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Neuroscience Letters 361 (2004) 47–51

Neuroscience Letters

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Mini-review

Cdk5: mediator of neuronal death and survival☆

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Abstract

Cdk5 (cyclin-dependent kinase 5) is a serine/threonine kinase implicated to play pivotal roles in neuronal development. Recently, its potential involvement as a regulator of neuronal death and survival has attracted considerable interests. Importantly, increasing evidence has linked Cdk5 to the etiopathology of neurodegenerative diseases such as Alzheimer's disease and amyotrophic lateral sclerosis. Here we summarize the recent findings on Cdk5 not only as an important participant in neuronal death, but also a key player in neuronal survival. Elucidating the mechanisms of regulation of Cdk5 and its downstream signaling might prove to be crucial in the therapeutic treatment of neurodegenerative diseases.

Keywords: p35; p39; Apoptosis; Alzheimer's disease; Neuronal survival; ErbB receptor; NMDA receptor

Introduction. Cyclin-dependent kinase 5 (Cdk5), a serine/-threonine kinase also known as neuronal Cdc2-like kinase, was originally identified as a member of the cyclin-dependent kinase family based on sequence homology [17,19]. Cyclin-dependent kinases are activated upon association with a family of regulatory proteins known as cyclins. Whereas Cdks are traditionally involved in regulating cell cycle progression [27], Cdk5 does not participate in cell cycle regulation. Analysis of the expression profile of Cdk5 in the embryonic mouse brain demonstrated that Cdk5 fails to co-localize with proliferating cells. Moreover, there is a lack of correlation between changes in Cdk5 activity during development and the period of cell proliferation [42]. Despite the demonstrated association of Cdk5 with cyclin D, activation of Cdk5 is not dependent on cyclin D [46,47]. Instead, two regulatory proteins that share little sequence homology with cyclins, p35 and p39, have been identified as activators of Cdk5 [10,40,41].

Cdk5 activators p35 and p25. Despite the ubiquitous expression of Cdk5, kinase activity of Cdk5 is largely detected only in the nervous system [42]. This enigma was later resolved by the isolation of its activators, p35 and p39, whose expression is found almost exclusively in the nervous system (both CNS and PNS) [41,49]. The correlation of Cdk5 activity with the expression pattern of p35 and p39 suggests that these two regulatory proteins are required for the activation of Cdk5. This hypothesis is corroborated by findings from transgenic mice studies. Cdk5 knockout mice display severe cortical lamination defects and perinatal death. While newly born neurons usually migrate to the outer cortical layers in an 'inside-out manner', this stratification of neocortex is absent in $Cdk5^{-/-}$ mice [29]. Remarkably, deletion of p35 results in similar abnormality in the formation of cortical lamina, although mortality of $p35^{-/-}$ mice is reduced to 15% and they generally live until 3 months of age [3]. On the other hand, $p39^{-/-}$ mice, display no overt phenotypic abnormality compared to wild-type [13]. The disparity in the phenotypes between the $p35^{-/-}$ and $p39^{-/-}$ mice underscores the importance of p35 during development. Importantly, simultaneous deletion of p35 and p39 results in phenotypes that are indistinguishable from Cdk5 null mice [13]. Taken together, these findings indicate that p35 and p39 are the key activators of Cdk5 in the nervous system.

In addition to the role of Cdk5 in corticogenesis during development [3], its action is also implicated in neurite outgrowth [28], neuronal differentiation and neuronal death (see ref. [27] for review). Recent evidence indicates that Cdk5 also exhibits extra-neuronal function, for example, in the regulation of neuromuscular junction formation [4,15]. In addition, Cdk5 has been shown to modulate apoptosis in leukemia [35] and astrocytoma cells [6].

Cdk5 required for neuronal survival. The first hint of

☆ This Mini-review is dedicated to Prof. Manfred Zimmermann on the occasion of his 70th birthday.

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0304-3940/03/$ - see front matter © 2003 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2003.12.117

Cdk5 playing a critical role as regulator of neuronal survival came from the study of Cdk5 knockout mice. Swelling of cell soma and nuclear margination was observed in the brainstem and spinal cord neurons of Cdk5$^{-/-}$ mice [29]. Reconstitution of Cdk5 function in Cdk5$^{-/-}$ mice abolishes the perinatal lethality of Cdk5 null mice, and reverses the chromatolytic morphology of Cdk5$^{-/-}$ neurons [38]. This suggests that Cdk5 activity is indispensable for neuronal survival during development. Recent findings by Li et al. [22] reveal an involvement of Cdk5 in regulating neuronal death pathways. Cdk5 attenuates activation of c-Jun N-terminal kinase 3 (JNK3) and phosphorylation of c-jun following UV irradiation by directly phosphorylating JNK3. Furthermore, apoptotic death induced by UV irradiation is enhanced in the absence of Cdk5 [22]. These observations suggest that Cdk5 promotes neuronal survival by inhibiting JNK3 when challenged with an apoptotic stimulus.

While the study by Li et al. demonstrated that Cdk5 can function to suppress apoptotic pathways, a second study by the same group provides evidence on the involvement of Cdk5 in the maintenance of survival signals in neurons. The PI3K/Akt pathway relays crucial survival signals in various cell types and is activated by a myriad of trophic factors upon binding to their respective receptors [2]. Li et al. demonstrated that PI3K and Akt activity is reduced in Cdk5$^{-/-}$ mice [20]. The down-regulated PI3K and Akt activity renders the Cdk5$^{-/-}$ neurons more susceptible to apoptotic stimuli. In addition, Cdk5 is required in the activation of PI3K and Akt following neuregulin-mediated survival of cortical neurons [20], suggesting that Cdk5 is indispensable for the maintenance of survival signals in neurons. The role of Cdk5 in neuronal survival is summarized in Fig. 1.

Cdk5 as inducer of neuronal death – p25: center stage. In contrast to the observed involvement of Cdk5 in neuronal survival, Cdk5 has also been shown to act as a death-inducing agent in neurons. p25, which is a cleaved fragment of Cdk5 activator p35, plays a central role in the function of Cdk5 under pathological condition. Despite the abundance of p35, the active Cdk5 complex initially isolated was associated with a ~25 kDa protein species [42]. Further studies revealed that the 25 kDa subunit is in fact the proteolytic cleavage product of p35 [18,41]. p35 is highly unstable and exhibits a half life of only 20–30 min [30]. Upon phosphorylation by Cdk5 itself, p35 is rapidly ubiquitinated and cleaved into p25 by proteosome. Proteolytic cleavage turns the p25 fragment into a much more stable protein, extending the half life by 3–5-fold compared to p35 to p25 [30,31]. Furthermore, cleavage of p35–p25 removes the myristoylation sequence from p35, thereby resulting in a re-distribution of the Cdk5 activator from membrane-associated to cytosolic form [16,31]. The generation of p25 releases Cdk5 activity into the cytosol and results in prolonged activation of Cdk5, which has been proposed to mediate neuronal death in various models of neurodegenerative diseases. Calpain was later identified as

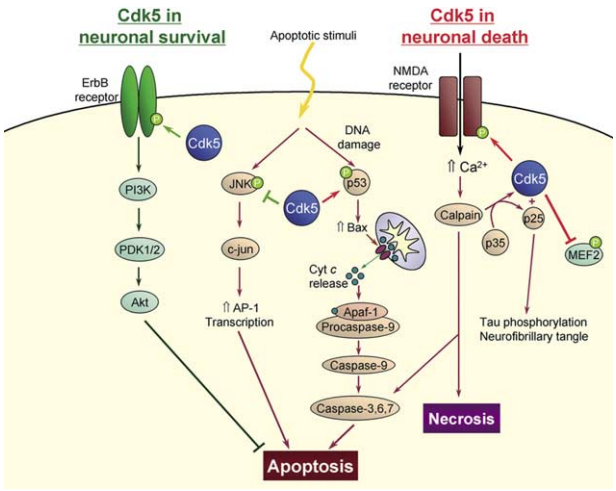

Fig. 1. The role of Cdk5 in neuronal survival and neuronal death. Cdk5 enhances neuronal survival by modulating two separate pathways. An Apoptotic stimulus such as UV irradiation induces activation of JNK, which results in c-jun phosphorylation. Phosphorylated c-jun then translocates to the nucleus to induce transduction of pro-apoptotic genes via increase in AP-1 transcription. Cdk5 diminishes the activation of the JNK pathway by directly phosphorylating JNK. Alternatively, Cdk5 is required in the upregulation of PI3K and Akt activity following binding of neuregulin to ErbB receptor. ErbB is a substrate for Cdk5 and phosphorylation by Cdk5 is essential for the survival-promoting effect of neuregulin. On the other hand, apoptotic stimuli induce neuronal death by stimulating expression of p53. Translocation of p53 to the nucleus increases the transcription of pro-apoptotic genes such as Bax. Bax subsequently enhances the release of cytochrome *c* (Cyt *c*) from the intermembrane space of mitochondria. Cytosolic cytochrome *c* then binds to apaf-1 and procaspase-9, resulting in the activation of caspase-9. Activated caspase-9 can activate other members of the caspase family, culminating in apoptosis. Cdk5 exacerbates neuronal death by phosphorylating p53, thereby increasing the transcription of Bax. Alternatively, Cdk5 phosphorylates NMDA receptors to increase calcium influx. This leads to enhanced calpain activation, and increased cleavage of p35 into p25, resulting in further and prolonged activation of Cdk5. The presence of this feed-forward loop augments neuronal death. Sustained activation of Cdk5 has also been demonstrated to inhibit the action of pro-survival transcription factor MEF2, thereby facilitating neuronal death by decreasing the cell's survival signals. The mode of cell death associated with excitotoxicity is controversial. Both apoptosis and necrosis are potentially involved, but the relative importance of each pathway remains unknown. Finally, upregulation of Cdk5 activity upon association with p25 has been shown to induce tau phosphorylation and neurofibrillary tangle, but the mechanisms by which cytoskeletal disruption contribute to neuronal death has not been identified.

the enzyme responsible for the truncation of p35 into p25 [14,16]. Recent evidence indicates that p39 is also cleaved into p29 by calpain. Similar to p35, p29 is more stable than p39, and redistribution of Cdk5 activity into the cytosol was observed following p39 cleavage [32]. Nonetheless, the function and significance of p29 has not been characterized. These observations suggest that calcium homeostasis is crucial in the regulation of Cdk5 activity, particularly under pathological condition where calcium homeostasis is often disrupted.

Involvement in the etiopathology of Alzheimer's disease. Initial evidence on the involvement of Cdk5 in neurode-

generative diseases came from the concomitant enhancement of hyperphosphorylated tau, p25 accumulation and Cdk5 activity in the post-mortem brains of Alzheimer's disease (AD) patients [31,33,43]. Indeed, Cdk5/p25 has been shown to phosphorylate tau and neurofilament in vitro, and expression of dominant-negative Cdk5/p25 abolishes tau phosphorylation in cortical neurons. In addition, expression of p25/Cdk5 results in higher incidence of neuronal death [31]. In agreement with this finding, it was subsequently shown that mice overexpressing p25 also exhibit tau and neurofilament hyperphosphorylation [1]. However, the correlation between p25 and tau phosphorylation has not been consistently demonstrated. Analysis of post mortem AD brains by other groups revealed that expression of p35, p25 and Cdk5 are comparable between the control and AD brains [23,39]. Furthermore, while induced cleavage of p35 to p25 following treatment with NMDA, glutamate and calcium ionophores enhances Cdk5 activity, tau phosphorylation decreases [12]. Contrary to a previous report [1], Takashima et al. reported that mice overexpressing p25 fail to display an enhancement in tau phosphorylation and cell death, with an enlarged pituitary gland as the only overt phenotype [37]. While the basis for the reported discrepancies is unclear, these conflicting data warrant further analysis to elucidate the precise involvement of Cdk5 in the etiopathology of AD.

Importance of Cdk5 activity in other models of neuronal death. Although the involvement of Cdk5 in tau hyperphosphorylation and AD remains obscure, implication of Cdk5 in other models of neuronal death has been demonstrated. Enhancement of Cdk5 and p35 immunoreactivity are observed in the cell body of apoptotic cells following ischemia [8] and in models of Parkinson's disease following injection of neurotoxins to induce selective destruction of substantia nigra neurons [9,26,50]. Furthermore, generation of the p25 fragment often accompanies apoptosis upon challenge by a variety of apoptotic stimuli, ranging from neurotoxicity, ischemia, oxidative stress, incubation with Aβ itself to nerve injury [5,16,25,50]. These correlative observations are substantiated by recent studies demonstrating a causal-relationship between Cdk5 activity and neuronal death. Expression of Cdk5/p25 induces apoptosis in primary cortical cultures [7,31]. In addition, p25/Cdk5 has been demonstrated to phosphorylate NMDA receptors, thereby amplifying calcium influx. Importantly, phosphorylation of NMDA receptors is required for the induction of cell death following ischemia in hippocampal neurons [21,45]. Finally, Cdk5 has recently been shown to inhibit the pro-survival effect of transcription factor MEF2 (myocyte enhancer factor) by phosphorylation at Ser^{444}. Phosphorylation of MEF2 by Cdk5/p25 renders cortical neurons more susceptible to excitotoxicity and oxidative stress [7]. Therefore deregulation of Cdk5 activity exacerbates neuronal death not only by enhancing cell death pathways, but also by impairing pro-survival signaling.

Despite the large amount of data linking the induction of apoptosis with enhanced Cdk5 activity and p25 accumulation, there have been conflicting reports on the role of Cdk5 in various models of cell death. Kerokoski et al. demonstrated that expressions of p25, p35 and Cdk5 are all down-regulated in hippocampal neurons after treatment with various apoptotic stimuli such as etoposide, cyclosporin A and okadiac acid [11]. In addition, Cdk5 expression is reduced in chick sympathetic neurons following dopamine toxicity [36]. Finally, protein expression of both Cdk5 and p35, together with Cdk5 kinase activity, is decreased following hypoxia/reperfusion injury [44]. These observations suggest that the involvement of Cdk5 in neuronal death may be dependent on neuronal subtypes and the type of death-inducing stimuli. In particular, since cleavage of p35 is mediated by calpain, it would be interesting to examine if p35 cleavage always accompanies disruption of calcium homeostasis in various neuronal death models. Elucidating the molecular mechanisms through which deregulated Cdk5 induces cell death would help to resolve the current controversy.

Cdk5 – regulator or apoptosis? While many of the studies listed demonstrated the essential involvement of Cdk5/p25 in neuronal death, the type of cell death involved in these paradigms is not clear. In fact, whether cell death associated with AD represents necrosis or apoptosis remains controversial [24]. In addition, although the mode of cell death induced by ischemia is presumably necrotic, involvement of apoptotic pathways has also been documented [34]. The same is true for excitotoxic insults and oxidative stress. Examination of nuclear morphology alone is insufficient to delineate between necrosis and apoptosis, as DNA degradation is observed in both types of cell death. Apoptosis must be confirmed by examining the involvement of other apoptotic machinery, such as the activation of caspases, or the modulation of members of the Bcl-2 family. The only piece of evidence linking upregulation of Cdk5 activity to the apoptotic machinery is provided by Zhang et al. [48]. Cdk5/p25 was observed to increase the expression of p53, a proto-oncogene serving as important mediator of apoptotic pathways in various models of apoptosis. The upregulated transcriptional activity of p53 in turn enhances the expression of Bax, a pro-apoptotic member of the Bcl-2 family [48]. Although caspase activation was not demonstrated in this study, the upregulation of Bax is associated with cytochrome *c* release and initiation of the caspase cascades (Fig. 1). This suggests that Cdk5 may directly interact with the apoptotic pathways to initiate apoptosis.

Conclusion. Based on the evidence provided by transgenic mice studies and the correlation between Cdk5 activity and Alzheimer's disease, the importance of Cdk5 in the life/death decision of a neuron is certain. Nonetheless, exactly when the activity of Cdk5 is required for survival, and the conditions upon which Cdk5 turns into an active participant of neuronal death remain unclear. Cleavage of p35 to p25 provides one of mechanisms through which the activity of Cdk5 turns pathological. However, answers to

several key questions are still much anticipated. Is Cdk5 implicated in neuronal survival only during development? Does Cdk5 directly modulate the apoptotic pathways? Can Cdk5 induce neuronal death in the absence of p25? Neuronal survival may ultimately hinge upon the precise regulation of Cdk5 activity rather than direct suppression of Cdk5 activity during pathological conditions. Unraveling the mechanisms of regulation for Cdk5 will undoubtedly advance our understanding on the significance of Cdk5 in neuronal death.

Acknowledgements

We thank Ka Chun Lok for his help on preparing the figure. The studies by N.Y. Ip were supported in part by the Research Grants Council of Hong Kong SAR (HKUST 6091/01M) and the Area of Excellence Scheme of the University Grants Committee (AoE/B-15/01). N.Y. Ip was the recipient of Croucher Foundation Senior Research Fellowship. Z.H. Cheung is a recipient of the Croucher Foundation Fellowship.

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