Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Gene Section
Review

CDC25A (Cell division cycle 25A)

Christine Dozier, Stéphane Manenti

Cancer Research Center of Toulouse (CRCT), UMR1037 INSERM, ERL5294 CNRS, Université Toulouse III Paul Sabatier, Toulouse, France. christine.dozier@inserm.fr

Published in Atlas Database: August 2015
Online updated version : http://AtlasGeneticsOncology.org/Genes/CDC25AID40004ch3p21.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/62938/08-2015-CDC25AID40004ch3p21.pdf
DOI: 10.4267/2042/62938

This article is an update of :
Ray D, Kiyokawa H. CDC25A (Cell division cycle 25A). Atlas Genet Cytogenet Oncol Haematol 2008;12(6)

Abstract

CDC25A phosphatase is essential for cell cycle progression by activating the cyclin-associated kinases CDK4/6, CDK2 and CDK1. Its invalidation in mice is embryonic lethal. Its expression is tigthtly regulated at many levels and its overexpression is observed in various cancers, often associated with high grade tumors and poor prognosis.

Keywords
CDC25, cell cycle, CDK/cyclin, apoptosis

Identity

HGNC (Hugo): CDC25A

Location: 3p21.31

Other names: CDC25A2

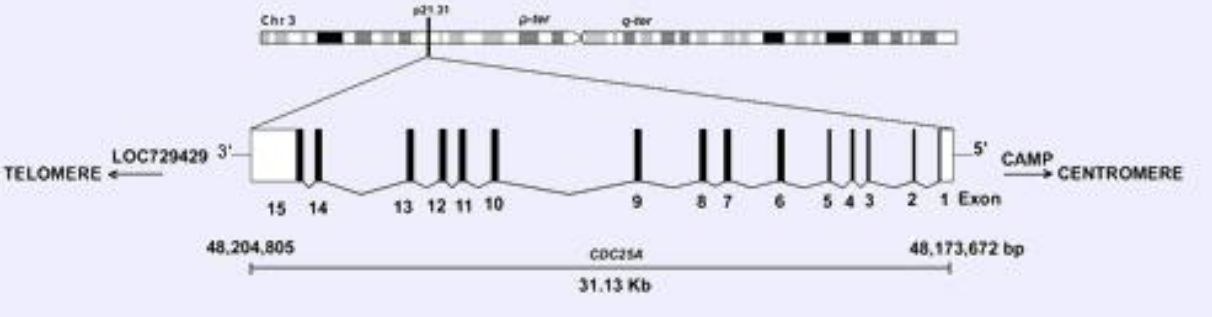
Local order

The gene is located telomeric to CAMP (cathelicidin antimicrobial peptide) and centromeric to LOC729349 (a pseudogene similar to 60S ribosomal protein L17 (L23)). The gene starts at 48,173,672 bp from pter and ends at 48,204,805 bp from pter with a total size of 31,133 bases.

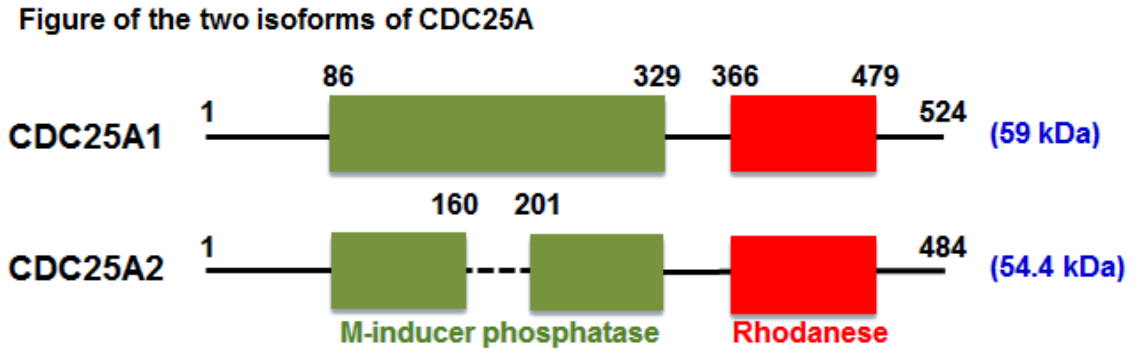
DNA/RNA

Description

CDC25A is about 31.13 Kb located on the short (p) arm of chromosome 3, in the centromere-to-telomere orientation. The gene has 15 exons and the start codon is located at the end of exon 1 and stop codon in the beginning of exon 15.



Genomic organization of human CDC25A gene on chromosome 3 p-ter.



Domains of different isoforms of CDC25A (A1 and A2). The splice variant A2 lacks an in-frame exon (exon 6) encoding 40 amino acids (amino acid 160-201), however, has the same N- and C-termini compared to isoform A1. The approx. molecular weight of each isoform is mentioned in parenthesis.

Transcription

The CDC25A transcript is 3704 bp in length. So far two major transcript variant have been reported, CDC25A1 and A2.
The transcript variant CDC25A2, has a deletion of 120 nucleotides (exon 6) resulting in a protein having truncation of 40 amino acids (between amino acid 160-201).
However, both the N-terminal and C-terminal end of the protein is the same in both splice variant.

Protein

Description

The full length CDC25A protein consists of 524 amino acids with an estimated molecular weight of 59 kDa.
The other reported isoform CDC25A2, consists of 484 amino acids with a molecular weight of 54.4 kDa (Wegener et al., 2000).. Both the isoforms have the same N- and C-terminal end, thus expected to have similar catalytic activity.
The N-terminal regulatory domain contains several phosphorylation sites and shows low sequence homology between CDC25 family members, whereas C-terminal end has conserved Rhodanese homology domain containing the active site cysteine.
The catalytic site contain the CX5R motif (C= cysteine; X= any amino acid; R= arginine) common to all protein tyrosine phosphatases (Boutros et al., 2006).
Upon apoptosis induction, CDC25A is cleaved at D223 (D=Aspartic acid) by caspase to generate a catalytically active CDC25A C-terminal 37Kda protein (Mazars et al., 2009; Chou et al., 2010).

Expression

CDC25A is expressed early during embryonic stages and in adults it is expressed in a variety of normal cells and tissues.
CDC25A is a highly expressed gene in a variety of human cancers including breast, esophageal, gastric, lung, thyroid, head and neck cancers and also in high grade lymphomas.

Localisation

CDC25A initially believed to be a nuclear protein. But using fluorescence loss in photobleaching (FLIP) a more dynamic nuclear-cytosolic shuttling of CDC25A localization has been reported.
At the very N-terminus end between amino acid 38-59, the nuclear export sequence (NES) is located, whereas between amino acid 272-294, a bipartite nuclear localization signal (NLS) was proved to be important for its nuclear localization (Källström et al., 2005).
Depending of the cell line, CDC25A is nuclear or nuclear and cytoplasmic.

Function

- CDC25A is essential for early embryonic development as Cdc25A-null mice die in utero by embryonic day 7(Ray et al., 2007).
- It is a member of the M-phase inducer (MPI) phosphatase family protein, which not only regulates mitotic progression by activating mitotic CDKs in a dosage-dependent manner, it is also equally important in G1 and for G1 to S-phase transition.
- During G1, CDC25A dephosphorylates CDK4/CDK6 on tyrosine 17 and 24, respectively, allowing their association with D-type cyclins and thus their activation (Bertero et al., 2013). During G1 to S transition, it activates CDK2 by removing two inhibitory phosphates on residues threonine 14 and tyrosine 15. During G2/M transition CDC25A similarly regulates the activity of CDK1 (CDC2).
- It is an inhibitor of apoptosis by inhibiting apoptosis signal-regulating kinase 1 (ASK1). in a phosphatase-independent manner, by activating the AKT-survival pathway in the cytoplasm and also by stimulating NF-kB activity through NFKBIA (IκB-α) destabilization (review Fernandez-Vidal et al., 2008; review Shen and Huang, 2012; Hong et al., 2012). But overexpressed nuclear CDC25A also exhibits pro apoptotic activity by activating the pro-

apoptotic factor FKHLR1 (review Fernandez-Vidal et al., 2008; review Shen and Huang, 2012).
- CDC25A plays an important role in spermatogenesis as decreased transcript level of Cdc25A is correlated with spermatogenic failure and failed sperm retrieval in infertile men. (Cheng et al., 2009).
-CDC25A also plays a role in meiotic maturation of oocytes, its activity is required for the metaphase II arrest in mouse oocytes (Oh et al., 2013).
- CDC25A was shown to function as a androgen receptor corepressor in prostate cancer cells (Chiu et al., 2009).
Regulation
- CDC25A is transcriptionally regulated by E2F, a transcription factor implicated at the G1/S transition, c-myc, STAT3, the p53-pathway via the transcription factor ATF3, TCF/beta-catenin, FOXM1, NANOG in embryonic stem cell and PROX1 in neural precursor (review Fernandez-Vidal et al., 2008; review Shen and Huang, 2012).
- CDC25A is also regulated at the translational level by the translation initiation factors EIF2S1 (eIF2alpha), EIF3M, the RNA-binding proteins BOLL in spermatogenesis, and various miRNAs such as let7b, 15a, 21, 449a, 449b, 483-3p, 424/503 cluster and 141-3p. Some of these miRNAs being deregulated in cancers can contribute to the overexpression of CDC25A in cancers.
- CDC25A activity can be regulated by phosphorylation events (review Fernandez-Vidal et al., 2008; review Shen and Huang, 2012). The kinases PIM-1, RAF1, CDK2, RSK, ROCK1 (p160Rock) and the phosphatase CDC14B have been shown to regulate CDC25A activity. The kinase CHK1 has been shown to phosphorylate CDC25A on serine 178 and threonine 507 preventing its interaction with its CDK/cyclin substrates.
- CDC25A is an unstable protein in interphase, or under several different stress conditions (DNA damage induced by ionizing radiation, ultraviolet light, replicative stress) being degraded by the proteasome after ubiquitination by $SCF^{\beta TrCP}$ E3 ubiquitin ligase. This ubiquitination is dependent on several phosphorylation events in the N-terminal part of the protein carried out by many kinases such as CHK1 (on serine 76, 124, 178, 279 and 293), CHK2 (on serine 124, 178 and 293), p38MAPK (on serine 76), GSK3-β (on serine 76), Plk3 (on threonine 80), NEK11 (on serine 82 and 88) and CK1alpha and epsilon (on serine 82) (review Fernandez-Vidal et al., 2008; review Shen and Huang, 2012).
- CDC25A protein is stabilized during mitosis due to phosphorylation on serine 18 and 116 by CDK1/cyclinB occuring at the G2/M transition (Mailand et al., 2002). At the mitotic exit and in early G1, CDC25A is degraded by the proteasome after ubiquitination by the E3 ubiquitine ligase APC/C (cyclosome) (review Fernandez-Vidal et al., 2008; review Shen and Huang, 2012).
- CDC25A protein level is important for oncogene-induced transformation and mouse mammary tumor virus (MMTV)-neu/ras induced mammary tumorigenesis (Ray et al., 2007).
- During early cell cycle progression glycogen synthase kinase 3-beta (GSK-3β) can phosphorylate allowing its proteasomal degradation. Interestingly, the same report showed that overproduction of CDC25A in some human cancers is correlated to the inactivation of GSK-3β (Kang et al., 2008).
- Overexpression of CDC25A in some human sarcomas has also been shown to be the result of transcriptional upregulation involving the transcription factor TCF/β-catenin upregulated upon activation of the wnt canonical signaling (Vijayakumar et al.,2011). HOMOLOGY CDC25A gene is highly conserved among mammals (99% homology with Chimpanzee; 90% with dog; about 86% with rat and about 85% with mouse). In mammals, CDC25A has two orthologs, CDC25B and CDC25C. Among them, the N-terminal regulatory region show low sequence homology (20-25% identity), however, the C-terminal catalytic region is quite conserved with about 64% homology with CDC25B and about 58% homology to CDC25C.

Mutations

Gene mutation or amplification is not commonly reported for CDC25A. A naturally occurring point mutation (C to A) of mouse Cdc25A gene has been reported where Histidine 128 (CAC) has been converted to Glutamine (CAA). This change caused an increase in CDC25A phosphatase activity and thereby affected erythropoiesis in mice only under certain genetic background (Melkun et al., 2002). A human polymorphism variant in which Serine 88 is converted to Phenylalanine has been described. This variant fails to interact with ASK1 and therefore does not suppress ASK1-mediated apoptosis, which leads to early embryonic lethality in mice and predisposes to cancer in human (Bahassi et al. 2011)..

Implicated in

Note
- CDC25A is overexpressed in a variety of human cancers including breast, hepatocellular, ovarian, colorectal, gastric, lung, thyroid, esophageal, laryngeal, head and neck cancers, retinoblastoma, glioma, and also in non-Hodgkin lymphoma. often associated with high grade tumours and bad prognosis (Boutros et al., 2007).

- Upregulation of CDC25A is also observed downstream of the NPM1 / ALK oncogene in anaplastic large cell lymphoma and participates to their enhanced proliferation (Fernandez-Vidal et al., 2009).
- CDC25A is overexpressed in erythroleukemia cell lines expressing the JAK2V617F oncogene, present in the majority of patients with polycythemia vera and one-half of those with essential thrombocythemia and primary myelofibrosis. This upregulation occurs at the translational level through the transcription factor STAT5 and the translational initiation factor eIF2alpha (Gautier et al., 2012).
- An upregulation of CDC25A activity due to its phosphorylation by deregulated CDK5 has been observed in Alzheimer's disease (Chang et al., 2012).

Breast cancer

Note

- In about 47% of early (T1) stage breast cancer patients CDC25A is reported to be overexpressed.
- In some breast cancer cell lines it was reported that CDC25A overexpression is mainly due to increased protein stability as oppose to gene amplification or transcriptional upregulation. (Löffler et al., 2003). In a subset of human breast cancers overexpression of the ubiquitin hydrolase DUB3, which deubiquitinates CDC25A preventing its degradation, is shown to be responsible for overexpression of CDC25A (Pereg et al., 2010).
- In mice, overexpression of CDC25A alone in mammary gland using mouse mammary tumor virus (MMTV) promoter, is not sufficient to induce mammary tumorigenesis. However, such mammary specific overexpression of CDC25A does cooperate with HER2/neu-ras signaling to form more aggressive tumors with enhanced genomic instability. (Ray et al., 2007).
- In contrast, hemizygous loss of Cdc25A in mice protected them significantly from MMTV-neu/ras-induced mammary tumorigenesis, possibly by restricting precancerous cell proliferation and also by enhancing G2-checkpoint response. Thus the protein level of CDC25A is crucial for the initiation and/or progression of breast tumorigenesis in mice (Ray and Kiyokawa, 2007).

Prognosis

Overexpression of CDC25A is correlated with more aggressive breast cancer with poor prognosis.

Cytogenetics

CDC25A overexpression in MMTV-CDC25A; MMTV-neu double transgenic mice caused faster tumor growth as compared to MMTV-neu single transgenic mice. Importantly, such CDC25A overexpressing tumor cells displayed
miscoordination of S phase and mitosis, and had severe genomic instability as evidenced by aneuploidy and deletion of fragile chromosomal regions (e.g., telomeric region of chromosome 4, which is homologous to human chromosome 1p31-36, a hotspot for several human cancers including breast cancer).

Hepatocellular carcinoma

Note

Overexpression of CDC25A mRNAs was found in 69% of hepatocellular carcinomas (HCCs) and this overexpression was also confirmed by Immunohistochemistry (56% HCCs exhibit overexpression of CDC25A) and western blot analysis (Xu et al., 2003). Different CDC25 inhibitor (such as vitamin K analog Cpd 5; phenyl maleimide compound PM-20; 2-Methoxyestadiol, a physiological metabolite of estrogen) are capable of inhibiting the hepatocellular carcinoma growth both in vitro and in vivo (Wang et al., 2001; Kar et al, 2006).

Disease

High expression of CDC25A was associated with dedifferentiated phenotype and portal vein invasion.

Prognosis

CDC25A overexpression is associated with poor prognosis of hepatocellular carcinoma.

Retinoblastoma

Note

Overexpression of CDC25A mRNAs was found in 48,33 % retinoblastomas, confirmed by immunohistochemistry (52,29 %) and western blotting (Shingh et al., 2014).

Prognosis

Expression of CDC25A showed significant correlation with poor tumour differentiation and tumour invasion.

Non-Hodgkin's lymphoma

Prognosis

High level of CDC25A mRNAs was found in 35 % of the tumors and were more frequently observed in aggressive than in indolent lymphomas. This was also confirmed at the protein level.

Gastric cancer

Note

By immunohistochemistry CDC25A was found expressed in 87.1 % of gastric carcinomas, correlated with c-myc overexpression (Xing et al., 2008).

Disease

Overexpression of CDC25A was independent of intestinal or diffuse type of gastric cancer.

Prognosis

Association between CDC25A expression and higher histological grade of differentiation.

References

Bahassi el M, Yin M, Robbins SB, Li YQ, Conrady DG, Yuan Z, Kovall RA, Herr AB, Stambrook PJ. A human cancer-predisposing polymorphism in Cdc25A is embryonic lethal in the mouse and promotes ASK-1 mediated apoptosis. Cell Div. 2011 Feb 10;6(1):4

Bartek J, Lukas J. Mammalian G1- and S-phase checkpoints in response to DNA damage. Curr Opin Cell Biol. 2001 Dec;13(6):738-47

Bertero T, Gastaldi C, Bourget-Ponzio I, Mari B, Meneguzzi G, Barbry P, Ponzio G, Rezzonico R. CDC25A targeting by miR-483-3p decreases CCND-CDK4/6 assembly and contributes to cell cycle arrest. Cell Death Differ. 2013 Jun;20(6):800-11

Boutros R, Dozier C, Ducommun B. The when and wheres of CDC25 phosphatases. Curr Opin Cell Biol. 2006 Apr;18(2):185-91

Boutros R, Lobjois V, Ducommun B. CDC25 phosphatases in cancer cells: key players? Good targets? Nat Rev Cancer. 2007 Jul;7(7):495-507

Chang KH, Vincent F, Shah K. Deregulated Cdk5 triggers aberrant activation of cell cycle kinases and phosphatases inducing neuronal death. J Cell Sci. 2012 Nov 1;125(Pt 21):5124-37

Cheng YS, Kuo PL, Teng YN, Kuo TY, Chung CL, Lin YH,

Liao RW, Lin JS, Lin YM. Association of spermatogenic failure with decreased CDC25A expression in infertile men. Hum Reprod. 2006 Sep;21(9):2346-52

Chiu YT, Han HY, Leung SC, Yuen HF, Chau CW, Guo Z, Qiu Y, Chan KW, Wang X, Wong YC, Ling MT. CDC25A functions as a novel Ar corepressor in prostate cancer cells. J Mol Biol. 2009 Jan 16;385(2):446-56

Chou ST, Yen YC, Lee CM, Chen MS. Pro-apoptotic role of Cdc25A: activation of cyclin B1/Cdc2 by the Cdc25A C-terminal domain. J Biol Chem. 2010 Jun 4;285(23):17833-45

Demetrick DJ, Beach DH. Chromosome mapping of human CDC25A and CDC25B phosphatases. Genomics. 1993 Oct;18(1):144-7

Fernandez-Vidal A, Mazars A, Gautier EF, Prévost G, Payrastre B, Manenti S. Upregulation of the CDC25A phosphatase down-stream of the NPM/ALK oncogene participates to anaplastic large cell lymphoma enhanced proliferation. Cell Cycle. 2009 May 1;8(9):1373-9

Galaktionov K, Beach D. Specific activation of cdc25 tyrosine phosphatases by B-type cyclins: evidence for multiple roles of mitotic cyclins. Cell. 1991 Dec 20;67(6):1181-94

Gautier EF, Picard M, Laurent C, Marty C, Villeval JL, Demur C, Delhommeau F, Hexner E, Giraudier S, Bonnevialle N, Ducommun B, Récher C, Laurent G, Manenti S, Mansat-De Mas V. The cell cycle regulator CDC25A is a target for JAK2V617F oncogene. Blood. 2012 Feb 2;119(5):1190-9

Hong HY, Choi J, Cho YW, Kim BC. Cdc25A promotes cell survival by stimulating NF-κB activity through IκB-α phosphorylation and destabilization. Biochem Biophys Res Commun. 2012 Apr 6;420(2):293-6

Källström H, Lindqvist A, Pospisil V, Lundgren A, Rosenthal CK. Cdc25A localisation and shuttling: characterisation of sequences mediating nuclear export and import. Exp Cell Res. 2005 Feb 1;303(1):89-100

Kang T, Wei Y, Honaker Y, Yamaguchi H, Appella E, Hung MC, Piwnica-Worms H. GSK-3 beta targets Cdc25A for ubiquitin-mediated proteolysis, and GSK-3 beta inactivation correlates with Cdc25A overproduction in human cancers. Cancer Cell. 2008 Jan;13(1):36-47

Kar S, Wang M, Carr BI. 2-Methoxyestradiol inhibits hepatocellular carcinoma cell growth by inhibiting Cdc25 and inducing cell cycle arrest and apoptosis. Cancer Chemother Pharmacol. 2008 Oct;62(5):831-40

Löffler H, Sylju̇åsen RG, Bartkova J, Worm J, Lukas J, Bartek J. Distinct modes of deregulation of the proto-oncogenic Cdc25A phosphatase in human breast cancer cell lines. Oncogene. 2003 Nov 6;22(50):8063-71

Mailand N, Falck J, Lukas C, Syljuâsen RG, Welcker M, Bartek J, Lukas J. Rapid destruction of human Cdc25A in response to DNA damage. Science. 2000 May 26;288(5470):1425-9

Mailand N, Podtelejnikov AV, Groth A, Mann M, Bartek J, Lukas J. Regulation of G(2)/M events by Cdc25A through phosphorylation-dependent modulation of its stability. EMBO J. 2002 Nov 1;21(21):5911-20

Mazars A, Fernandez-Vidal A, Mondesert O, Lorenzo C, Prévost G, Ducommun B, Payrastre B, Racaud-Sultan C, Manenti S. A caspase-dependent cleavage of CDC25A generates an active fragment activating cyclin-dependent kinase 2 during apoptosis. Cell Death Differ. 2009 Feb;16(2):208-18

Melkun E, Pilione M, Paulson RF. A naturally occurring point substitution in Cdc25A, and not Fv2/Stk, is associated with altered cell-cycle status of early erythroid progenitor cells. Blood. 2002 Nov 15;100(10):3804-11

Oh JS, Susor A, Schindler K, Schultz RM, Conti M. Cdc25A activity is required for the metaphase II arrest in mouse oocytes. J Cell Sci. 2013 Mar 1;126(Pt 5):1081-5

Pereg Y, Liu BY, O'Rourke KM, Sagolla M, Dey A, Komuves L, French DM, Dixit VM. Ubiquitin hydrolase Dub3 promotes oncogenic transformation by stabilizing Cdc25A. Nat Cell Biol. 2010 Apr;12(4):400-6

Ray D, Kiyokawa H. CDC25A levels determine the balance of proliferation and checkpoint response. Cell Cycle. 2007 Dec 15;6(24):3039-42

Ray D, Terao Y, Nimbalkar D, Hirai H, Osmundson EC, Zou X, Franks R, Christov K, Kiyokawa H. Hemizygous disruption of Cdc25A inhibits cellular transformation and mammary tumorigenesis in mice. Cancer Res. 2007 Jul 15;67(14):6605-11

Shen T, Huang S. The role of Cdc25A in the regulation of cell proliferation and apoptosis. Anticancer Agents Med Chem. 2012 Jul;12(6):631-9

Singh L, Pushker N, Sen S, Singh MK, Bakhshi S, Chawla B, Kashyap S. Expression of CDC25A and CDC25B phosphatase proteins in human retinoblastoma and its correlation with clinicopathological parameters. Br J Ophthalmol. 2015 Apr;99(4):457-63

Vijayakumar S, Liu G, Rus IA, Yao S, Chen Y, Akiri G, Grumolato L, Aaronson SA. High-frequency canonical Wnt activation in multiple sarcoma subtypes drives proliferation through a TCF/β-catenin target gene, CDC25A. Cancer Cell. 2011 May 17;19(5):601-12

Wang Z, Southwick EC, Wang M, Kar S, Rosi KS, Wilcox CS, Lazo JS, Carr BI. Involvement of Cdc25A phosphatase in Hep3B hepatoma cell growth inhibition induced by novel K vitamin analogs. Cancer Res. 2001 Oct 1;61(19):7211-6

Wegener S, Hampe W, Herrmann D, Schaller HC. Alternative splicing in the regulatory region of the human phosphatases CDC25A and CDC25C. Eur J Cell Biol. 2000 Nov;79(11):810-5

Xiao Z, Chen Z, Gunasekera AH, Sowin TJ, Rosenberg SH, Fesik S, Zhang H. Chk1 mediates S and G2 arrests through Cdc25A degradation in response to DNA-damaging agents J Biol Chem 2003 Jun 13;278(24):21767-73

Xing X, Chen J, Chen M. Expression of CDC25 phosphatases in human gastric cancer Dig Dis Sci 2008 Apr;53(4):949-53

Xu X, Yamamoto H, Sakon M, Yasui M, Ngan CY, Fukunaga H, Morita T, Ogawa M, Nagano H, Nakamori S, Sekimoto M, Matsuura N, Monden M. Overexpression of CDC25A phosphatase is associated with hypergrowth activity and poor prognosis of human hepatocellular carcinomas Clin Cancer Res 2003 May;9(5):1764-72

Zou X, Tsutsui T, Ray D, Blomquist JF, Ichijo H, Ucker DS, Kiyokawa H. The cell cycle-regulatory CDC25A phosphatase inhibits apoptosis signal-regulating kinase 1 Mol Cell Biol 2001 Jul;21(14):4818-28

This article should be referenced as such:

Dozier C, Manenti S. CDC25A (Cell division cycle 25A). Atlas Genet Cytogenet Oncol Haematol. 2016; 20(6):316-321.