abrogates its neuroprotective effect against MPTP toxicity [57]. These findings collectively suggest that deregulated Cdk5 contributes to neuronal loss by impairing the cellular antioxidative defense in models of Parkinson's disease. Because Cdk5 also phosphorylates ataxia telangiectasia mutated (ATM), another enzyme implicated in DNA damage response [60], it will be interesting to examine whether phosphorylation of ATM by Cdk5 also contributes to disease pathology.

Mitochondrial abnormality

Several missense mutations associated with familial cases of Parkinson's disease are mapped to mitochondrial proteins, including Parkin, PINK1, HtrA2, LRRK2 and DJ1 [61], underscoring the importance of mitochondrial dysfunction in the pathophysiology of the disease. Patients with Parkinson's disease display reduced mitochondrial complex I activity [62]. Parkin and PINK1 also facilitate mitochondrial fission, a cellular event that is linked to apoptosis [63], suggesting that Parkin and PINK1 mutations may result in neuronal loss through regulation of mitochondrial morphology. Of note, Cdk5 was found to phosphorylate several mitochondrial proteins implicated in Parkinson's disease. Cdk5 phosphorylates serine

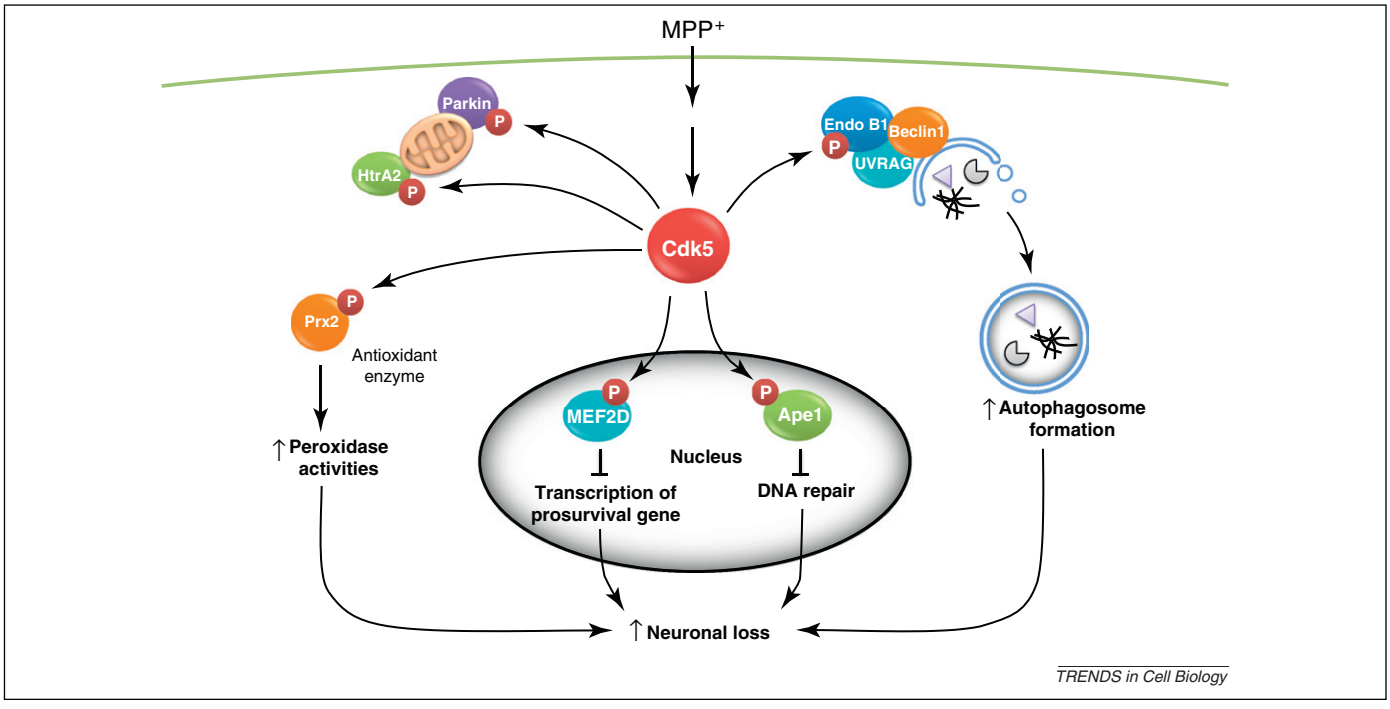

Figure 2. Cdk5 mediates cell death in models of Parkinson's disease by phosphorylating various cytoplasmic and nuclear substrates. Cdk5 activity is increased by MPP^+ treatment or MPTP injection. In the nucleus, phosphorylation of the prosurvival transcription factor MEF2D and DNA repair enzyme Ape1 by Cdk5 reduces their activity, resulting in cell death. Cdk5 exacerbates oxidative stress by phosphorylating antioxidative enzyme Prx2 to inhibit its peroxidase activity. Cdk5-dependent phosphorylation of endophilin B1 mediates autophagy deregulation in models of Parkinson's disease, which also contributes to neuronal loss. Cdk5 also phosphorylates two proteins localized to the mitochondria, the E3 ubiquitin ligase Parkin and serine protease HtrA2, but additional studies are required to address how these phosphorylation events contribute directly to neuronal loss.

protease HtrA2 at S400, a residue that is adjacent to the G399S mutation of HtrA2 in familial Parkinson's disease [64]. The phosphorylation is important for preservation of mitochondrial transmembrane potential because overexpression of the S400A HtrA2 mutant fails to reverse the reduction in mitochondrial transmembrane potential induced by HtrA2 knockdown. Importantly, S400 phosphorylation is significantly inhibited in the brain lysate of transgenic animals expressing G399S mutant HtrA2, suggesting that attenuated phosphorylation of S400 may contribute to the pathology of HtrA2-mutated familial Parkinson's disease [64]. In addition, Cdk5 phosphorylates Parkin at S131 to reduce its E3 ubiquitin ligase activity and aggregation [65]. Another study reported that compound phosphorylation of Parkin by Cdk5 and casein kinase 1 triggers aggregation of Parkin, resulting in its inactivation [66]. These studies collectively reveal Cdk5 as an important regulator of Parkin function and aggregation. Further studies are essential for delineation of the physiological significance of Parkin phosphorylation by Cdk5.

Autophagy deregulation

Autophagy is a homeostatic process for turning over cytoplasmic contents and organelles in the cell. Mounting evidence has revealed aberrant autophagy in several neurodegenerative diseases [67]. Accumulation of autophagosomes, double-membraned vesicles that are formed during autophagy, has been observed in the postmortem brains of Parkinson's disease patients [68]. In addition, autophagy and chaperone-mediated autophagy (CMA) have both been implicated in the degradation of α-synuclein, the major constituent of Lewy bodies [69,70]. Furthermore, A30P and A53T mutations of α-synuclein, which are mutations observed in familial Parkinson's disease, impair CMA-mediated degradation of α-synuclein [69]. Interestingly, we recently identified Cdk5 as a regulator of autophagy induction in neurons [53]. Endophilin B1, a lipid-binding protein that is required for autophagy induction in fibroblasts, was identified as a Cdk5 substrate. Importantly, inhibition of Cdk5 activity or its phosphorylation of endophilin B1 at Thr145 abolishes autophagy induction triggered by starvation, treatment with MPP^+ or overexpression of A53T α-synuclein. In addition, inhibition of Cdk5- or endophilin B1-dependent autophagy attenuates neuronal loss induced by MPP^+ treatment or A53T α-synuclein overexpression [53], demonstrating that autophagy deregulation may also contribute to neuronal loss under certain pathological conditions.

It should be noted that A30P and A53T mutants of α-synuclein also inhibit degradation of prosurvival transcription factor MEF2D by CMA, resulting in cytosolic accumulation of MEF2D, attenuated MEF2D activity and cell death [71]. Inactivation of MEF2D is associated with neuronal loss in MPTP toxicity, and Cdk5 mediates its inactivation [55]. Cdk5 phosphorylates MEF2D to inhibit its activity and facilitate its caspase-dependent cleavage [72,73], thereby inactivating MEF2D. It will thus be interesting to examine whether Cdk5 also regulates degradation of MEF2D by CMA, thereby mediating neuronal loss in models of Parkinson's disease.

The role of Cdk5 in Parkinson's disease pathology has been consistent, with the literature supporting a detrimental role of elevated Cdk5 activity in Parkinson's disease pathophysiology. In agreement with these findings, a Cdk5 inhibitor is protective against neuronal loss in Parkinson's disease. The current focus should be to further determine whether Cdk5 activity is also implicated in other cellular deficiencies preceding neuronal loss.

Huntington's disease

In contrast to the emerging detrimental role of Cdk5–p25 activation in Alzheimer's and Parkinson's diseases, the literature supports a protective role for Cdk5 in Huntington's disease pathology. Cdk5 activity is inhibited in a Huntington's disease mouse model expressing the first 171 residues of mutant huntingtin (htt), concomitant with reduced association of Cdk5 with p35 [74]. Diminished Cdk5 and p35 levels were also observed in postmortem samples of Huntington's disease patients [75], although another study reported an elevated p25/p35 ratio in immortalized striatal cells expressing mutant htt and in human brain samples of Huntington's disease patients [76]. Additional studies are required to further delineate how Cdk5 activity is deregulated in the disease, but Cdk5 lowers htt aggregation by phosphorylating the protein at Ser434, which reduces its cleavage by caspases [74]. DNA damage also triggers Cdk5-mediated phosphorylation of htt at Ser1181 and Ser1201. Phosphorylation at these sites protects cultured striatal neurons from mutant htt-induced toxicity [75]. Furthermore, Cdk5 inhibits aggregation of mutant htt by disrupting the microtubule network [77]. These findings collectively suggest that Cdk5 activity is required to limit mutant htt toxicity, and may serve a protective role in Huntington's disease (Figure 3). Development of therapeutics to stimulate Cdk5 activity may provide a neuroprotective effect against disease pathology.

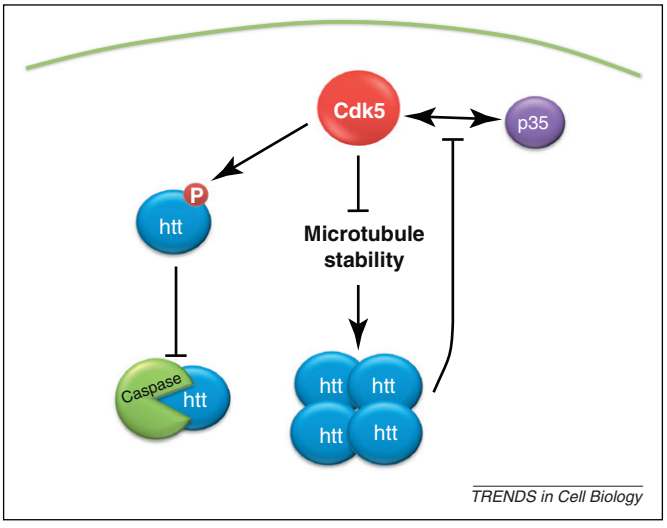

Figure 3. Cdk5 limits accumulation of mutant huntingtin in models of Huntington's disease. Mutant huntingtin (htt) has been observed to reduce Cdk5 activity and inhibit the interaction between p35 and Cdk5, although an elevated p25/p35 ratio has also been observed in models of Huntington's disease. Cdk5 decreases htt accumulation by directly phosphorylating htt to reduce its cleavage by caspases. Cdk5 also limits htt aggregation by disrupting the microtubule network.

Concluding remarks

It has become increasingly clear that deregulation of Cdk5 activity in both directions plays a crucial role in the pathophysiology of several neurodegenerative diseases, although each involves different pathogenic mechanisms and affects different brain regions. Although the actions of Cdk5 in Alzheimer's, Parkinson's and Huntington's diseases are somewhat different, certain similarities can be derived from the studies. For example, Cdk5 has been implicated in the regulation of the level and aggregation of the toxic species in these neurodegenerative diseases, such as the generation of Aβ and the degradation and aggregation of htt [16,17,19,74,77]. Cdk5 has also been suggested to regulate Parkin aggregation [65], but how Parkin aggregation contributes to Parkinson's disease pathology remains incompletely understood. The identification of Cdk5 as part of the autophagic machinery [53] further supports a role of Cdk5 in regulating protein aggregation, because autophagy is recognized as a key pathway for clearance of intracellular protein aggregates [68]. Furthermore, autophagy deregulation is not limited to Parkinson's disease but is also observed in Alzheimer's and Huntington's diseases [67]. It will thus be interesting to examine whether Cdk5-mediated aberrant autophagy activation in Parkinson's disease is also implicated in the control of autophagy in the other two diseases. In addition, modulation of oxidative stress by Cdk5 is likely to play a role in multiple neurodegenerative diseases, given the prominent association of oxidative stress with neurodegeneration. Indeed, although Cdk5-dependent phosphorylation of antioxidative enzyme Prx2 was found to mediate MPTP toxicity [56], it is also linked to Aβ-induced oxidative stress and mitochondrial damage [78]. Last but not least, the essential role of Cdk5 in synaptic transmission and the observed altered neurotransmission in various neurodegenerative diseases also suggest that Cdk5 may contribute to the synaptic dysfunction in these diseases before neuronal death occurs. Collectively, the current literature continues to support an important role for Cdk5 in multiple pathogenic mechanisms of neurodegeneration, thus making Cdk5 a highly attractive candidate for development of therapeutics against these diseases. Future studies aimed at further elucidating the mechanistic action of Cdk5 are essential for the development of treatment with maximal effectiveness and minimal side effects, especially given the double-edged nature of Cdk5 deregulation in diseases.

Acknowledgments

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