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Gene Section
Review

CDCP1 (CUB domain containing protein 1)

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Abstract: Review on CDCP1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: CD318, SIMA135, TRASK

HGNC (Hugo): CDCP1

Location: 3p21.31

DNA/RNA

Note

CDCP1 (CUB Domain Containing Protein) was independently identified by several research groups. CDCP1 was initially isolated as a gene expressed in colorectal cancer (Scherl-Mostageer et al.,2001). The CDCP1 gene product was independently identified as a protein phosphorylated during mitosis and cellular detachment by Src kinases (Bhatt et al., 2005) and it is also known as Trask (Transmembrane and Associated with Src Kinases).

Description

The CDCP1 gene comprises 9 verified exons.

Transcription

Two alternative transcripts have been described (Perry et al., 2007).

The full length transcript (isoform 1) is approximately 6.4 kb in length, spans all 9 exons and encodes a transmembrane protein. The isoform 2 transcript is 1.4 kb in length, contains the first four 5'exons of the CDCP1 gene. The isoform 2 transcript continues from the exon 4 end into the adjacent intron, where it terminates shortly at an alternative polyadenylation signal, giving rise to a truncated transcript (Perry et al., 2007). The isoform 2 encodes a truncated, secreted protein of 343 amino acids, that contains the N-terminal part of the extracellular domain (and one CUB domain) of CDCP1 and lacks the transmembrane and intracellular modules. Currently, most studies have been focused on the more prominently expressed isoform 1.

The function and expression of isoform 2 remains poorly understood.

Pseudogene

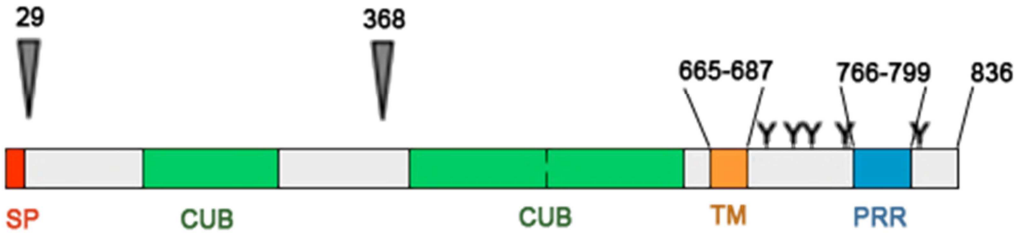
No pseudogenes, related to CDCP1 are present in the human genome.

Protein

Note

The full-length CDCP1 protein consists of 836 amino acids. The SDS PAGE migration of CDCP1 protein is approximately 140 kDa, which differs from its calculated molecular weight (approximately 90 kDa) due to extensive glycosylation (Bhatt et al., 2005).

CDCP1 is cleaved by serine proteases at the extracellular domain next to Arg368 to generate a truncated molecule of 80 kDa size (Bhatt et al., 2005) (in some cases it is referred as 70kDa). Different cell lines express different amounts of p140 and p80, depending on the activity of endogenous serine proteases (Spassov et al., 2012). In vivo, CDCP1 is not cleaved during normal physiological circumstances, but its cleavage can be induced during tumorigenesis or tissue injury. (Spassov et al., 2011; Spassov et al., 2013).



CDCP1 contains a signal peptide and a transmembrane region for proper membrane localization. The larger extracellular domain contains two or three CUB domains. The triangles indicate the naturally occurring cleavage sites after the signal peptide and at Arg368 of the extracellular domain. Abbreviations indicate the signal peptide (SP), CUB domains, transmembrane region (TM), proline-rich region (PRR). The intracellular domain contains 5 tyrosine residues (indicated by Y) all of which can be specifically phosphorylated by Src family kinases.

Description

The full-length CDCP1 protein is a type I transmembrane protein. The proper membrane localization is ensured by the presence of a signal peptide and a transmembrane domain (Bhatt et al., 2005).

The extracellular region is large and it is reported to contain two or three CUB domains. This difference arises because one of the Cub domains has a very weak degree of homology and may not be recognized readily as a Cub domain depending on the software used.

The CUB (Complement protein components C1, Urchin embryonic growth factor and Bone morphogenic protein 1) domains are characterized by immunoglobulin-like folds and are involved in protein-protein interactions and are found in functionally diverse, mostly developmentally regulated proteins and in peptidases. The intracellular domain of CDCP1 contains five tyrosine residues - Y707, Y734, Y743, Y762 and Y806. Phosphorylation of CDCP1 is exclusively mediated by Src kinases (Bhatt et al., 2005).

Expression

CDCP1 is predominantly expressed in epithelial tissues and its expression is not detectable in fibroblasts and other mesenchymal cells (Spassov et al., 2009). CDCP1 also has been reported to be expressed in hematopoietic progenitor cells but not in mature blood cell types (Bühring et al., 2004).

Localisation

CDCP1 is a transmembrane protein and is located on the cell membrane.

Function

CDCP1, when phosphorylated, functions to inhibit integrin signaling, disrupt focal adhesions and oppose cell adhesion (Spassov et al., 2011). Phosphorylation of CDCP1 depends on the adherence state of the cells (Spassov et al., 2009). The loss of anchorage or cellular detachment is associated with the phosphorylation of CDCP1 as well as the concomitant dephosphorylation of focal adhesion proteins, consistent with the dismantling of focal adhesions (Spassov et al., 2011). Contrary, during cellular attachment CDCP1 is dephosphorylated, allowing the phosphorylation of focal adhesion proteins. Knockdown of CDCP1 leads to increased adhesiveness and experimentally induced over-expression and phosphorylation of CDCP1 decreases cell adhesion and leads to cell rounding and a detached phenotype (Spassov et al., 2011). CDCP1 regulates cellular migration and both loss of function and gain of functions of CDCP1 can lead to inhibition of migration (Spassov et al., 2011). The knockdown of CDCP1 leads to permanent cell attachment to substratum, while its excessive phosphorylation inhibits cell spreading and cell motility. The anti-adhesion and anti-migratory functions of CDCP1 are mediated through negative regulation on integrin receptors (Spassov et al., 2011). When phosphorylated by Src kinases, CDCP1 appears in complexes containing β1 integrin, interfering with integrin clustering and preventing the mechanical and signaling events that link the intracellular cytoskeleton with the extracellular matrix. This is mediated through the inhibition of integrin clustering without affecting integrin affinity state or ligand binding activity (Spassov et al., 2011).

Homology

The human genome does not contain other genes related to CDCP1. The degree of homology within the CUB domains of other proteins is low (maximum 20% identity). More importantly other CUB domain containing proteins do not contain the intracellular module that is regulated and phosphorylated by Src kinases. This indicates that there is no other related gene in the human genome that may play a redundant role with CDCP1. CDCP1 homologs are present only in the vertebrate species, including zebra fish, Xenopus, chicken and mammals. CDCP1 is not present in invertebrates and lower organisms.

Mutations

Note

CDCP1 is localized on chromosomal region (3p21.31), which is very frequently deleted in human cancers (Ji et

al., 2005). LOH of CDCP1 is frequent (90-100%) in lung cancers and has been observed in breast cancers and other cancer types.

Germinal

Germinal mutations associated with disease have not been described yet. Several polymorphic sites are described in the gene databases. The role of these polymorphic sites is currently unknown.

Somatic

Somatic mutations in cancer are infrequent. According to COSMIC database (http://cancer.sanger.ac.uk) currently (June 2013) 38 somatic cancer mutations have been identified from 7080 tumor samples (0.5%). Some cancer types show somewhat elevated mutational frequency; for instance 2.4% in melanoma and 1.4 % in colon cancer. It is unclear at this moment if these mutations have functional significance or represent passenger mutations.

Implicated in

Tumorigenesis

Note

Expression and phosphorylation in tumors

The expression of CDCP1 relative to the normal epithelium is reduced or lost in some tumors, particularly in breast, colon, prostate and lung cancers (Wong et al., 2009; Spassov et al., 2012). This is due to loss of heterozygosity in CDCP1 genomic region and/or promoter methylation (Spassov et al., 2012). CDCP1 is widely and abundantly expressed in human epithelial tissues, but its phosphorylation is not detectable in normally anchored epithelial layers (Spassov et al., 2009). However, phosphorylation of CDCP1 is seen in many epithelial tumors from all stages including early stage carcinomas, invasive, and metastatic tumors (Wong et al., 2009). The phosphorylation of CDCP1 in tumors suggests that they may exist at an abnormal or deficient state of anchorage in vivo (Spassov et al., 2011). This may be due to abnormalities in the composition of the surrounding matrix, defective assembly of adhesion complexes, or defective signaling through the integrin adhesion complex. Specifically, this may be due to the absence of a continuous basal lamina which typically underlies the basal surface of epithelial cells in the normal epithelium but is highly abnormal or missing in epithelial tumors.

Animal model

Mice lacking CDCP1 do not exhibit gross morphologic, reproductive or behavioral abnormalities compared with wild-type mice, and histologic examination of multiple organ systems found no significant pathology and no observed histologic differences (Spassov et al., 2013). Mammary tumors driven by the PyMT oncogene and skin tumors driven by activation of Hedgehog pathway developed with accelerated kinetics in CDCP1 null mice, establishing a tumor suppressing function for this gene during cancer initiation and evolution (Spassov et al., 2013). Mechanistic investigations in mammary tumor cell lines derived from CDCP1-deficient mice revealed a de-repression of integrin signaling and an enhancement of integrin-growth factor receptor cross-talk; hence increased growth factor signaling and cell proliferation of CDCP1 null cancer cells (Spassov et al., 2013).

Metastasis

The role of CDCP1 in cellular migration may suggest a potential role of this gene in cancer metastasis. However, this role may be a complex one, considering that both loss of function and gain of function of CDCP1 inhibit migratory capacity of the cells. Inducible expression and phosphorylation of CDCP1 in breast cancer MCF7 cell line decreased the number of lymph node metastasis after orthotopic mammary fat pad implantation (Spassov et al., 2012). Similarly, the inducible expression of CDCP1 in v-src transformed NIH3T3 cells significantly decreased the lung colonization capacity of the cells after tail vein inoculation (Spassov et al., 2012). Knockdown of CDCP1 have also been reported to decrease experimental metastasis of lung and melanoma cell lines (Uekita et al., 2007; Liu et al., 2011). Future work is required to elucidate the functions of CDCP1 in cancer metastasis and whether there will be clinical benefits of targeting this gene. Several efforts have been made to target CDCP1 with monoclonal antibody that recognizes the extracellular domain of the protein. Such antibodies induce the phosphorylation of CDCP1 and have been shown to suppress experimental metastasis in preclinical models (Siva at al., 2008; Casar et al., 2012). It is unclear if this is due to effects on CDCP1 function or if it is mediated through immunological mechanisms.

Hybrid/Mutated gene

No hybrid genes, containing CDCP1 are known.

Abnormal protein

No fusions with CDCP1 have been reported.

Oncogenesis

CDCP1 null mice show accelerated oncogenesis in genetically modified experimental models of skin and breast cancers.

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