

CDK5

A new lead to survival

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The protein kinase CDK5 was originally discovered at a time when cyclin-dependent kinases were thought to be involved exclusively in cell cycle control. The CDK5 catalytic subunit was first identified based on its nucleotide sequence homology to other known CDK family members (*cdc2*, CDK2),¹ while the enzyme activity was identified by protein purification of a tau kinase relevant to Alzheimer disease² and, independently, of a novel kinase exhibiting *cdc2*-like substrate specificity in brain.³ These activities were referred to as tau kinase II and brain proline-directed kinase, respectively, which, upon purification were shown to be one and the same enzyme. In addition to isolation of the active form of CDK5, purification revealed a bound p25 regulatory subunit of novel sequence, and molecular cloning revealed the full-length precursor of this subunit, p35.⁴

CDK5 has since garnered much attention because of its uniqueness as a CDK in three ways: (1) its association with the non-cyclin-like regulatory subunits p35 and p39; (2) its novel role as a cyclin-dependent kinase in non-dividing cells and (3) regulation by cleavage of p35 to p25 *in vivo*. In the first case, early work revealed that p25 displayed little to no homology with cyclins, yet structural analysis revealed that p25 adopted a cyclin-like fold capable of binding to and activating CDK5. Like cyclins, p25 was necessary for activation of the CDK5 catalytic subunit, resulting in virtually identical substrate sequence specificity to that of CDK1/cyclinB and CDK2/cyclinA. Identification of active CDK5/p25 in neurons explained the phosphorylation of neuronal proteins such as neurofilaments at CDK-specific sites, when conventional CDKs were absent from these cells.⁴

The second unique feature is the ubiquitous expression of the CDK5 catalytic subunit in all cells and tissue types, while expression of p35 is restricted mainly to neurons, consistent with early observations that CDK5/p35 occupied neuronal-specific function.⁵ The signaling role of CDK5 in neurons has emerged to be broad-based, unlike the historical cases of PKA and MAP kinase whose signaling pathways have been revealed to be effectively linear and well-defined. A current list of meaningful CDK5 substrates include over 50 in number, most of which are associated with neuronal migration, neurite outgrowth, synaptic function and neurodegenerative disease.⁵ Upstream regulation of CDK5/p35 remains poorly understood, except for cleavage of the p35 subunit by calpain, generating the toxic CDK5/p25 species that is linked to various neurodegenerative conditions. Targeted deletion of CDK5 or p35 genes are associated exclusively with neurological defects, confirming the predominantly neurological role this enzyme plays.⁵

The wide tissue distribution of the CDK5 catalytic subunit across cells and tissues otherwise absent of an activating subunit suggests that the global function CDK5 is only starting to be described. Recently the reporting of novel functions of CDK5 in extra-neuronal tissues has grown in prominence. Most significant is the role of CDK5/p35 in glucose tolerance in pancreas, interferon- γ signaling in myeloid cells, neutrophil-mediated inflammation and T-cell activation and insulin resistance and obesity.⁶ In addition, activation of CDK5 by novel regulatory proteins such as cyclins I or G have been described and shown to be involved in apoptosis and cancer processes,

respectively.⁶ These newly appreciated roles of CDK5 are further testimony to the broad role this enzyme plays in brain function and the body overall.

Third, the most intriguing aspect of CDK5 regulation has perhaps been the conversion of the p35 regulatory subunit to p25 in neurons. It is clear that CDK5/p35 is essential for neurodevelopment, while proteolytic cleavage of the p35 N-terminal 98 amino acids by calpain results in CDK5/p25 and cell death. CDK5/p25 is toxic when overexpressed in cells, and both conversion of endogenous p35 to p25 and p25 overexpression has been linked to Alzheimer, Parkinson, ALS and other neurodegenerative disease-like symptoms in animal models. The cumulative evidence implies that a similar link exists in humans. CDK5/p25 is toxic to all cells, including extraneuronal cells that do not contain tau, an historically significant target of CDK5/p25 whose pathological aggregation is key to Alzheimer disease.⁵

Various stress-induced stimuli lead to calpain-mediated conversion of p35 to p25. While a number of death-related substrates have been described, the exact mechanism causing neural toxicity is not known. Although it has been widely thought that CDK5/p25 is enzymatically hyperactive compared with CDK5/p35, a recent study strongly refutes this.⁷ The catalytic activity toward *in vitro* substrates, steady-state kinetic parameters, substrate specificity and sites of phosphorylation in tau all appear to be the same between the two complexes.⁷ Alternatively, CDK5/p35 is a plasma membrane-associated protein, while cleavage of p35 to p25 results in cytosolic, nuclear and perinuclear re-distribution of CDK5. Granted, subcellular redistribution alone does not easily account for the

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toxic response, since early work showed that a non-membrane-associated form of CDK5/p35 mutant is not toxic.⁵

The most recent development in the area of CDK5/p25-induced toxicity has been the demonstration that a peptide corresponding to the leading N-terminal domain (p10) of p35, alone protects against the toxicity associated with CDK5/p25 both in neurons and extra-neuronal cells.⁸ The evidence suggests that p10 functions as an anti-death sequence when expressed either separately or contiguously as the N-terminal domain of p35. The data explain how proteolysis of p35 followed by degradation of the p10 product may trigger CDK5/p25 toxicity. A long-standing

question of the field has been: what is the mechanism of toxicity of CDK5/p25? The answer may now be framed by asking: what is the target of p10, and how does p10 protect against CDK5/p25 toxicity? Answers to these questions will shed light on how CDK5/p35 circumvents toxicity in normal neurons (and other cells), while CDK5/p25 readily initiates cell death. If conversion of p35 to p25 causes neuron death in humans, it is tempting to ask if artificial delivery of p10 to the brain could ultimately protect against neurodegeneration. One thing is for certain, the apparent pro-survival function of p10 suggests yet a further unique property of this unusual enzyme.

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