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Gene Section

Review

CDK2 (cyclin dependent kinase 2)

Anette Gjörloff Wingren, Barnabas Nyesiga

Biomedical science, Health and society, Malmö University, Malmö, Sweden
nyesigabarnabas@gmail.com; anette.gjorloff-wingren@mah.se

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Abstract

Review on CDK2, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
CDK2; Cell cycle; Mitosis; Apoptosis; Glioblastoma; Cholangiocarcinoma; Breast cancer; Prostate cancer; Oral squamous cell carcinoma; Ovarian cancer; Pemphigus vulgaris

Other names
Cyclin Dependent Kinase 2, Cell Division Protein Kinase 2, EC 2.7.11.22, CDKN2, CDC2-Related Protein Kinase, Cyclin-Dependent Kinase 2, P33(CDK2), EC 2.7.11

HGNC (Hugo)
CDK2

Location
12q13.2

Identity

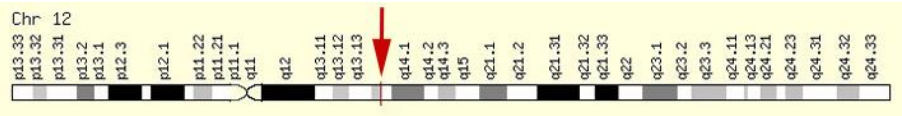

Figure 1. Mapping of CDK2 gene on chromosome 12q13 (from GeneCards CDK2 gene)

DNA/RNA

Description

One of the two different human cDNAs that can complement cdc28 mutations of budding yeast Saccharomyces cerevisiae cloned by Ninomiya et al. corresponds to the CDK2 gene (Ninomiya 1991). Elledge et al. identified CDK2 as a second functional p34 homolog with the help of a human cDNA expression library to search for suppressors of cdc28 mutations in S. cerevisiae (Elledge 1991). CDK2 gene is mapped to 12q13 (Demetrick 1994) (Fig. 1). The cloning of approximately 2.4-kilobase pair genomic DNA fragment from the upstream region of the human CDK2 gene has been described (Shiffman 1996). The CDK2 gene fragment was found to contain 5 transcription initiation sites within a 72-bp stretch. A 200-bp subfragment that confers 70% of maximal basal promoter activity was shown to contain 2 synergistically acting Sp1 sites (Shiffman 1996). The intron-exon boundaries of 7 exons in this gene were also identified (Shiffman 1996). There are other reports of CDK2 gene expressed as a 2.1 kb transcript encoding a polypeptide of 298 amino acids and encodes the human homolog of the Xenopus Eg1 gene, sharing 89% amino acid identity (Elledge 1991).

Transcription

The presence of CDK2 mRNA was observed late in G1 or in early S phase, slightly before CDC2 mRNA, under growth stimulation in normal human fibroblast cells (Ninomiya 1991). CDK2 mRNA has also been shown to be induced by serum in several cultured cell types (Shiffman 1996).

Protein

Description

The CDK2 protein was found to be highly homologous to p34CDC2 kinase (65% identical) and more significantly homologous to Xenopus Eg1 kinase (89% identical), suggesting that CDK2 is the human homolog of Eg1 (Ninomiya 1991). CDK2 protein has a biological activity closely related to the CDC28 and CDK1 (Cdc2, p34CDC2) kinases (Ninomiya 1991) and the protein retains nearly all of the amino acids highly conserved among previously identified p34 homologs from other species (Elledge 1991). CDK2 is a mammalian Ser/Thr kinase that plays a critical role in controlling the progression from G1 to S phase of the cell cycle (Morgan 1997) and is functionally homologous to the well-studied cdc28a S. cerevisae protein (Zhao 2011). Monomeric CDK2 lacks regulatory activity requiring to be aroused by its positive regulators, cyclins E and A, or catalytic segment phosphorylation (Yan 2015). CDK2 activation is a two-step process; step one requires its association with the regulatory subunit cyclins A or E and step two involves phosphorylation of the residue Thr160 (Marcos 2011, Morris 2002, Pavletich 1999).

The crystal structure of the human CDK2 apoenzyme and its Mg2+ATP complex have been determined to 2.4 Å resolution (De Bondt 1993) while the crystal structure of CDK2-ATP complex has been determined at 2.3 Å resolution (Jeffrey 1995). Monomeric CDK2 is made of 298 amino acids (PDB code: 1HCL, residues 1-298), and folds into a typical bilobal structure, composed of a smaller N-terminal lobe (residues 1-85) that consists of antiparallel five-strand β-sheet and a major C-helix, together with a larger C-terminal lobe primarily composed of α-helix (De Bondt 1993). The two terminal domains are linked by a single peptide strand (residues 81-83) which acts as a hinge linker making sure that the two lobes can rotate with respect to each other without disruption of the secondary structure of this kinase (Cox 1994). Three binding sites have been reported in the monomeric CDK2 structure; the adenosine triphosphate (ATP) binding site (Site I) and two non-competitive binding sites (Site II and III). An allosteric binding site (Site IV) is generated as a result of structural changes that yield a variation of the ATP binding site when the kinase is subjected to the cyclin binding process (Yan 2015). Competitive binding site (Site I) is the most well-known ATP binding site, situated deep at the junction of the N and C domains. It includes the pivotal catalytic residues with high sensitivity and linker region (residues 81-83), and consists of 136 consecutive amino acids (10-145) on the CDK2 (Knockaert 2002). There is no association between non-competitive binding sites (site II and III) and catalytic subunits (Li 2013). Site III is also known to accommodate short peptides that partially dissociate the CDK2/cyclin E complex, thus obstructing the enzymatic activity of CDK2 (Chen 2009). The allosteric binding site (site IV) also known as ANS fluorophore 8-anilino-1-naphthalene sulfonate) binding pocket is located in a region that is adjacent to the C-helix, away from the ATP site, approximately halfway of the ATP site and the C-helix (Yan 2015).

Localisation

The nuclear translocation of CDK2/cyclin E and cyclin E binding are needed for CDK2 enzymatic activation and substrate targeting because the CDK2 activating enzyme (CAK) and many of the CDK2 targets reside in the nucleus (Blanchard 2000, Dietrich 1997, Keenan 2001). Intracellular trafficking of CDK2 is unclear though some studies suggest that cyclins may play a role in the translocation of the cyclin/CDK complex via the classical importin α/β pathway (Moore 1999, Moore 2002). It is suggested that importin α binds to the nuclear localization signal on cyclins whereas importin β binds to nuclear transport machinery proteins as well as to cyclin-bound importin α. Translocation of the cyclin/CDK/importin α/β complex into the nucleus then occurs via an energy-dependent process (Flores 2010). Other studies have demonstrated consistent concentration of CDK2/cyclin E in the nucleus in both Drosophila embryos and cultured human cells (Knoblich 1994, Ohtsubo 1995), whereas CDK1 (Cdc2)/ CCNB1 (cyclin B1) is retained in the cytoplasm in interphase, entering the nucleus at the earliest stages of mitosis (Lehner and O'Farrell 1990, Pines and Hunter, 1994). Other studies using egg extracts have shown how accumulation of CDK2/cyclin E in the nucleus is needed both for initiating DNA replication (Chevalier 1996) and preventing re-replication (Hua 1997, Walter 1998). There are indications that CDK2 nuclear translocation is associated with the formation of molecular complexes containing active MAP Kinase and is dependent on MAP Kinase activation (Blanchard 2000).

Function

CDK2 activity has been indicated to be regulated by protein CDNK1B (p27KIP1) which inhibits CDK2 kinase activity in G0 and early G1 phase and leads to cell-cycle arrest (Polyak 1994). Once combined with its positive regulatory subunits, CDK2 fosters the transition of the well-established G1/S phase

boundary and drives the cell cycle through S interval (Shapiro 2006, Sherr 1994, Pines 1991). CDK2/cyclin A is a necessity for orderly S-phase progression (Sherr 1994), while phosphorylation of retinoblastoma protein (RB1) to facilitate the G1/S transition is mediated by CDK2/cyclin E complex (Pines 1991). CDK2/cyclin E phosphorylates Rb leading to the release and activation of E2F transcription factors required to promote transcription of genes that encode proteins required for G1 to S phase progression (Dyson 1998, Nevins 1998). CDK2 associates with both inactive and activated MAP Kinase and its activation is linked to formation of CDK2/ MAP Kinase complexes (Blanchard 2000). CDK2 is one of the most essential regulators for the transition and progression in a cell-division cycle and plays a crucial role in regulating multiple events of cell division cycle including centrosome duplication, DNA synthesis, G1-S transition, and modulation of G2 progression (Chohan 2015, De Boer 2008, Fiset 2011, Omar 2010). CDK2 is a requirement for robust DNA damage checkpoint signalling and loss of CDK2 was observed to cause a marked deficiency in the G2/M arrest which is a basic response to DNA damage in cells that were also nullizygous for P53 (Chung and Bunz, 2010). CDK2 plays a critical role in facilitating robust DNA damage checkpoint control by the ATR- CHEK1- CDC25A pathway. CDK2 seems to promote the formation of active ATR complexes by ATRIP phosphorylation and by CDC6 stabilization (Chung and Bunz, 2010). There is a possibility of CDK2 also controlling checkpoint signaling via additional mechanisms such as the recently described CDK2 interacting protein (CINP) which facilitates robust ATR signalling (Lovejoy 2009). In addition, loss of CDK2 was demonstrated to alter the regulation of several proteins that are known to regulate S-phase progression, but also control mitotic entry, including CDC25A, CHK1, CDC6 and ATRIP (Donzelli and Draetta, 2003, Borlado and Mendez 2008, Cimprich and Cortez, 2008). Expression of CCNE1-CDK2 at physiologic levels of ATP results in phosphorylation of CDKN1B at thr187, leading to elimination of CDKN1B from the cell and progression of the cell cycle from G1 to S phase (Sheaff 1997). At low ATP levels, the inhibitory functions of CDKN1B are enhanced, thereby arresting cell proliferation (Sheaff 1997). Apoptosis of human endothelial cells after growth factor deprivation is associated with rapid and dramatic upregulation of cyclin A-associated CDK2 activity (Levkau 1998). In apoptotic cells, the carboxyl-termini of the CDK inhibitors CDKN1A and CDKN1B are truncated by specific cleavage aided by CASP3 and/or a CASP3-like caspase. After cleavage, CDKN1A loses its nuclear localization sequence and exits the nucleus. Cleavage of CDKN1A and CDKN1B resulted in a substantial reduction in their association with nuclear cyclin-CDK2 complexes, leading to a dramatic induction of CDK2 activity. Dominant-negative CDK2, as well as a mutant CDKN1A resistant to caspase cleavage, partially suppressed apoptosis. CDK2 activation, through caspase-mediated cleavage of CDK inhibitors, may be instrumental in the execution of apoptosis following caspase activation (Levkau 1998). Forkhead box O (FOXO) are key regulators of cell survival and CDK2 is known to specifically phosphorylate FOXO1 at ser249 in vitro and in vivo resulting into cytoplasmic localization and inhibition of FOXO1 (Huang 2006). Functional interaction between CDK2 and FOXO1 provides a mechanism that regulates apoptotic cell death after DNA strand breakage (Huang 2006). Proto-oncogenes such as MYC and RAS promote normal cell growth, fuel tumor development when deregulated and if over-activated can trigger intrinsic tumor suppressor mechanisms leading to apoptosis and senescence (Hydbring and Larsson, 2010). Ras is known to suppress Myc-induced apoptosis while Myc was recently discovered to repress Ras-induced senescence. The ability of Myc to suppress senescence is dependent on its phosphorylation at Ser 62 by CDK2. Using CDK2 as a cofactor, Myc is able to directly control major genes involved in senescence. Selective pharmacological inhibition of CDK2 was observed to force Myc/Ras expressing cells into cellular senescence, an indication that CDK2 is a potential therapeutic target for treatment of tumors driven by Myc or Ras (Hydbring and Larsson, 2010).

Implicated in

Among all the CDKs, CDK2 is known to be an important kinase in tumorigenesis and proliferation in many cancer types including lung cancer, liver cancer, colon cancer and breast cancer (Opyrchal 2014, Shi 2015, Lim 2014). There is strong evidence showing that CDK2 is functionally linked with hyper proliferation in multiple cancer cells and is a potential therapeutic target for cancer therapy (Chohan 2015).

Prostate cancer

CDK2 has been found to play a pivotal role in cell proliferation of prostate cancer (Omar 2010).

Breast cancer

CDK2 is also crucial for malignant transformation of breast epithelial cells. Suppression of CDK2 activity can effectively inhibit the proliferation of human breast cancer cells (Ali 2009). Active CDK2 in the form of a cyclin D1/CDK2 fusion protein induces tumors that contain an invasive component that exhibits multiple features in common with human basal-like tumors and tumor-derived cell lines (Corsino 2008). Cyclin D1/CDK2 complexes were detected in human breast cancer cell lines (Sweeney

1998), and the levels of these complexes correlated well with the degree of cyclin D1 overexpression.

Ovarian cancer

The role of cyclin E and its associated kinase CDK2 in ovarian cancer has been investigated by screening primary, metastatic, recurrent and benign ovarian tumors. Using gene amplification, Cyclin E was shown to be amplified in 21% and CDK2 in 6.4% of the cases analyzed. Additionally, Cyclin E RNA was overexpressed in 29.5% and CDK2 in 6.5% of ovarian tumors tested. Cyclin E and CDK2 were overexpressed mostly in primary ovarian cancers (32% and 10%, respectively) compared to metastatic and recurrent diseases (Marone 1998).

Glioblastoma

Wang et al. identified CDK2 expression to be significantly elevated in glioma tumor especially in Glioblastoma Multiforme (GBM) and was functionally required for GBM cell proliferation and tumorigenesis (Wang 2016). CDK2 expression was identified to be significantly enriched in GBM tumors and functionally required for tumor proliferation both in vitro and in vivo. Additionally, high CDK2 expression was associated to poor prognosis in GBM patients. Radio resistance is a major factor of poor clinical prognosis and tumor recurrence in GBM patients. CDK2 was found to be one of the most up-regulated kinase encoding genes in GBM after radio treatment. CDK2-dependent radio resistance is indispensable for GBM tumorigenesis and recurrence after therapeutic treatment (Wang 2016).

Cholangiocarcinoma

Elevated levels of CDK2 expression have been observed in human cholangiocarcinoma tissues where apoptosis-related protein-1 dependent suppression of CDK2 induced cell cycle arrest and restrained tumor growth (Zheng 2016).

Oral squamous cell carcinoma (SCC)

CDK2 overexpression in oral squamous cell carcinoma (SCC) may elevate pRB phosphorylation and permit more rapid entry of the cancer cells into S phase. In a clinicopathological survey of oral SCC, incidence of CDK2 expression was high in the poorly differentiated lesions, and was associated with the mode of tumor invasion, lymph node involvement and survival, an indication that change in CDK2 expression is associated with oral cancer progression (Mihara 2001). CDK2 expression was significantly correlated with lymph node involvement, tumor differentiation, mode of tumor invasion, and shorter survival period. Increased expression of CDK2 is both a critical factor in oral cancer progression and a negative predictive marker of the patients' prognosis (Mihara 2001).

Lung cancer

CDK2 has been found to play a pivotal role in cell proliferation of non-small cell lung cancer (Kawana 1998).

Pemphigus vulgaris (PV)

Pemphigus vulgaris (PV) is an autoimmune blistering disease that affects skin and mucous membranes. CDK2 appeared to have a role in the development of PV lesions (Lanza 2008). Exposing of synchronized human keratinocytes to PV serum increased the proportion of cells in S phase, caused cell rounding and cell-cell detachment, elevated CDK2 expression in a dose-dependent manner, and altered the expression of over 500 genes especially those that are involved in cell communication and cell- cell junction formation. Small interfering RNA against CDK2 reversed PV serum-induced CDK2 overexpression and reduced cell-cell detachment. By utilizing a neonatal mouse model in which PV lesions were induced by a single intraperitoneal injection of whole serum obtained from a PV patient, it was shown that pre-treatment of mice with a pharmacologic CDK2 inhibitor prevented skin lesion development and PV serum-induced changes in gene expression. Histochemical analysis of PV patient skin revealed CDK2 overexpression around the site of the acantholytic cleft and along suprabasal layers in perilesional sites. It was finally concluded that activation of CDK2-mediated signaling is an essential event in the development of PV lesions (Lanza 2008).

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