Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Review

CD2AP (CD2 associated protein)

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Abstract

CD2AP gene encodes for an adaptor protein with high homology to Cin85. It was originally cloned as CD2 interacting protein and, in an independent study, as p130-Cas interacting protein. It contains three SH3 domains, a proline-rich motif and a coiled-coil domain that allow it to form complexes with numerous proteins and to participate in different physiological processes. Several evidences suggest that it links cell surface proteins and specialized junctions with the actin cytoskeleton and that it regulates the assembly of actin filaments to guide cell shape and movements.

Notably, CD2AP plays a crucial role in the glomerular cells differentiation and in the maintenance of the kidney filtration barrier, and CD2AP-deficient mice die of renal failure before the age of six weeks. Mutations resulting in a lower expression of CD2AP were found in FSGS kidney disease patients. It is also involved in neuronal disorders and two single nucleotide polymorphisms of the gene have been associated with increased risk of Alzheimer' s disease. Finally, although the protein is expressed in the majority of the cell types, it was proposed as optimal marker for BPDCN hematological malignancy.

Keywords

CD2AP, CD associated protein, CMS, actin binding, cell junction

Identity

Other names

CMS, METS1

HGNC (Hugo)

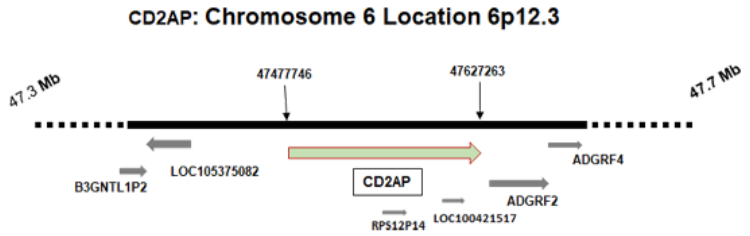
CD2AP associated protein (:14258)

Location

6p12.3. The gene is located on Chromosome 6, starts at 47477746 according to NCBI (47477789 according to ensembl) and ends at 47627263 .

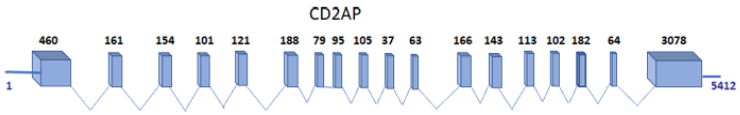
Local order

CD2AP gene is surrounded by LOC105375082 on the 5' end and ADGRF2 on the 3' end (NCBI 2017, Aug 2017). Two pseudogenes (LOC100421517 and RPS12P14) overlap with it.



Chromosomal location of human CD2AP gene, according to NCBI. CD2AP gene is located on Chromosome 6, starting at 47477746 and ending at 47627263. The gene orientation is on the plus strand.

DNA/RNA



The longest transcript of CD2AP gene. It is 5412 bases long and consists of eighteen exons (represented as vertical bars) divided by 17 introns (represented as lines). Two short non coding regions at 5' and 3' complete the transcript. The length of each exon is reported (in number of bases).

Description

The human CD2AP gene is located on chromosome 6p12, it is 149.517 bps long and comprises 18 exons (NCBI Gene ID: 23607, 2017)

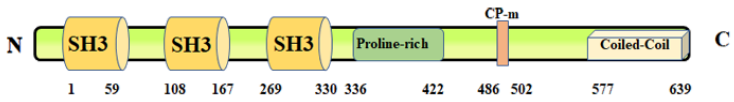
Transcription

The longest transcript is 5412 bases long, and comprises 18 exons. This transcript codes for the full lenght protein; four short transcripts (less than 700 bases) have been reported, but their functional role is unknown (Ensemble, Aug 2017). Two of these non-coding isoforms retain part of introns.

Pseudogene

None

Protein



Schematic representation of the CD2AP protein. Three SH3 domains occupy the amino terminal region of the protein (aa 1-330), followed by a short proline-rich motif (336-422). The carboxyl-terminal region contains an actin capping protein (CP) binding motif and a coiled-coil region (577-638) (Dikic 2002, Bruck et al. 2006).

Description

CD2AP protein is an adaptor protein composed of several regions with binding functions: three SH3 domains, one proline rich region, four actin binding domains, AP-2 and CP binding motifs and a coiled-coil region. The protein is 639 aminoacids long and has a predicted molecular weight of 71,451 Dalton. The SH3 domains are located at the amino terminus of the protein and mediate complexes formation. Actually, SH3 domains are short modules of 60 amino acids commonly involved in the assembly and regulation of signalling processes by recognizing polyproline motifs, shaped in a left-handed type II helix, on the surface of the target proteins. In particular, CD2AP SH3 domains selectively recognize polyproline regions containing the consensus PXXXPR. One of this motif is contained in the p53 trascription factor, only in one of the two p53 polymorphic variants P72R, and allows the adaptor protein to selectively bind the 72 R variant (Panni et al. 2015). The crystal structure of two of the SH3 domains of CD2AP have been solved, showing that the domains conserve the typical beta-barrel shape, with five beta strands (Moncalian et al.2006; Yao et al. 2007). Two AP-2 binding motif (FXDXFX) overlap with the first and third SH3 domains respectively, while a third motif lies between the second and the third SH3 (Brett et al. 2002). Beyond these domains, the proline rich region (aa 336-422) contains motifs recognized by the SH3 domains of p130Cas, Src, Fyn, Yes and PI3K, all proteins involved in signal transduction (Kirsch et al. 1999, Dikic 2002). The presence of four putative actin binding sites (aa 534-538; 599-603; 610-614; 631-635) was observed in (Kirsch et al. 1999; Dikic 2002) and the direct binding of CD2AP to actin was shown in (Lehtonen et al. 2002), while the in vivo colocalization and co-immunoprecipitation of CD2AP with actin was demonstrated in (Yuan et al. 2002; Gaidos et al. 2007). Instead a CP (actin barbed-end capping protein) binding motif is present

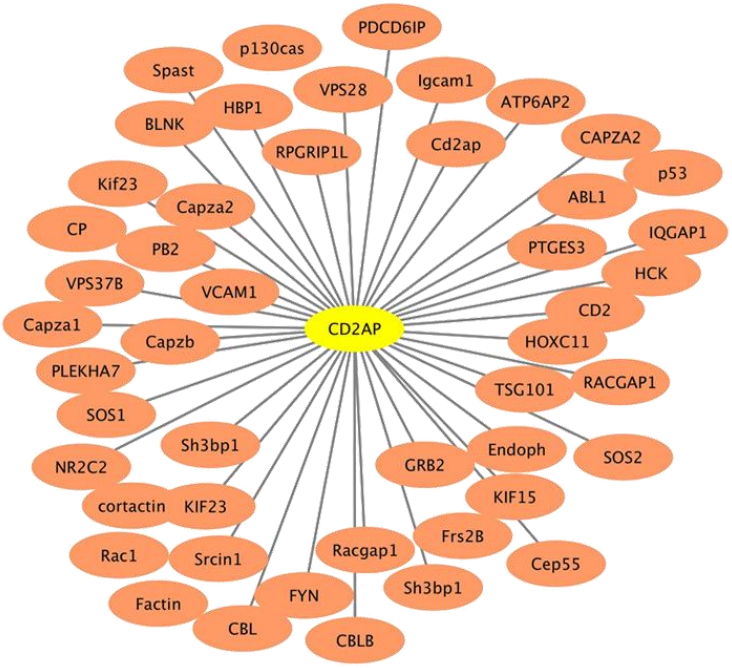
at amino acids 486-502 and mediates the binding of CD2AP to CP (which in turn binds to actin) and the resulting inhibition of the protective function of CP on actin filaments (Bruck et al. 2006; Takeda et al. 2010). The Carboxyl-terminal region adopts a coiled-coil conformation that allows the protein to homodimerise or heterodimerise with the homolog Cin85. (Kirsch et al. 1999, Gaidos et al. 2007)

Expression

CD2AP mRNA is ubiquitously expressed in human tissues (Kirsch et al. 1999). In particular, it is strongly expressed in the placenta, colon, kidney, pancreas and thymus, while a lower expression was detected in aorta, skeletal muscle, bladder and uterus (Kirsch et al. 1999).

Localisation

CD2AP protein is localised mainly to the plasma membrane and to the cytosol

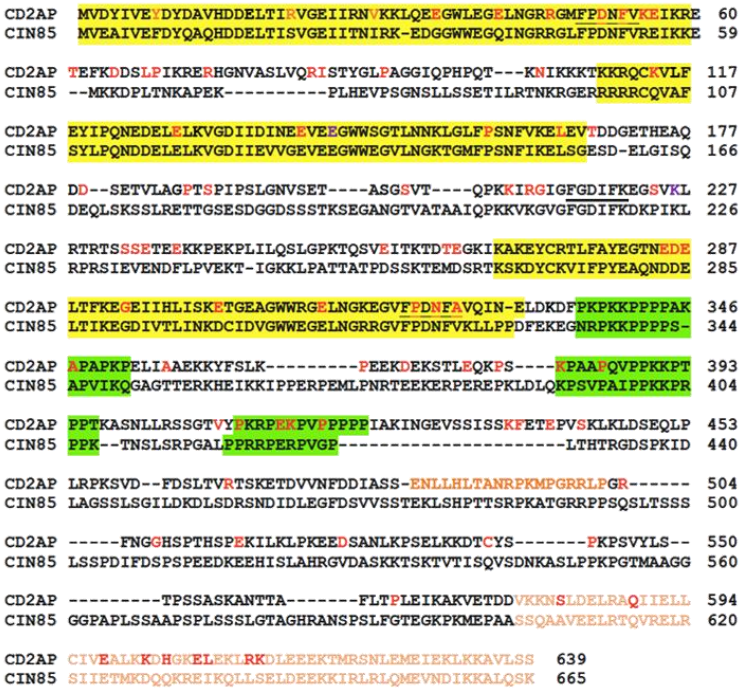


CD2AP Interaction Network. The network was downloaded from the Intact Database (except for some nodes that were manually added) and visualized with Cytoscape (Orchard et al. 2014; Shannon et al. 2003). Both direct interactions and indirect associations of CD2AP are shown.

Function

The presence of binding domains allows CD2AP to control the assembly of multiprotein complexes and to transmit signals involved in different biological processes. The protein was first identified as p130-Cas interactor (and named CMS as "Cas ligand with Multiple SH3") and its colocalization with p130-Cas and F-actin strongly suggested for a function in the regulation of the actin cytoskeleton as an adaptor protein (Kirsch et al. 1999). This role was largely confirmed by subsequent observations: in normal cells, monomeric actin (G actin) polymerises in filaments (F actin) that bind to CD2AP (Gaidos et al. 2007); in podocytes the absence of CD2AP causes a dramatic defect due to the loss of their specialised actin-rich foot processes that operate the filtration in kidney (Shih et al 1999 ; Gaidos et al. 2007). It was further shown that to guarantee stability to the actin polymer, its barbed ends are in complex with the actin-capping protein CP that avoid the addiction and the loss of monomers. In the presence of CD2AP, CP is prevented to bind actin filaments barbed end, and actin filaments can be extended or shortened (Bruck et al. 2006). Notably, CD2AP is required to recruit CP to the cell periphery during lamellipodia formation (Zhao et al. 2013) and to regulate actin accumulation at the adherens junctions (Tang and Brieher 2013). An independent work identified mouse CD2AP as CD2 receptor clustering activator in the specialized junctions between T cells and antigen-presenting cells (Dustin et al. 1998). This interaction also connects surface receptors to the actin cytoscheleton. A similar model was proposed in Drosophila, where Cindr, the CD2AP homolog, was shown to link cell-cell adhesion junctions with actin cytoscheleton by binding to E-Cadherin and IgCAM Roughest (Johnson et al. 2008; Johnson et al. 2012). It was also observed that upon

EGF treatment CBL associates to CD2AP that recruits it to membrane ruffles where they both colocalize (Kirsch et al. 2001; Lynch et al. 2003), linking endocytosis to actin polymerization. RAC1 was found in membrane ruffles in complex with CTTN (cortactin) and CD2AP (Van Dujin et al. 2011). Recently it was suggested that the adaptor protein may anchor a fraction of the 72R variant of the TP53 protein in the cytosol, connecting it with membrane receptors and actin cytoscheleton (Panni et al. 2015). All these observations suggest for a role of CD2AP in regulating membrane proteins and specialized cell junctions and to connect them with actin cytoscheleton dynamics.



The sequence alignment of the two homolog human proteins CD2AP and Cin85. The SH3 domains are highlighted in yellow and the proline-rich in green. Pink letters indicate the CP binding motif and the Coiled-Coil region. AP2 binding motifs are underlined and positions annotated as potential missense or nonsense mutations in Cosmic database (Forbes et al. 2017) are represented by red letters.

Homology

CD2AP is a member of the Cin85/CMS family of adaptor proteins which comprises two paralogs: CD2AP (CMS) and Cin85 (Figure 5) . They are conserved among mammalian species, but not in C. elegans and yeast. The D. melanogaster homolog, Cindr, only share 30% of homology with CD2AP (Blast Alignment tool https://blast.ncbi.nlm.nih.gov/Blast.cgi).

Mutations

101 missense substitutions plus 8 nonsense substitutions mapping in the coding region of CD2AP gene have been annotated in the Cosmic Database (Forbes et al. 2017) from tumorigenic tissues analysis (positions involved are shown as red letters in Figure 5) , however none of them has been clearly associated with the tumorigenic tissue analysed. Mutation R612STOP was also found in one patient affected from focal segmental glomerulosclerosis (FSGS, see below) and it was shown that the mutation impairs gene expression (Lowik et al. 2007). 32 synonymous mutations have also been reported in Cosmic (not shown in the figure).

Two mutations of the splicing acceptor site of exon seven, that result in a lower expression of the gene, have been reported from FSGS patients (Kim et al. 2003).

Implicated in

CD2AP gene is clearly implicated in Focal Segmental Glomerulosclerosis, and its polymorphisms have been associated with Alzheimer Disease. Instead, although it was shown to interact with many proteins involved in signal transduction and with p53, its involvement in the development of cancer is not well documented. According to data provided by Human Protein Atlas and obtained with antibodies against CD2AP, the protein is strongly expressed in pancreatic, gastric, colorectal, prostate, breast, ovarian and urothelial cancers and in it is used as a prognostic marker in pancreatic cancer and urothelial cancer. It is a marker for plasmacytoid dendritic cell neoplasm too (see below).

It has been proposed as a promising target for ErbB2 overexpressing tumors since it participates in the inhibition of activated ErbB2 (Mineghishi et al. 2013).

Focal Segmental Glomerulosclerosis

Mice CD2AP-/- die by 6-7 weeks of age for severe kidney pathology and proteinuria. In particular they showed glomerular injury with loss of podocyte foot processes and slit diaphragm integrity and with extracellular deposits of fibronectin and collagen (Shih et al. 1999). At molecular level, CD2AP immunoprecipitates with nephrin, the major component of the slit diaphragm (Shih et al. 1999 ; Shih et al. 2001), suggesting that the pathology arises from a deregulation of actin polymerisation in foot processes and loss of connection between nephrin and the actin cytoscheleton. Mice with CD2AP haploinsufficiency develop glomerular defects similar to the human focal segmental glomerulosclerosis disease, and in human patients mutations in CD2AP coding sequence or in the splicing regulatory regions were associated with the pathology (Kim et al. 2003; Lowik et al. 2007; Chen & Liapis, 2015)

Disease

Focal Segmental Glomerulosclerosis (FSGS) is a progressive glomerular disease characterized by localised sclerotic lesions (only some of the glomeruli are involved and only a part of them is affected) and podocyte loss. Glomerulus is a specialized apparatus to filter blood in kidney and the filtration barrier is constituted by endothelial cells, glomerular basement membrane and foot processes called podocytes (Shih et al. 1999). In FSGS patients, non functional podocytes are detached from the glomerular basement membrane which results in severe nephrosis with proteinuria and glomerulosclerosis (Nagata et al, 2017). Extracellular deposits of collagens and other fibrous proteins are also observed in affected glomeruli. 30% of all nephrotic syndromes in adults are due to FSGS with elevated costs to health care (Nagata et al. 2017).

Alzheimer Disease

CD2AP polymorphisms were found associated with late onset Alzheimer's disease (LOAD, see below) in two genome-wide association studies (Hollingworth et al. 2011; Naj et al. 2011). In particular, SNPs rs9296559 and rs9349407 were found associated with increased LOAD risk. Very little is known about how the protein may affect the AD risk and what function it exerts in brain. Its role in vescicular transport to the lysosome and in the formation of synapses may be relevant to its involvment (Karch & Goate, 2015). It was recently shown that CD2AP knock-down mice have a compromised blood-brain barrier with increased permeability, and the function of CD2AP in maintaining blood barrier integrity was proposed to be related with the higher predisposition to the disease (Cochran et al. 2015). It was also shown that the deletion of CD2AP determine a decrease in Aβ levels (Liao et al. 2015).

Disease

The Alzheimer's Disease (AD) is a complex multifactorial neuronal disease characterized by extensive neuronal loss due to extracellular deposition of beta amyloid plaques (Aβ) and intracellular development of neurofibrillary tangles (NTF). AD is classified in late-onset AD (LOAD), that occurs in elderly people and is one of the most common cause of dementia, and early-onset AD (EOAD) when the disease occurs in young people (Rosenthal and Kamboh et al. 2014).

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

CD2AP has been proposed as a specific marker to diagnostic BPDCN among other hematological neoplastic disorders because it is expressed at high level in both normal and transformed pDC cells. The molecular diagnosis of myeloproliferative disorders is based on markers such as CD4 or CD56 that are expressed in different cell types. Instead CD2AP, unless it was originally cloned in T cells, was shown to strongly react to specific antibodies only in pDC cells, suggesting that it may represent an interesting marker for pDC derived malignancies (Marafioti et al. 2008; Rizvi et al. 2012).

Disease

Blastic Plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematological malignancy involving plasmacytoid dendritic cells (pDC), that was classified in 2008 under acute myeloid leukemia (Riaz et al. 2014). It represents only 0.44% of the hematological malignancies however patients have poor outcomes, with median survival ranging from 12 to 16 months. Most patients present cutaneous lesions, while bone marrow, peripheral blood and lymph nodes are also involved (Riaz et al. 2014).

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