## Phylogeny

Cyclin-dependent kinase 5 (CDK5) is classified within the CMGC group of eukaryotic protein kinases, which also includes Cyclin-dependent kinases (CDKs), Mitogen-activated protein kinases (MAPKs), Glycogen synthase kinases (GSKs), and Cdc-like kinases (CLKs) (manning2002theproteinkinase pages 1-2, johnson2023anatlasof pages 2-3). Within this group, CDK5 is a member of the CDK family, sharing sequence homology with other CDKs but exhibiting unique functions, particularly in the nervous system (manning2002theproteinkinase pages 7-8, johnson2023anatlasof pages 4-4). Another classification places CDK5 within the cyclin-dependent kinase-like (CDKL) family, which is phylogenetically close to but distinct from the classical CDK family (manning2002theproteinkinase pages 4-5). CDK5 is a highly conserved, unduplicated member of its subfamily, with single orthologs identified in humans, worms, and flies (manning2002theproteinkinase pages 3-3).

## Reaction Catalyzed

CDK5 is a serine/threonine kinase that catalyzes the transfer of the terminal (gamma) phosphate group from an ATP molecule to the hydroxyl group of serine or threonine residues on substrate proteins (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 4-4, johnson2023anatlasof pages 12-18). This phosphorylation reaction results in the formation of a phosphoserine or phosphothreonine on the substrate and ADP as a byproduct (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 7-7).

## Cofactor Requirements

The catalytic activity of CDK5 requires ATP as the phosphate donor cofactor (johnson2023anatlasof pages 3-4, johnson2023anatlasof pages 7-7). The kinase reaction also depends on a divalent metal ion cofactor, typically Mg2+, which stabilizes ATP binding and facilitates the phosphate transfer (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 4-4, zhang2007theactivationand pages 8-9). Mn2+ may also serve as a cofactor (johnson2023anatlasof pages 23-26).

## Substrate Specificity

CDK5 is a proline-directed kinase, meaning it preferentially phosphorylates serine or threonine residues that are immediately followed by a proline residue at the +1 position (johnson2023anatlasof pages 2-3, johnson2023anatlasof pages 4-4). This consensus substrate motif is commonly represented as S/T-P (johnson2023anatlasof pages 12-18). Other studies define the motif as S/TPXK/R (sharma1999identificationofsubstrate pages 1-2). Based on its specificity, CDK5 is grouped in Cluster 2 with other proline-directed kinases (johnson2023anatlasof pages 12-18).

## Structure

CDK5 has a bilobal kinase fold, with a smaller N-terminal lobe composed mostly of beta-sheets and a single alpha-helix (the C-helix), and a larger, predominantly helical C-terminal lobe (zhang2007theactivationand pages 1-2). The ATP-binding pocket is located at the interface between these two lobes (zhang2007theactivationand pages 1-2). Key regulatory elements include the glycine-rich loop (G-loop) and the activation loop (T-loop), which are critical for catalysis (zhang2007theactivationand pages 1-2, sharma1999identificationofsubstrate pages 2-3). Unlike other CDKs, CDK5 activation does not require phosphorylation of its activation loop; instead, binding of an activator protein like p25 induces a conformational change that stabilizes the active state (mapelli2005mechanismofcdk5p25 pages 1-2). The crystal structure of the CDK5/p25 complex has been resolved at 2.2–2.3 Å resolution, providing insight into its domain organization and the mechanism of inhibitor binding (mapelli2005mechanismofcdk5p25 pages 1-2, mapelli2005mechanismofcdk5p25 pages 2-4). Homology models of CDK5 have been built using the CDK2-cyclin A crystal structure (PDB ID: 1FIN) as a template (sharma1999identificationofsubstrate pages 1-2).

## Regulation

Monomeric CDK5 is enzymatically inactive and requires association with a regulatory activator, p35 or p39, for its kinase activity (cruz2004cdk5deregulationin pages 1-2, barnett2011theroleof pages 1-2). These activators are neuron-specific and have short half-lives due to ubiquitin-proteasome-mediated degradation, which tightly controls physiological CDK5 activity (cruz2004cdk5deregulationin pages 1-2, tsai2004cdk5atherapeutic pages 1-2). Under neurotoxic conditions such as ischemia or amyloid-beta exposure, elevated intracellular calcium activates the protease calpain (cruz2004cdk5deregulationin pages 1-2, shukla2012deregulatedcdk5activity pages 4-5). Calpain cleaves the p35 activator to produce a truncated, more stable fragment called p25 (cruz2004cdk5deregulationin pages 1-2, barnett2011theroleof pages 2-4). The p25 fragment lacks the N-terminal myristoylation signal of p35, leading to mislocalization of the CDK5/p25 complex from the membrane to the cytoplasm and nucleus (cruz2004cdk5deregulationin pages 1-2, shukla2012deregulatedcdk5activity pages 4-5). This results in prolonged, deregulated, and hyperactive CDK5 activity (barnett2011theroleof pages 2-4, kesavapany2007peptidesderivedfrom pages 1-2). Post-translational modifications also regulate CDK5. Phosphorylation at Tyr15 by kinases such as Fyn, EphA, and Abl promotes CDK5 activation (gupta2019cdk5amain pages 1-8, gupta2019cdk5amain pages 8-13, lau2003roleofcdk5 pages 5-6). A regulatory feedback mechanism exists where CDK5 phosphorylates p35 at Ser8 and Thr138, which inhibits its cleavage by calpain (gupta2019cdk5amain pages 1-8). Other regulatory mechanisms include inhibition by competing proteins like cyclin E and nitrosylation (odajima2011cyclineconstrains pages 2-4, gupta2019cdk5amain pages 8-13).

## Function

CDK5 is a proline-directed serine/threonine kinase predominantly expressed in post-mitotic neurons (barnett2011theroleof pages 1-2, bibb2003roleofcdk5 pages 1-2). It is essential for neuronal development, including neuronal migration, differentiation, axon guidance, and dendritic morphology (barnett2011theroleof pages 1-2, gupta2019cdk5amain pages 8-13). In the mature brain, CDK5 modulates synaptic plasticity, learning, and memory by regulating neurotransmitter release, synaptic vesicle recycling, dendritic spine formation, and receptor density (barnett2011theroleof pages 1-2, barnett2011theroleof pages 2-4, bibb2003roleofcdk5 pages 1-2). CDK5 phosphorylates numerous key neuronal substrates, including Tau, microtubule-associated protein 1B (MAP1B), dopamine- and cAMP-regulated phosphoprotein 32kDa (DARPP-32), amyloid precursor protein (APP), delta-catenin, dynamin I, amphiphysin I, PSD-95, MEF2, and HDAC1 (barnett2011theroleof pages 1-2, barnett2011theroleof pages 8-10, bibb2003roleofcdk5 pages 1-2, cruz2004cdk5deregulationin pages 1-2). Through phosphorylation of DARPP-32, CDK5 modulates dopamine signaling pathways (bibb2003roleofcdk5 pages 3-4, tsai2004cdk5atherapeutic pages 1-2). In the nucleus, CDK5 interacts with HDAC1 and MEF2 to regulate gene expression and neuronal pruning (barnett2011theroleof pages 8-10, barnett2011theroleof pages 4-5).

## Inhibitors

Several experimental small molecule inhibitors of CDK5 have been identified. Roscovitine (also known as Seliciclib or CYC202) is a purine analog that acts as an ATP-competitive inhibitor of CDK5, as well as CDK1, CDK2, CDK7, and CDK9 (mapelli2005mechanismofcdk5p25 pages 2-4, unknownauthors2015roscovitineincancer pages 1-2, unknownauthors2011theroleof pages 2-3). It has an IC50 of 0.16 µM for CDK5 and its (S)-stereoisomer has demonstrated neuroprotective effects in animal models of stroke (unknownauthors2015roscovitineincancer pages 1-2, menn2010delayedtreatmentwith pages 5-7). Other identified inhibitors include aloisine-A, indirubin-3’-oxime, flavopiridol, and hymenialdisine, many of which also inhibit other kinases like GSK-3β and CK1 (mapelli2005mechanismofcdk5p25 pages 2-4, pitchuanchom2012cyclindependentkinases5 pages 6-6, unknownauthors2011theroleof pages 2-3).

## Other Comments

Aberrant, hyperactive CDK5, resulting from the calpain-mediated conversion of p35 to p25, is strongly implicated in the pathogenesis of several neurodegenerative diseases (barnett2011theroleof pages 1-2, shukla2012deregulatedcdk5activity pages 4-5). In Alzheimer’s disease (AD), the CDK5/p25 complex is considered a central pathological driver (lau2003roleofcdk5 pages 1-2, cruz2004cdk5deregulationin pages 1-2). It contributes to both hallmark lesions of AD by causing hyperphosphorylation of tau, leading to neurofibrillary tangle (NFT) formation, and by phosphorylating APP at Thr668, which influences amyloid-beta generation (lau2003roleofcdk5 pages 2-3, cruz2004cdk5deregulationin pages 1-2, kesavapany2007peptidesderivedfrom pages 1-2). Elevated levels of p25 and increased CDK5 activity are observed in human AD brains (lau2003roleofcdk5 pages 3-4, cruz2004cdk5deregulationin pages 2-3). CDK5 deregulation is also linked to Parkinson’s disease, amyotrophic lateral sclerosis (ALS), and neuronal death following ischemia (cruz2004cdk5deregulationin pages 2-3, kesavapany2007peptidesderivedfrom pages 1-2). While no disease-causing mutations in the CDK5 gene itself have been reported in the context of AD, familial AD mutations in genes like APP and presenilins are known to increase amyloid-beta, which can in turn activate the p25/CDK5 pathway (lau2003roleofcdk5 pages 2-3, shukla2012deregulatedcdk5activity pages 1-2).

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