CDT1 (chromatin licensing and DNA replication factor 1)

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Identity

Other names: DUP; RIS2
HGNC (Hugo): CDT1
Location: 16q24.3
Note: CDT1 gene is present in the contig NT-010542.14 of GenBank, 430803-436282.

DNA/RNA

Description
DNA size 5.48 kb; mRNA size 2674 bp; 10 exons.

Protein

Description
546 amino acids; 60433 Da.
CDT1 contains cyclin binding motif 68-70 (3), and region for geminin interaction 150-190 (41).

Cyclin-binding motif is the target for phosphorylation by cyclin A-dependent kinases, which results in the binding of Cdt1 to the F-box protein Skp2 and subsequent degradation. Interaction with geminin, a small regulatory protein active during S, G2, and M phases of the cell cycle, protects CDT1 from ubiquitin mediated degradation. Six natural variants, A135V (VAR-029163), R172C (VAR-029164), R234C (VAR-054504), T262A (VAR-054505), E456A (VAR-029165), and A537V (VAR-024408) have been reported.

Isoforms: There are three different isoforms, aApr07 (complete), bApr07 (partial), and cApr07 (COOH complete); all three isoforms putatively encode good proteins.

Post translational modifications: Phosphorylation occurs at position Thr29, Ser31, Ser118, Ser372, and Ser394; however, phosphorylation does not affect binding to geminin.
Expression
Widely expressed, highly expressed in liver, thymus, and predominantly expressed in uterus and cervix of female reproductive system.

Localisation
Nucleus.

Function
The CDT1 protein is required for the formation of the pre-replicative complexes. CDT1 cooperates with CDC6 to promote loading of the mini-chromosome maintenance complex (MCM2-7) onto chromatin to form pre-replication complex necessary for the initiation of DNA replication. Moreover, CDT1 associates with the CDC7 kinase and recruits CDC45 to chromatin during S phase. Chromatin-bound CDT1 is first stabilized and subsequently displaced by CDC7 activity, which ensures timely execution of DNA replication. CDT1 is also a potential oncogene; overexpression of CDT1 promotes rereplication and generates a DNA damage senescence and response that activates the antitumor barriers of senescence and apoptosis.

Regulation: CDT1 is regulated either by cell cycle dependent proteolysis during S and G2 phase or by geminin. Proteolysis of CDT1 during S and G2 phases is dependent on the CDK2 -cyclin A mediated phosphorylation of CDT1 and subsequent proteolysis by SCF-Skp2 complex. CDT1 activity is also inhibited by the tight binding of geminin that blocks the ability of CDT1 to load MCM2-7 onto DNA.

Homology
The percent identity below represents identity of CDT1 over an aligned region in UniGene.
- Mus musculus: 82% (percent identity)
- Bos taurus: 76.2%
- Canis familiaris: 74.54%
- Rattus norvegicus: 74.49%
- Xenopus laevis: 62.5%
- Danio rerio: 60%.

Mutations
Note
The RRL --->AAA mutation in the cyclin binding motif abolishes the binding of Cyclin A-dependent protein kinases with CDT1.

Implicated in

Lung carcinoma
Note
In a subset of non-small-cell lung carcinomas (NSCLCs), CDT1 is significantly overexpressed that is positively correlated with CDC6 levels. Overexpression of CDT1-CDC6 in concert with p53-mutation is associated with higher tumor growth values and frequent aneuploidy compared with tumor bearing intact p53. These suggest a synergistic effect between CDT1-CDC6 overexpression and mutant-p53 over tumor growth and chromosomal instability in non-small-cell lung carcinomas.

Colon cancer
Note
CDT1 is highly expressed in human neoplastics lesions of the colon; however, its cell cycle phase specific expression profile appears to be preserved during human carcinogenesis. Overexpression of CDT1 results in rereplication, a form of endogenous DNA damage.

Chromosomal damage
Note
Overexpression of CDT1 induces chromosomal damage and activation of ATM-Chk2 without rereplication, resulting in chromosomal instability in normal human foreskin fibroblasts (HFF2) immortalized by telomerase. Deregulated CDT1 overexpression causes chronic chromosomal damage and instability that can eventually results in carcinogenesis. CDT1 is also highly expressed in cancer cells CaSkI, HeLa, LNCap, MCF7, MDM231, and Saos. Overexpression of CDT1 may be at least partly due to increased transcription or increased gene copy number and CDT1 protein levels are much less affected by contact inhibition.

References


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