Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section

Mini Review

CDC6 (cell division cycle 6 homolog (S. cerevisiae))

Michael Zachariadis, Vassilis G Gorgoulis

Department of Anatomy, Faculty of Medicine, University of Athens, Athens, Greece (MZ); Department of Histology and Embryology, Molecular Carcinogenesis Group, Faculty of Medicine, University of Athens, Athens, Greece (VGG)

Published in Atlas Database: January 2008

Online updated version: http://AtlasGeneticsOncology.org/Genes/CDC6ID40014ch17q21.html
DOI: 10.4267/2042/38568

Identity

Hugo: CDC6
Other names: CDC18L; cdc6; hCDC6; HsCDC18; HsCDC6; p62
Location: 17q21.3
Local order: centrosome ---- CASC3-RAPGEFL1-WIPF2-CDC6-RARA-TOP2A

DNA/RNA

Accession N°	Transcript length (bp)	Notes
NM_001254	3053	RefSeq
CR598029	1802	mRNA
BC025232	2861	mRNA
HSU77949	2653	mRNA
AF022109	2021	mRNA

Description

The gene starts at 35697672 bp from pter and ends at 35712939 bp from pter. Its size is 15267 bases and its orientation lie at the plus strand.
The 5' promoter region contains putative sites for transcriptional control, including an initiator element, a CHR element, two main binding sites for E2F, a putative Sp1 site, and a CCAAT region. No consensus TATA box is evident. This resembles the organization of other genes encoding proteins associated with the G1/S transition.

Transcription

The gene has 12 exons. The five putative transcripts (see table below) encode the same product of 560aa. There are about 230 EST sequences.

Pseudogene

There are no known pseudogenes.

Protein

Description

The CDC6 protein or p62 is composed of 560 amino acids with a molecular weight of 62720 Da. The central portion of the protein contains a conserved nucleotide binding/ATPase domain, which classifies it to a large superfamily of ATPases known as "ATPases associated with various cellular activities" (AAA) proteins and specifically to the AAA+ subfamily. The Walker-A motif GXXGXGK(T/S) (nucleotide binding) of the AAA+ domain spans aa 202-209, while the Walker-B motif D(D/E)XX (nucleotide hydrolysis) spans aa 284-287. The domain contains also a leucine zipper (aa 306-327), and a caspase dependent cleavage site DQL290DS.
The N-terminal domain contains: three consensus phosphorylation sites at serine (S)54, S74 and S106, which are phosphorylated in vivo by CDK-related activity at the G1/S boundary; a putative conserved nuclear localization sequence ((S/T)PXK57R58(L/I)); two putative destruction boxes (D-box (aa 56-64) and KEN box (aa 81-83)), which target CDC6 for proteolysis by APCCDH1 during early G1 or G0, but

not S, G2 or M; and a cyclin binding domain mapped to a Cy-motif (aa 93-100) that is similar to the cyclin binding regions in p21/WAF1/SDI1 and E2F-1.
The C-terminal domain contains: a putative classical nuclear export signal (NES) between residues 462-488 (ILVCSLMLLIRQLKI), a caspase dependent cleavage site SEV442DG, and a conserved winged-helix domain (WHD) with unknown function; it possibly mediates protein-protein interactions or a direct interaction with the DNA helix.

Expression

It is expressed in all proliferating cells but not in quiescent or differentiated cells.

Localisation

Even though it was believed at first that p62CDC6 was nuclear during G1 and cytoplasmic during S and G2, lately it has been found that there is an endogenous fraction of the protein that remains chromatin-bound throughout the cell cycle.

Function

- ATP binding
- Chromatin binding
- Nucleoside-triphosphatase activity
- Nucleotide binding
- Protein binding
- Loading factor for MCM2-7: Cdc6/Cdc18 is recruited to replication origins by ORC. Once localized at replication origins, Cdc6 helps to recruit and load MCM factors onto DNA in a process that requires CDC6-mediated ATP hydrolysis. After loading of MCM2-7 on DNA, CDC6 is not necessary for origin firing and dissociates from the complex, through a phosphorylation-dependent procedure. It seems though that CDC6 has additional roles related to S/M checkpoint control. Accumulating evidence suggests that CDC6 is required for proper control of mitotic entry.Deregulation of CDC6 results in mitotic block, aberrant mitotic progression, or apoptosis.

Homology

ORC1

Mutations

Note: No known mutations.

Implicated in

Carcinogenesis

Note: Because of its key role in DNA replication, deregulation of CDC6 could lead to genomic instability fueling the risk for neoplastic transformation. Indeed, CDC6 upregulation has been observed in many cancerous lesions, including brain tumors, non-small cell lung carcinomas, mantle cell lymphomas, and various cervical neoplasias. Interestingly, in aggressive prostate cancer, CDC6 is downregulated.
CDC6 encompasses certain oncogenic characteristics that manifest themselves when CDC6 expression is deregulated. For example, CDC6 induces DNA replication in quiescent cells, while in certain occasions overexpression of CDC6 leads to DNA overreplication in tumour cells.
While cells have mechanisms to prevent aberrant DNA replication, deregulation of CDC6, or /and its partner in pre-RCs, CDT1 may lead to abrogation of the antitumor barriers of senescence and apoptosis. In addition their stable expression in premalignant papilloma cells lead to transformation of these cells, which upon injection into nude mice produce tumors, an activity that clearly portrays the oncogenic potential of CDC6 deregulation.
Moreover, deregulation of CDC6 may lead to inactivation of the INK4/ARF locus through recruitment of histone deacetylases HDAC1 and HDAC2 and heterochromatinization of the INK4/ARF locus. This locus encodes the tumour suppressor genes p16INK4a, p15INK4b, and ARF, and inactivation of this locus is closely related to cancer.

References

Williams RS, Shohet RV, Stillman B. A human protein related to yeast Cdc6p. Proc Natl Acad Sci USA 1997;94(1):142-147.

Hateboer G, Wobst A, Petersen BO, Le Cam L, Vigo E, Sardet C, Helin K. Cell cycle-regulated expression of mammalian CDC6 is dependent on E2F. Mol Cell Biol 1998;18(11):6679-6697.

Ohtani K, Tsujimoto A, Ikeda M, Nakamura M. Regulation of cell growth-dependent expression of mammalian CDC6 gene by the cell cycle transcription factor E2F. Oncogene 1998;17(14):1777-1785.

Saha P, Chen J, Thome KC, Lawlis SJ, Hou ZH, Hendricks M, Parvin JD, Dutta A. Human CDC6/Cdc18 associates with Orc1 and cyclin-cdk and is selectively eliminated from the nucleus at the onset of S phase. Mol Cell Biol 1998;18(5):2758-2767.

Yan Z, DeGregori J, Shohet R, Leone G, Stillman B, Nevins JR, Williams RS. Cdc6 is regulated by E2F and is essential for DNA replication in mammalian cells. Proc Natl Acad Sci USA 1998;95(7):3603-3608.

Fujita M, Yamada C, Goto H, Yokoyama N, Kuzushima K, Inagaki M, Tsurumi T. Cell cycle regulation of human CDC6 protein. Intracellular localization, interaction with the human mcm complex, and CDC2 kinase-mediated hyperphosphorylation. J Biol Chem 1999;274(36):25927-25932.

Herbig U, Marlar CA, Fanning E. The Cdc6 nucleotide-binding site regulates its activity in DNA replication in human cells. Mol Biol Cell 1999;10(8):2631-2645.

Jiang W, Wells NJ, Hunter T. Multistep regulation of DNA replication by Cdk phosphorylation of HsCdc6. Proc Natl Acad Sci USA 1999;96(11):6193-6198.

Petersen BO, Lukas J, Sørensen CS, Bartek J, Helin K. Phosphorylation of mammalian CDC6 by cyclin A/CDK2 regulates its subcellular localization. EMBO J 1999;18(2):396-410.

Takei Y, Yamamoto K, Tsujimoto G. Identification of the sequence responsible for the nuclear localization of human Cdc6. FEBS Lett 1999;447(2-3):292-296.

Coverley D, Pelizon C, Trewick S, Laskey RA. Chromatin-bound Cdc6 persists in S and G2 phases in human cells, while soluble Cdc6 is destroyed in a cyclin A-cdk2 dependent process. J Cell Sci 2000;113 (Pt 11):1929-1938.

Herbig U, Griffith JW, Fanning E. Mutation of cyclin/cdk phosphorylation sites in HsCdc6 disrupts a late step in initiation of DNA replication in human cells. Mol Biol Cell 2000;11(12):4117-4130.

Méndez J, Stillman B. Chromatin association of human origin recognition complex, cdc6, and minichromosome maintenance proteins during the cell cycle: assembly of prereplication complexes in late mitosis. Mol Cell Biol 2000;20(22):8602-8612.

Petersen BO, Wagener C, Marinoni F, Kramer ER, Melixetian M, Lazzerini Denchi E, Gieffers C, Matteucci C, Peters JM, Helin K. Cell cycle- and cell growth-regulated proteolysis of mammalian CDC6 is dependent on APC-CDH1. Genes Dev 2000;14(18):2330-2343.

Delmolino LM, Saha P, Dutta A. Multiple mechanisms regulate subcellular localization of human CDC6. J Biol Chem 2001;276(29):26947-26954.

Ohta S, Koide M, Tokuyama T, Yokota N, Nishizawa S, Namba H. Cdc6 expression as a marker of proliferative activity in brain tumors. Oncol Rep 2001;8(5):1063-1066.

Biermann E, Baack M, Kreitz S, Knippers R. Synthesis and turn-over of the replicative Cdc6 protein during the HeLa cell cycle. Eur J Biochem 2002;269(3):1040-1046.

Blanchard F, Rusiniak ME, Sharma K, Sun X, Todorov I, Castellano MM, Gutierrez C, Baumann H, Burhans WC. Targeted destruction of DNA replication protein Cdc6 by cell death pathways in mammals and yeast. Mol Biol Cell 2002;13(5):1536-1549.

Bonds L, Baker P, Gup C, Shroyer KR. Immunohistochemical localization of cdc6 in squamous and glandular neoplasia of the uterine cervix. Arch Pathol Lab Med 2002;126(10):1164-1168.

Cook JG, Park CH, Burke TW, Leone G, DeGregori J, Engel A, Nevins JR. Analysis of Cdc6 function in the assembly of mammalian prereplication complexes. Proc Natl Acad Sci USA 2002;99(3):1347-1352.

Fujita M, Ishimi Y, Nakamura H, Kiyono T, Tsurumi T. Nuclear organization of DNA replication initiation proteins in mammalian cells. J Biol Chem 2002;277(12):10354-10361.

Robles LD, Frost AR, Davila M, Hutson AD, Grizzle WE, Chakrabarti R. Down-regulation of Cdc6, a cell cycle regulatory gene, in prostate cancer. J Biol Chem 2002;277(28):25431-25438.

Clay-Farrace L, Pelizon C, Santamaria D, Pines J, Laskey RA. Human replication protein Cdc6 prevents mitosis through a checkpoint mechanism that implicates Chk1. EMBO J 2003;22(3):704-712.

Pelizon C. Down to the origin: Cdc6 protein and the competence to replicate. Trends Cell Biol 2003;13(3):110-113. (Review).

Vaziri C, Saxena S, Jeon Y, Lee C, Murata K, Machida Y, Wagle N, Hwang DS, Dutta A. A p53-dependent checkpoint pathway prevents rereplication. Mol Cell 2003;11(4):997-1008.

Cook JG, Chasse DA, Nevins JR. The regulated association of Cdt1 with minichromosome maintenance proteins and Cdc6 in mammalian cells. J Biol Chem 2004;279(10):9625-9633.

Karakaidos P, Taraviras S, Vassiliou LV, Zacharatos P, Kastrinakis NG, Kougiou D, Kouloukoussa M, Nishitani H, Papavassiliou AG, Lygerou Z, Gorgoulis VG. Overexpression of the replication licensing regulators hCdt1 and hCdc6 characterizes a subset of non-small-cell lung carcinomas: synergistic effect with mutant p53 on tumor growth and chromosomal instability--evidence of E2F-1 transcriptional control over hCdt1. Am J Pathol 2004;165(4):1351-1365.

Ayad NG. CDKs give Cdc6 a license to drive into S phase. Cell 2005;122(6):825-827. (Review).

Duursma A, Agami R. p53-Dependent regulation of Cdc6 protein stability controls cellular proliferation. Mol Cell Biol 2005;25(16):6937-6947.

Mailand N, Diffley JF. CDKs promote DNA replication origin licensing in human cells by protecting Cdc6 from APC/C-dependent proteolysis. Cell 2005;122(6):915-926.

Murphy N, Ring M, Heffron CC, Martin CM, McGuinness E, Sheils O, O'Leary JJ. Quantitation of CDC6 and MCM5 mRNA in cervical intraepithelial neoplasia and invasive squamous cell carcinoma of the cervix. Mod Pathol 2005;18(6):844-849.

Takeda DY, Shibata Y, Parvin JD, Dutta A. Recruitment of ORC or CDC6 to DNA is sufficient to create an artificial origin of replication in mammalian cells. Genes Dev 2005;19(23):2827-2836.

Gonzalez S, Klatt P, Delgado S, Conde E, Lopez-Rios F, Sanchez-Cespedes M, Mendez J, Antequera F, Serrano M. Oncogenic activity of Cdc6 through repression of the INK4/ARF locus. Nature 2006;440(7084):702-706.

Lau E, Zhu C, Abraham RT, Jiang W. The functional role of Cdc6 in S-G2/M in mammalian cells. EMBO Rep 2006;7(4):425-430.

Pinyol M, Salaverria I, Bea S, Fernández V, Colomo L, Campo E, Jares P. Unbalanced expression of licensing DNA replication factors occurs in a subset of mantle cell lymphomas with genomic instability. Int J Cancer 2006;119(12):2768-2774.

Yim H, Hwang IS, Choi JS, Chun KH, Jin YH, Ham YM, Lee KY, Lee SK. Cleavage of Cdc6 by caspase-3 promotes ATM/ATR kinase-mediated apoptosis of HeLa cells. J Cell Biol 2006;174(1):77-88.

Bartkova J, Rezaei N, Liontos M, Karakaidos P, Kletsas D, Issaeva N, Vassiliou LV, Kolettas E, Niforou K, Zoumpourlis VC, Takaoka M, Nakagawa H, Tort F, Fugger K, Johansson F, Sehested M, Andersen CL, Dyrskjot L, Orntoft T, Lukas J, Kittas C, Helleday T, Halazonetis TD, Bartek J, Gorgoulis VG. Oncogene-induced senescence is part of the tumorigenesis barrier imposed by DNA damage checkpoints. Nature 2006;444(7119):633-637.

Borlado LR, Méndez J. CDC6: from DNA replication to cell cycle checkpoints and oncogenesis. Carcinogenesis 2007;[Epub ahead of print].

Hall JR, Kow E, Nevis KR, Lu CK, Luce KS, Zhong Q, Cook JG. Cdc6 stability is regulated by the Huwe1 ubiquitin ligase after DNA damage. Mol Biol Cell 2007;18(9):3340-3350.

Liontos M, Koutsami M, Sideridou M, Evangelou K, Kletsas D, Levy B, Kotsinas A, Nahum O, Zoumpourlis V, Kouloukoussa M, Lygerou Z, Taraviras S, Kittas C, Bartkova J, Papavassiliou AG, Bartek J, Halazonetis TD, Gorgoulis VG. Deregulated overexpression of hCdt1 and hCdc6 promotes malignant behavior. Cancer Res 2007;67(22):10899-10909.

This article should be referenced as such:

Zachariadis M, Gorgoulis VG. CDC6 (cell division cycle 6 homolog (S. cerevisiae)). Atlas Genet Cytogenet Oncol Haematol.2008;12(5):362-364.