

CDKs

Key References

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Overview

Cyclin dependent kinases (CDKs) are typical serine/threonine kinases that display the 11 subdomains shared by all kinases. The complete sequence of the *Homo sapiens* genome shows that among the ~30,000 predicted genes, there are 13 CDKs and 25 cyclins. Eleven CDKs and their associated cyclins have been characterized in man.

The structure of CDK2 consists of an amino-terminal lobe rich in β -sheets and a larger, mostly α -helical, carboxy-terminal lobe. The ATP binding site is located in a deep cleft between the two lobes that contain the conserved catalytic residues. Crystallographic studies have shown the importance of cyclin binding upon CDK2 as it forces the kinase subunit into an active conformation. The T-loop, which blocks substrate access in monomeric CDK2, moves to the outside of the catalytic cleft after binding cyclin A. This then permits the activating phosphorylation of Thr¹⁶⁰ (by CDK7/cyclinH/MAT1). The second conformational change induced by cyclin binding is found within the ATP-binding site where a reorientation of the amino acid side chains induces the alignment of the triphosphate of ATP, which is necessary for phosphate transfer. The high degree of sequence homology between the catalytic domains of different CDKs suggests that their 3-dimensional structures will be similar. This has been essentially confirmed with CDK5 and CDK6.

Progression through the G1, S, G2, M phases of the cell cycle is directly controlled by CDKs. In early-mid G1, extracellular signals modulate the activation of CDK4 and CDK6, which are associated with D-type cyclins. These complexes phosphorylate and thereby inactivate the retinoblastoma protein pRb, resulting in the release of E2F and

DP1 transcription factors that control the expression of genes required for the G1/S transition and S phase progression. The CDK2/cyclin E complex, which is responsible for the G1/S phase transition, also regulates centrosome duplication. During S phase, CDK2/cyclinA phosphorylates different substrates allowing DNA replication and the inactivation of G1 transcription factors. Around the S/G2 phase transition, CDK1 associates with cyclin A. Later, CDK1/cyclinB appears and triggers the G2/M phase transition by phosphorylating a large set of substrates. Phosphorylation of the anaphase promoting complex (APC) by CDK1/cyclin B is required for the transition to anaphase and completion of mitosis. These successive waves of CDK/cyclin assemblies and activations are tightly regulated by post-translational modifications and by intracellular translocations. They are coordinated and dependent on the completion of previous steps, through so-called "checkpoint" controls. Recent studies using knock-out experiments performed in mice suggest that CDK2 and CDK3 may be dispensable, whereas CDK1, CDK5 and CDK11 are essential genes.

Some CDKs directly regulate transcription. CDK7/cyclin H/MAT1 is a component of the transcription factor TFIIF. Both CDK7/cyclinH and CDK8/cyclin C phosphorylate the C-terminal domain of the largest subunit of RNA polymerase II, which is required for elongation. CDK9/cyclin T is a component of the positive transcription elongation factor P-TEFb. It is responsible for the Tat-associated kinase activity involved in HIV-1 Tat transactivation.

CDK5 activity is important for outgrowth of neurites and neuronal development, for myogenesis and for somite organization in

embryos. An interesting aspect of CDK5 is the nature of its associated regulatory subunits, p35 or p25, a proteolytic cleavage product. Despite their evolutionary distance from cyclins, the predicted structure of p35/p25 shows a similar fold to that of cyclins, which explains the efficient activation of CDK5. Conversion of p35 to p25 leads to constitutive activation of CDK5 and alteration of its cellular localization. CDK5/p25 expression in cultured primary neurons triggers apoptosis. A considerable amount of evidence links CDK5 activity to cytoskeletal abnormalities that can lead to neuronal death as observed in Alzheimer's disease. CDK2, CDK5 and CDK11 have an essential function in apoptosis. CDK5 also acts as a downstream element of dopamine signaling by phosphorylating the striatum-specific DARPP-32 protein which then becomes an inhibitor of PKA.

The involvement of CDKs in many physiological functions and diseases has led to the identification of over 70 potent pharmacological inhibitors. Over 30 of these inhibitors have been co-crystallized with CDK2, CDK5 or CDK6. Pharmacological inhibitors of CDKs are currently being evaluated for therapeutic use against cancer, alopecia, neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke), cardiovascular disorders (restenosis), glomerulonephritis, viral infections (HCMV/HIV/HSV) and parasitic protozoa (*Plasmodium*).

CDKs

FAMILY MEMBERS	CDK1	CDK2 (C8866)	CDK3
OTHER NAMES	Cdc2, cyclin-dependent kinase 1	Cyclin-dependent kinase 2	Cyclin-dependent kinase 3
MOLECULAR WEIGHT/ STRUCTURAL DATA	34 kDa 297 aa	33 kDa 298 aa	35 kDa 305 aa
ISOFORMS	Not known	Not known	Not known
SPECIES	Present in all species	Present in all species	Present in all species
DOMAIN ORGANIZATION	Kinase scaffold	Kinase scaffold	Kinase scaffold
PHOSPHORYLATION SITES	Thr ¹⁴ , Tyr ¹⁵ , Thr ¹⁶¹	Thr ¹⁴ , Tyr ¹⁵ , Thr ¹⁶⁰	Not known
TISSUE DISTRIBUTION	Dividing cells	Dividing cells	Not known
SUBCELLULAR LOCALIZATION	Cytoplasmic, nuclear	Cytoplasmic, nuclear	Not known
BINDING PARTNERS/ ASSOCIATED PROTEINS	p9CKS, RanBPM, CK2 cyclin F	p9CKS	Not known
UPSTREAM ACTIVATORS	CDC25, CDK7	CDC25, CDK7	Not known
DOWNSTREAM ACTIVATION	Histone H1 (H5505), cyclin B lamins, Cdc25C, vimentin (V4383), APC, nucleolin, Plk1, separase	pRb, nucleophosmin, Cdc6, NPAT, Smad3, p27Kip1	Not known
ACTIVATORS	Cyclin A1, A2, cyclin B1-B3, Ringo	Cyclin A1, A2, cyclin E1, E2, E3	Ik3-1 cyclin C
INHIBITORS	Olomoucine (O0886), roscovitine (R7772), purvalanol A (P4484), kenpauillone (K3888), indirubins (I0404), aloisines, flavopiridol, staurosporine (S4400)	p21cip1/WAF, p27kip1, p57kip2, olomoucine (O0886), roscovitine (R7772), purvalanol A (P4484), kenpauillone (K3888), alsterpauillone (A4847), indirubins, aloisines, flavopiridol, staurosporine (S4400)	Roscovitine (R7772)
SELECTIVE ACTIVATORS	Not known	Not known	Not known
PHYSIOLOGICAL FUNCTION	Cell cycle (G2/M)	Cell cycle, (G1/S, S, G2) apoptosis	Cell cycle (G ₀ /G ₁)
DISEASE RELEVANCE	Cancer, Alzheimer's disease	Cancer, glomerulonephritis viral infections, (herpes, cytomegalovirus)	Not known

FOOTNOTES

CDKs

FAMILY MEMBERS	CDK4	CDK5 (C0690 (b), C8739 (h))	CDK6
OTHER NAMES	PSK-J3, cyclin-dependent kinase 4	Cyclin-dependent kinase 5	Tau PK II, cyclin-dependent kinase 6
MOLECULAR WEIGHT/ STRUCTURAL DATA	33 kDa 303 aa	33 kDa 292 aa	36 kDa 326 aa
ISOFORMS	Not known	Not known	Not known
SPECIES	Present in all species	Present in all species	Present in all species
DOMAIN ORGANIZATION	Kinase scaffold	Kinase scaffold	Kinase scaffold
PHOSPHORYLATION SITES	Not known	Not known	Not known
TISSUE DISTRIBUTION	Dividing cells	Mostly, but not only, neuronal cells	Dividing cells
SUBCELLULAR LOCALIZATION	Not known	Membrane, cytoplasmic	Not known
BINDING PARTNERS/ ASSOCIATED PROTEINS	Rac	Not known	v-Cyclin
UPSTREAM ACTIVATORS	Not known	Not known	Not known
DOWNSTREAM ACTIVATION	pRb, Smad3	Tau (T7675 (b), T9392 (h)), MAP-2B (M4914), DARPP-32, Pak1, Huntingtin, Cables	pRb
ACTIVATORS	Cyclin D1-D3	p35/p25 (P1371), p39, cyclin D1	Cyclin D1-D3
INHIBITORS	p15INK4A, p18INK4C, p19INK4D, flavopiridol, fascaplysin	Olomoucine (O0886), roscovitine (R7772), purvalanol A (P4484), kenpauillone (K3888), indirubins (I0404), aloisines, flavopiridol, staurosporine (S4400)	p15INK4A, p18INK4C, p19INK4D
SELECTIVE ACTIVATORS	Not known	Not known	Not known
PHYSIOLOGICAL FUNCTION	Cell cycle (G1 and G2/M)	Neurite outgrowth, Rac signaling, apoptosis, exocytosis	Cell cycle (G1)
DISEASE RELEVANCE	Cancer	Neurodegeneration, Alzheimer's disease, Parkinson's disease, stroke, Amyotrophic lateral sclerosis (ALS), Nieman-Pick's disease	Cancer

FOOTNOTES

CDKs

FAMILY MEMBERS	CDK7	CDK8	CDK9
OTHER NAMES	MO15, CAK, cyclin-dependent kinase 7	Cyclin-dependent kinase 8	Cyclin-dependent kinase 9
MOLECULAR WEIGHT/ STRUCTURAL DATA	39 kDa 346 aa	53.3 kDa 464 aa	42.8 kDa 372 aa
ISOFORMS	Not known	Not known	Not known
SPECIES	Present in all species	Present in all species	Present in all species
DOMAIN ORGANIZATION	Kinase scaffold	Kinase scaffold	Kinase scaffold
PHOSPHORYLATION SITES	Not known	Not known	Not known
TISSUE DISTRIBUTION	All	All?	All?
SUBCELLULAR LOCALIZATION	Not known	Not known	Not known
BINDING PARTNERS/ ASSOCIATED PROTEINS	MAT 1	Not known	Not known
UPSTREAM ACTIVATORS	Not known	Not known	Not known
DOWNSTREAM ACTIVATION	CTD RNA pol II	CTD RNA pol II	CTD RNA pol II
ACTIVATORS	Cyclin H	Cyclin C	Cyclin K, cyclin T1
INHIBITORS	Roscovitine (R7772)	Not known	Roscovitine (R7772), flavopiridol
SELECTIVE ACTIVATORS	Not known	Not known	Not known
PHYSIOLOGICAL FUNCTION	Transcription, cell cycle	Transcription	Transcription
DISEASE RELEVANCE	Cancer	Not known	HIV

FOOTNOTES

CDKs

FAMILY MEMBERS	CDK10	CDK11
OTHER NAMES	Cyclin-dependent kinase 10	cdc2L1, cdc2L2, cyclin-dependent kinase 11
MOLECULAR WEIGHT/ STRUCTURAL DATA	41 kDa 360 aa	92.7 kDa 777/795 aa
ISOFORMS	Not known	Not known
SPECIES	Present in all species?	Present in all species?
DOMAIN ORGANIZATION	Kinase scaffold	Kinase scaffold
PHOSPHORYLATION SITES	Not known	Not known
TISSUE DISTRIBUTION	All tissues?	All tissues?
SUBCELLULAR LOCALIZATION	Not known	Not known
BINDING PARTNERS/ ASSOCIATED PROTEINS	Ets2	RNA polymerase II CK2, RanBPM
UPSTREAM ACTIVATORS	Not known	Not known
DOWNSTREAM ACTIVATION	Not known	Not known
ACTIVATORS	Not known	Cyclin L2/Ania-6
INHIBITORS	Not known	Not known
SELECTIVE ACTIVATORS	Not found	Not found
PHYSIOLOGICAL FUNCTION	Transcription, cell cycle ?	Splicing, apoptosis, cell cycle (G2/M), neuronal functions
DISEASE RELEVANCE	Not known	Cancer

FOOTNOTES