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Special Issue on "Cdk5 and Brain Disorders": Prologue

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Abstract

Cyclin-dependent kinase 5 (Cdk5) was identified almost two decades ago as a Tau kinase specific to the nervous system. Shortly after its discovery, it was revealed that this atypical member of the CDK family does not partner with cyclins but with two other proteins, p35 and p39. P35 is predominantly expressed in post-mitotic neurons, whereas p39 is expressed in many different tissues including the brain, pancreas, muscle cells, neutrophils, and many other cell types. A proline-directed serine/threonine (S/T) kinase, predominantly active in the nervous system, Cdk5 regulates a multitude of functions including nervous system development, neuronal migration, cytoskeletal dynamics, axonal guidance, synaptic plasticity, neurotransmission, neuronal survival and death, to mention a few. In association with its ubiquitous expression in other tissues, Cdk5 is implicated in a wide range of functions, such as gene transcription, vesicular transport, apoptosis, cell adhesion, migration, exocytosis, etc. A focal point of investigation surrounding Cdk5 is its deregulation in pathogenic processes of neurodegenerative disorders, which has emphasized on its hyperactivation by p25, a calpain-cleaved product of p35 leading to Tau and neurofilament hyperphosphorylation followed by neuronal death. What has intrigued researchers about Cdk5 is its tight regulation in carrying out many normal physiological functions while its deregulation under pathological conditions, is linked to neurodegenerative diseases like amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Neiman Pick's Type C disease and others. Between these two so-called 'good Cdk5 (Cdk5/p35)' and 'bad Cdk5 (Cdk5/p25)', the latter has become the target for therapeutic intervention in neurodegenerative disorders.

Two decades ago, studies on kinases responsible for phosphorylation of neuronal cytoskeletal proteins specifically in their S/T-P residues revealed that cyclin dependent kinase 5 (Cdk5) is one of the principal kinases involved in their phosphorylation [1]. Later on, it became clear that although Cdk5 is ubiquitously expressed in all cells and shares a high degree of homology with other members of the cyclin-dependent kinase family (CDKs), its activity is prevalent in post-mitotic neurons because one of its activators, p35 is expressed at a relatively higher level [2]. Cdk5 is a multi-functional S/T protein kinase that is involved in a wide range of neuronal functions from neurite outgrowth and neuronal migration to synaptic activity and cell survival [3].

With its activity tightly regulated in the developing nervous system, Cdk5-null (KO) mice are lethal exhibiting abnormal corticogenesis due to defective neuronal migration and other abnormalities before dying between E16 and P0 [4]. Experimental re-expression of Cdk5 in neurons of Cdk5 KO mice *in vivo* completely restores the wild type phenotype, clearly demonstrating that neuronal and not glial Cdk5 activity is necessary for normal development and survival [5].

More importantly, Cdk5 has been identified as a prime candidate for neurodegenerative pathogenesis [6,7] on the basis of the fact that in neuropathological conditions, such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Neiman Pick's Type C (NPC) disease and others, proline directed S/T-P residues on cytoskeletal proteins are aberrantly hyperphosphorylated within cell bodies, resulting in the accumulation of abnormal cellular aggregates and massive neuronal cell death.

During neuronal insults, increase in intracellular calcium and activation of calpains result in the cleavage of p35 to p25 thereby inducing deregulation and hyperactivation of Cdk5. In outcome, aberrant hyperphosphorylation of cytoskeletal proteins (e.g. NFs, MAPs, Tau) occurs, forming aggregates of these proteins in the cell body and consequently inducing neuronal death. This process has been associated with a large number of neurodegenerative diseases [2]. In primary cortical neuron cultures, Cdk5/p25 complex phosphorylates Tau more efficiently than does the Cdk5/p35 complex [8]. *In vitro* Tau phosphorylation assays have demonstrated that p25 accelerates Cdk5 catalytic activity by ~2.4-fold over p35 [9]. Further evidence comes from the preferential increase in Tau phosphorylation in p25 transgenic mice [10,11], while p35 transgenic mice displaying increased Cdk5 catalytic activity, do not show increased Tau phosphorylation [12]. These findings are complemented by the observation that Cdk5-deficient mice show decreased Tau phosphoryaltion [5]. Surprisingly, however, a new strain of p35-deficient mice display increased Tau phosphorylation [13]. It is possible that in these mice Tau phosphorylation occurs due to the compensatory increases in another Cdk5 activator, p39 level as was reported in p35-deficient mice [14]. Moreover, p39-mediated Tau phosphorylation is more efficient than p35-mediated Tau phosphorylation [15] and p39-derived p29 is also potent in phosphorylating Tau [16].

Despite its reported pathological role, studies also implicate p25 as a "normal" player in modulating synaptic function, LTD, learning and memory in specific brain regions in young animals [17-19]. Transgenic mice expressing either low level of p25, or with expression restricted spatiotemporally to specific brain regions, show a Cdk5/p25 positive transient effect on LTD in the hippocampus and water maze learning in these animals, although prolonged expression of p25, in older animals, induces Tau phosphorylation and neurodegeneration [3,11].

The differential phosphoryaltion potentials of Cdk5/p25 and Cdk5/

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p35 are also associated with another Cdk5 substrate, amyloid precursor protein (APP), which is involved in neurodegeneration. Cdk5 phosphorylates APP in its cytoplasmic domain at Thr668 [15] and increased APP Thr668 phosphorylation is observed in p25 transgenic mice in which Cdk5/p35 activity remains unaltered [11]. However, the role of Cdk5/p25 in various neuropathological diseases is far more complex than previously assumed as lack of p35/p25 in mice does not slow the onset or progression or improve the neuropathology of NPC [20].

Cdk5 is not only involved in phosphorylating the NFs, MAPs, and Tau but also involved directly or indirectly in modulating other kinase activities that phosphorylate the same proteins as well as other proteins. Cross-talk of Cdk5 with many different signal transduction pathways is involved in nervous system development and neurodegeneration [21]. Because of its multifunctional role, as it exerts both positive and negative effects on neuronal function and survival, Cdk5 is characterized as a "Jekyll and Hyde" kinase [3].

In Alzheimer's disease (AD), extracellular accumulation of Aβ42 that readily aggregates into amyloid plaques, occurs due to an altered ratio of Aβ generation and clearance [22]. One of the downstream events of this elevated Aβ42 levels is the aberrant activation of kinases and inhibition of phosphatases that results in neurofibrillary tangle formation and neuronal death. Many reports now link Cdk5 to Aβ42 toxicity and Tau pathology leading to neurodegeneration. In primary neurons, Aβ42 induces the cleavage of p35 to p25 [23-25]. P25 accumulation is found in mutant APP transgenic mice that display elevated Aβ42 levels [26], while inhibition of Cdk5 activity attenuates Aβ42-induced neuronal death [23,24]. These findings indicate that Aβ42 is an inducer of p25 generation, and therefore, a potent activator of Cdk5/p25.

For obvious reasons, Cdk5/p25 is a potential target for intervention in neurodegeneration [27,28] and several inhibitors for the Cdk5/p25 have been reported [29,30]. Two polypeptides CIP (Cdk5/p25 inhibitory peptide) and P5, derivatives of p35, show therapeutic potential, since they specifically inhibit Cdk5/p25 activity [31,32], and efforts continue for pharmaceutical interventions [30]. The special issue, "Cdk5 and Brain Disorders" is intended to provide an ideal platform for bringing together recent advances in the field by consolidating the findings of various investigators.

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