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Encyclopedic Reference of Cancer

With 261 Figures and 64 Tables

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CT Scan

Definition

A computerized tomography (CT) scan is a computerized-assisted evolution of the simple X-Ray exam that allows three-dimensional reconstruction of the studied organ; can be performed using contrast materials.

CTLA1

Synonyms

- → CSP-B
- GZMB
- → granzyme B
- granzyme 2
- CGL-1
- CSP-B
- CCPI

Definition

Cytotoxic T-lymphocyte-associated serine esterase 1.

CTLs

Definition

→ Cytotoxic T lymphocytes.

Cyclin B1

Definition

Cyclin B1, also known as Ccnb1 and Ccnb is a protein of 433 amino acids and 48 kD. The human CCNB1 or CCNB gene locus maps to 5q12 and the mouse ccnb1 gene locus to chromosome 13 (56.00 cM). Cyclin B1 is essential for the control of the cell cycle at the G2/M (mitosis) transition. It interacts with the Cdc2 protein kinase to form MPF (mitosis promoting activator). G2/M cyclins accumulate steadily during G2 and are abruptly destroyed at mitosis. Increased expression is often found in cancer cell lines and tumors.

Cyclin D

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Definition

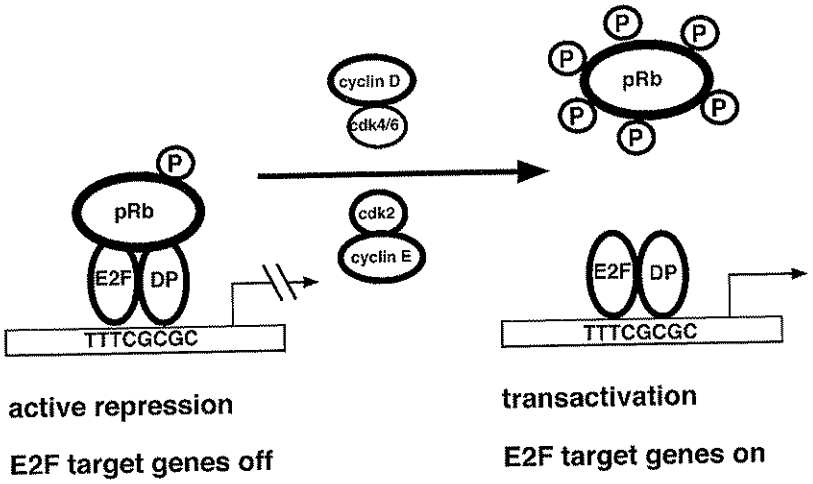
D type cyclins belong to a family of related proteins that bind to and activate several protein kinases named cyclin-dependent kinases (CDKs), which are involved in regulation of the cell division cycle.

Characteristics

D-type cyclins are encoded by three closely related genes (cyclins D1, D2 and D3) that are expressed in a tissue-specific fashion. Biochemically, D type cyclins act as regulatory subunits of a group of related protein kinases (CDKs), primarily the CDKs 4 and 6. Cyclin D/CDK4/6 complexes, together with cyclin E/CDK2, cause phosphorylation of the family of retinoblastoma proteins (→ pRb, p107 and p130) in the G1 phase of the cell cycle, resulting in abrogation of their growth inhibitory activity. Phosphorylation of the retinoblastoma proteins leads to release of → E2F transcription factors from the retinoblastoma proteins and to progression to the S phase of the cell cycle (Fig. 1).

Regulation of D cyclins

D type cyclins are major downstream targets of extracellular signaling pathways, which act to transduce mitogenic signals to the cell cycle machinery. Transcriptional induction of D type cyclins occurs in response to a wide variety of mitogenic stimuli, including the → Ras signaling cascade and the → APC-β-catenin-Tcf/



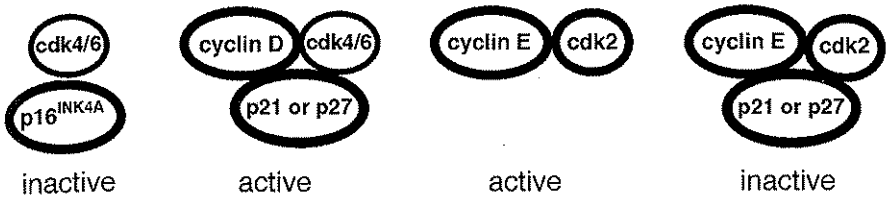
Cyclin D. Fig. 1 – Regulation of E2F activity through pRb phosphorylation. In the G1 phase of the cell cycle the retinoblastoma protein pRb is hypophosphorylated, allowing it to bind E2F transcription factors. E2F/pRb complexes are able to bind DNA but are inactive in transcription activation. Phosphorylation of pRb by cyclin D/CDK4 and cyclin E/CDK2 complexes causes the release of E2F from pRb. Free E2F is then able to activate transcription of E2F target genes (genes with TTTCGCGC-like E2F sites in their promoters), allowing cells to enter the DNA synthesis phase (S phase) of the cell cycle.

Lef pathway. In addition, cyclin D1 protein turnover and subcellular localization is highly regulated during the cell cycle. Phosphorylation of cyclin D1 by GSK-3β in resting cells renders the protein a target for rapid destruction by the proteasome. In contrast, mitogenic stimulation of cells leads to inhibition of GSK-3β and stabilization of cyclin D1 protein. In response to DNA damage, cells initiate an immediate G1 arrest, which is caused by rapid proteolysis of cyclin D1. Together with activation of the p53 tumor suppressor protein, cyclin D1 destruction causes a fast withdrawal from the cell cycle to allow repair of the damaged DNA before DNA synthesis resumes.

Binding of D type cyclins to their CDK partner is antagonized by the → INK4 family of CDK inhibitors (→ CKI). INK4 proteins bind to CDK4 and 6 and thereby prevent association of D type cyclins to these CDKs (Fig. 2). The most prominent member of this family is $p16^{INK4A}$. Mutations in $p16^{INK4A}$ (also known as → CDKN2A) are found in a variety of spontaneous tumors, and heterozygosity for $p16^{INK4A}$ in the germ line predisposes to melanoma. A second family of CKIs consists of three related proteins that bind to cyclin/CDK complexes. Members of this family include $p21^{cip1}$ and $p27^{kip1}$. This class of CKIs has quite divergent effects on the different cyclin/CDK complexes. Whereas cyclin E/CDK2 is inhibited by both $p21^{cip1}$ and $p27^{kip1}$, cyclin D/CDK4/6 complexes are active when complexed with this class of inhibitors (Fig. 2). In fact, formation of active cyclin D/CDK4/6 complexes requires the presence of $p21^{cip1}$ or $p27^{kip1}$ to act as 'assembly factors' of cyclin D/CDK complexes. These opposing effects of $p21^{cip1}$ and $p27^{kip1}$ on cyclin E/CDK2 and cyclin D/CDK4 complexes endows cyclin D/CDK4 complexes with an important second, non-catalytic function during the G1 phase of the cell cycle. Synthesis of cyclin D1 by mitogenic stimulation leads to absorption of $p21^{cip1}$ or $p27^{kip1}$ into active ternary complexes, thereby facilitating activation of cyclin E/CDK2 by removal of inhibitors.

CDK-independent activities of D type cyclins

Apart from their role in activation of CDKs, D type cyclins can have several profound effects on cellular physiology independent of their CDK partners. In → breast cancer, cyclin D1 can bind directly to the estrogen receptor, thereby causing hormone-independent activation of the estrogen receptor. This activity of



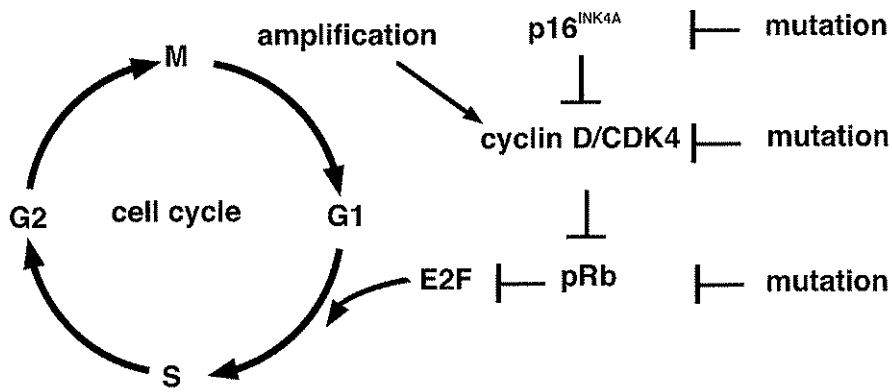
Cyclin D. Fig. 2 – Effect of CDK inhibitors on cyclin/CDK complexes. CDKs 4 and 6 are activated by binding of D type cyclins. Association of cyclin D to CDKs 4 and 6 is prevented by $p16^{INK4A}$ that binds with high affinity to these CDKs. Thereby, binding of cyclin D to these CDKs is prevented. The CDK inhibitors $p21^{cip1}$ and $p27^{kip1}$ bind both to cyclin E/CDK2 and to cyclin D/CDK4 complexes, although with different consequences. Even though these inhibitors antagonize cyclin E/CDK2 activity, they are required for proper assemblage and activity of cyclin D/CDK4/6 complexes.

cyclin D1 may contribute to resistance to antihormonal therapy that is often seen in the clinic. In addition, D type cyclins can modulate the activity of Myb transcription factors. Of particular interest in this respect is the Myb-like transcription factor DMP1, which has anti-proliferative activity. Expression of cyclin D inhibits this effect on cell proliferation of DMP1 through direct binding to DMP1, which prevents DNA binding by DMP1.

Clinical Relevance

Because of their critical role in linking cytoplasmic signals to nuclear responses it is perhaps not surprising that D type cyclins are frequently deregulated in several types of cancer. *Cyclin D1* → amplification or overexpression is found in a number of human malignancies, the most prominent being breast cancer, in which up to 50% of all cases have elevated levels of cyclin D1 protein. Chromosomal translocations involving *cyclin D1* are found in parathyroid adenoma and in mantle cell lymphoma.

Not only is *cyclin D1* itself often directly mutated in human cancer, its upstream regulators such as $p16^{INK4A}$ and its downstream target pRb are frequent targets in human carcinogenesis as well. It is generally believed that this $p16^{INK4A}$-cyclin D1-pRb pathway is deregulated in virtually all human cancers (Fig. 3).



Cyclin D. Fig. 3 – The p16-cyclin D-pRb pathway: a frequent target in human cancer. E2F transcription factors contribute to G1-S phase progression through the activation of specific target genes. E2F activity is negatively regulated by its binding to the retinoblastoma tumor suppressor gene product, pRb. The ability of pRb to bind E2F is regulated by cyclin D/CDK complexes. The activity of cyclin D/CDK complexes in turn is negatively regulated by $p16^{INK4A}$ that is encoded by the CDKN2A tumor suppressor gene.

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Cyclin D2

Definition

Cyclin D2 is a member of the growth factor inducible family of D-type cyclins, which in concert with cyclin dependent kinases (CDK) 4 and 6 promote G_0 exit and early G_1 progression in the cell cycle.

Cyclin-dependent Kinase

Definition

Cyclin-dependent kinases (CDK) are complexes that consist of two different proteins: one molecule of cyclin (which is the regulatory subunit) plus one molecule of the actual cyclin-dependent kinase (cdk, which is the catalytic subunit). CDKs are the 'engine of the cell cycle' and they direct the events required for cellular proliferation. Without CDK activity, cell growth does not take place.

- cyclinD/cdk4: CDK complex consisting of one molecule cyclinD plus one molecule cdk4
- cyclinD/cdk6: CDK complex consisting of one molecule cyclinD plus one molecule cdk6
- cyclinE/cdk2: CDK complex consisting of one molecule cyclinE plus one molecule cdk2
- cyclinA/cdk2: CDK complex consisting of one molecule cyclinA plus one molecule cdk2

Cyclin-dependent Kinase (CDK) Inhibitor

Definition

There are two groups of cyclin-dependent kinase (CDK) inhibitors (CKIs); the → Cip/Kip family and the cyclin → INK4 family.

Cyclin-dependent Kinase Inhibitor 1B

Definition

Cyclin-dependent kinase inhibitor 1B (CDKNB1B) is also known as p27 and Kip1; Cip/Kip family [→ CIP/KIP family].

Cyclobutane Pyrimidine Dimers

Definition

Cyclobutane pyrimidine dimers (CPD) are UV-induced DNA lesions between two adjacent pyrimidines (C or T).