Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL INIST-CNRS

Gene Section
Review

CPM (carboxypeptidase M)

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Published in Atlas Database: July 2013

Online updated version : http://AtlasGeneticsOncology.org/Genes/CPMID51348ch12q15.html
DOI: 10.4267/2042/53079

Abstract

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

Identity

HGNC (Hugo): CPM

Location: 12q15

Note

CPM was mapped to chromosome 12q13-qter by chromosome assignment in somatic cell hybrids. Fluorescent in situ hybridisation located CPM distal to D12S375 and proximal to the D12S8 microsatellite markers. After completion of the reference sequence of chromosome 12, CPM was located in 12q14.3.

DNA/RNA

Description

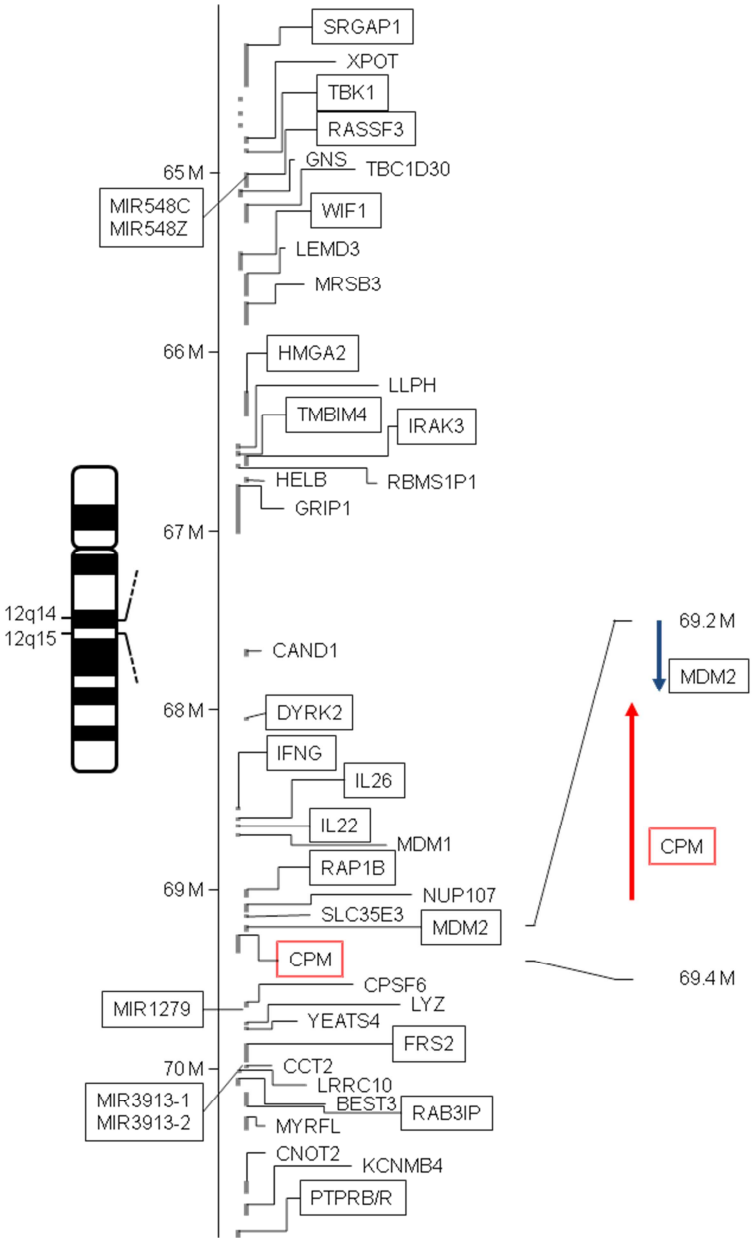
The intron/exon structure of the CPM gene was determined from screening human kidney and placenta cDNA libraries (Bektas et al., 2001). The CPM gene contains 11 exons and spans 112.5 kb. The coding region is located in exons 2-9.

Transcription

Transcription is initiated from multiple transcription start sites clustered in two distinct regions that are flanked by two independent, functional promoters. The proximal promoter (~ 350 bp upstream of the coding region) is characterized by the presence of CpG islands, a classical TATA box (25 bp upstream of the major initiation site), an initiator sequence (Inr) around the TATA box, and a putative downstream promoter element (DPE). A number of potential transcription factor binding sites were identified in the 5' region flanking the proximal initiation sites, including a vitamin D3 responsive element and Sp1. The distal promoter (~ 30 kb upstream of the coding region) differs from the proximal promoter in that it mainly consists of repetitive elements and lacks common promoter elements. Inr sequences and a putative DPE were found together with putative Ets, C/EBP, Oct-1, AP-1 and NF-kB sites. Basal transcriptional activity of the proximal and distal promoter regions was cell type-dependent pointing towards a tissue-specific expression of CPM. Transcriptional initiation from the distal start site appeared less common (Li et al., 2002).

Apart from the full length CPM mRNA, three alternatively splice variants of CPM were detected. Missing exon 3 and/or 5, these products lead to a premature stop codon and possibly to the generation of truncated CPM proteins (Pessoa et al., 2002). Several bands ranging from about 2.4 kb to 15 kb were detected in Northern blots of CPM mRNA from various human tissues, with a major band at 4.2 kb (Tan et al., 1989; Nagae et al., 1993). Heterogeneity in the CPM mRNA was observed, principally ensuing from the 3' region. Together with alternative splicing of three separate exons (1, 1A and 1B), the utilization of various transcription start sites contributes to heterogeneity at the 5' region. 5' and 3' heterogeneity however did not change the CPM protein sequence (Li et al., 2002).

The Ensemble database (viewed June 2013) lists 13 transcripts for CPM of which 3 are coding for the full-length protein and 4 are coding for shorter forms. Of the remainder, there is 1 non-coding processed transcript, 3 are labelled non-sense mediated decay and 2 have a retained intron.



The 12q14-15 chromosomal region contains some known oncogenes and genes involved in cell cycle control, differentiation, receptor signalling and cytokine biology, as well as some miRNAs. The names of those genes are placed in boxes. The approximate length and positions of the genes on the + (right) and - (left) strands are depicted as grey blocks. Pseudogenes and uncharacterized loci are not shown. The information was retrieved from the Gene data bank (NCBI). The expanded region illustrates how CPM is located just downstream of the tumor biomarker and oncogene MDM2 on the complementary strand.

Protein

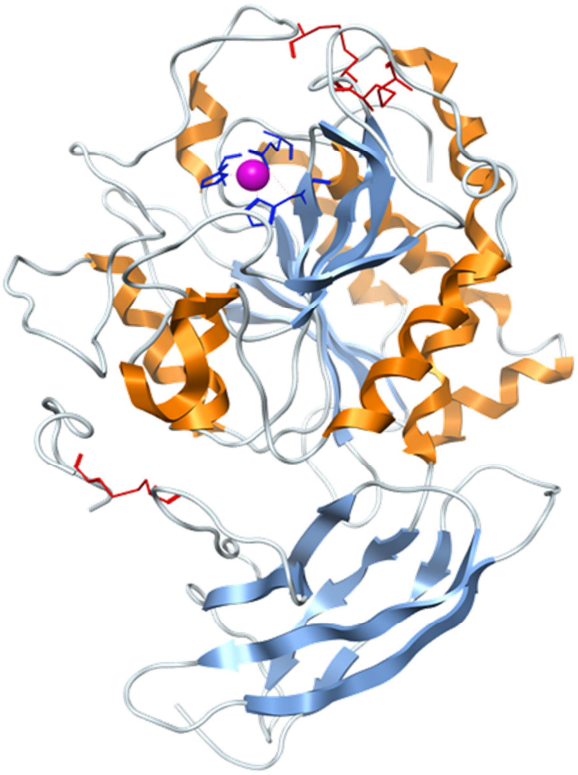
Note

CPM is a basic metallo-carboxypeptidase. The NC-IUBMB code assigned to CPM is EC 3.4.17.12. In the MEROPS database CPM belongs to clan MC, family M14, subfamily B.

Description

The CPM structure consists of two domains, the classical carboxypeptidase domain and the C-terminal domain. The spherical carboxypeptidase domain (first 295 amino acids) is arranged in a typical α/β hydrolase fold and carries the catalytic site. A funnel-shaped entrance gives access to the active site. The C-terminal domain (86 residues) consists of a seven-stranded β-barrel and resembles the plasma protein transthyretin/prealbumin (Reverter et al., 2004). CPM is attached to the outer membrane by a glycosyl-phosphatidyl-inositol (GPI) anchor located at the C-terminus (Deddish et al., 1990).

The coding region of CPM is depicted by alternating blue en black letters to highlight the exon junctions (exon 2 to 9). The translated amino acid sequence is shown above the nucleotide sequence. The secretion signal peptide is shown in italics, the Zn^{2+} ligands in bold. Amino acids located in α-helices are highlighted in red and the β-sheets in yellow.



The 3D-structure of CPM was determined by X-ray crystallography (Reverter et al., 2004). It is shown in this figure as a ribbon drawing with α-helices and β-strands respectively shown in orange and blue, and the residual chain in grey. The catalytic carboxypeptidase domain is shown on top and the cup-shaped C-terminal domain on bottom of the structure. The disordered linker connecting the C-terminal domain and the GPI-anchoring segment is not visible in the structure. The catalytic zinc ion is depicted as a pink sphere, whereas the three zinc ligands are shown in dark blue. The cysteine residues involved in disulfide bridges are depicted in red. PDB-code: 1UWY. Drawn with MOE 2009.10.

Expression

CPM is widely expressed in the different organs, but expression levels vary and it is only expressed by certain cell types. Expression was studied in some detail in the lung, in the female reproductive system, and in the kidney.

In the lung CPM is a marker of type I pulmonary alveolar epithelial cells (Nagae et al., 1993).

CPM expression is locally regulated during the different phases of the menstrual cycle, endometrial maturation and implantation. Overall, CPM is likely involved in the control of proliferation and functional differentiation of many cellular system within the female reproductive system (Yoshioka et al., 1998; Fujiwara et al., 1999; Fujiwara et al., 2005; Nishioka et al., 2003).

In the kidney, CPM expression is high at the apical surface of proximal and distal tubuli and the thick ascending limbs of the loop of Henle. Soluble CPM was detected in the tubular lumina. CPM was also expressed at the parietal epithelium beneath the Bowman's basement membrane and in glomerular mesangial cells (Denis et al., 2013).

In the central and peripheral nervous systems CPM expression is associated with myelin and myelin-forming cells (Nagae et al., 1992; Kang et al., 2011).

A soluble form of CPM, lacking the membrane anchor, was found in urine, amnion and seminal fluid and in broncho-alveolar lavage fluid.

CPM was at least twice discovered as the target of antibodies raised against cell surface antigens: once on mature macrophages and once on the human B-lineage acute lymphoblastic leukemia cell line Pre ALP. Expression of CPM was reported in late stages of myeloid cell development and in particular stages of B lymphocyte development, i.e. committed precursors and germinal center cells. The expression of CPM in different stages of hematopoietic stem cell differentiation was comprehensively reviewed (Deiteren et al., 2009; Denis et al., 2012).

The reader is referred to the publications listed in these reviews; some highlights are repeated below. CPM expression was evident in hematopoietic progenitors (CFU-GM, CFU-Meg and BFU-E). The surface expression of CPM was upregulated during ex vivo expansion of cord blood $CD34^+$ stem cells to CFU-GM and CFU-Meg (Marquez-Curtis et al., 2008).

CPM expression is weak on freshly isolated blood monocytes. In contrast to macrophages maturated in vitro, macrophages of body fluids (pleural, peritoneal and alveolar) and tissue macrophages in situ express only low levels of CPM. In defined pathological conditions, some exudate macrophages did express considerable levels of CPM, e.g. alveolar macrophages. Inflammatory macrophages in situ were CPM negative except those associated with rejected renal allografts (Andreesen et al., 1988). CPM is expressed selectively in tissue granulomas and foam cells (Tsakiris et al., 2012) and on tumor associated macrophages (Denis et al., 2013; Tsakiris et al., 2008). Peripheral granulocytes all possessed CPM surface expression. The expression of CPM on several immortalized cell lines was reviewed (Denis and Lambeir, 2013). THP-1 cells, that are close to the mature macrophage, express high levels of CPM.

CPM expression was observed early in mesenchymal differentiation, i.e. in mesenchymal stem cells (MSC) and CFU-F progenitor cells (Marques-Curtis et al., 2008). CPM was upregulated in early and late stages of bone marrow or adipose tissue derived MSC differentiation into the osteogenic, chondrogenic and adipogenic lineages (Lui at al., 2007). CPM expression was greatly increased in early and late stadia of MSC differentiation into the adipocyte and osteogenic lineage compared to the chondrogenic lineage.

Differential transcript analysis identified CPM as a surface marker of heterogeneous peripheral blood-derived smooth muscle progenitor cells (Wang et al., 2012).

Localisation

The GPI anchor directs CPM to lipid rafts in the outer membrane of cells, such as macrophages. In the kidney CPM is found in the lumen and on the luminal side of epithelial cells in proximal and distal tubules.
Intracellular CPM immunoreactivity was also observed (Denis et al., 2013).

Function

The function of CPM in the different cells and organs is not well understood. The expression pattern of CPM in specific cells in the different systems suggests roles in development and/or differentiation.
On the one hand CPM may be important for the recycling of amino acids or the local release of arginine.
On the other hand, CPM may function by modulating signaling cascades of its substrates (Deiteren et al., 2009). The classical substrates for CPM are anaphylatoxins and kinins, produced during inflammation. However, many other potential substrates have been identified, including hormones, chemokines and growth factors. A functional association of CPM with the bradykinin-1 receptor (a G-protein coupled receptor) has been demonstrated (Zhang et al., 2008; Zhang et al., 2011). CPM enhances bradykinin-1 receptor signaling on two levels: (1) by converting bradykinin to a better agonist (des-arg-bradykinin), and (2) by altering the conformation of the receptor on the membrane. Therefore, one can speculate that the functions of CPM are linked to the functions of bradykinin, e.g. release of inflammatory cytokines, vasodilation and pain.

Homology

CPM has significant homology with the M14B subfamily members CPN, CPH/E, CPZ, CPD, CPX-1, CPX-2 and adipocyte enhancer-binding protein 1 (AEBP1).

Mutations

Note
In the NCBI databases a number of variants can be found in the CPM genomic sequence that were reported in association studies related to blood pressure regulation and heart function (Vasan et al., 2007) and asthma and smoking (Litonjua et al., 2008; Pan et al., 2010). However the clinical relevance of these findings is unknown.

Implicated in

Liposarcoma

Note
CPM gene amplification was detected in well-differentiated liposarcomas but not in atypical lipomatous tumors. Using FISH and chromogenic in situ hybridization, amplification of the CPM gene was shown to discriminate well-differentiated liposarcoma from lipomas (Erickson-Johnson et al., 2009). These well-differentiated liposarcomas typically show telomeric associations, supernumerary ring chromosomes, and giant rod marker chromosomes.
The abnormal chromosomes consist of amplified genomic sequences derived from chromosome bands 12q13-15 and comprise several genes, including the MDM2 gene.
MDM2/CPM amplification was proposed as a tool for classification of lipomatous tumors and evaluation of the impact of surgical procedures on the risk of local recurrence (Zhang et al., 2010).

Clear cell lung carcinoma

Note
In lung adenocarcinoma, CPM and epidermal growth factor receptor (EGFR) protein expression appeared to be heterogeneous. CPM and EGFR were mainly restricted to tumor cell membranes. CPM expression was not limited to a specific histotype, and did not correlate with tumor grade nor stage.
CPM negatively correlated with disease survival (Tsakiris et al., 2008). 80% of the CPM-positive adenocarcinoma were EGFR-positive. The coexistence of CPM and EGFR strongly predicted a poor outcome.
An unfavourable role for CPM-EGFR co-expression was suggested in early tumor stages. Two cases of CPM^--$EGFR^+$ primary lung adenocarcinoma became CPM^+-$EGFR^+$ when metastasized to the brain, suggesting CPM is an inducible protein.

Renal cell carcinoma

Note
Tumor cells of renal cell carcinoma subtypes lose CPM expression upon dedifferentiation. In a study of 7 clear cell renal carcinoma specimens and 1 chromophobe renal cell carcinoma CPM was colocalized with CD31 (endothelium), vimentin (tumor marker) and CD68 (macrophages) (Denis et al., 2013). Denis et al., 2013 also studied coexpression of CPM and EGFR by immunohistochemistry using a tissue microarray containing 104 cases of various renal tumors and diseased renal tissue.
An association between the CPM histology-score (H-score) and tumor grade was observed for clear cell carcinoma. Cluster analysis of the CPM and EGFR H-scores in this study showed coexisting high scores for CPM and EGFR only for papillary renal carcinoma.
In papillary renal carcinoma expression of CPM is upregulated along with tumoral dedifferentiation. Molecular genetic analysis of papillary renal cell tumors revealed loss of the chromosome Y markers together with trisomy of chromosomes 3q, 7, 8, 12, 16, 17 and 20. Trisomy of 12, 16 and 20 possibly are related to tumor progression. Allelic duplications were detected at the 12q12-14 chromosomal regions (to which the CPM gene maps), among others.

Adenocarcinoma

Note

Transcript analysis indicated that adenocarcinoma cells are positive for CPM (Ramaswamy et al., 2003).

Endometrium and myometrium tumor tissue

Note

Transcript analysis indicated an upregulation of CPM compared to healthy tissue (Pessoa et al., 2002).

Invasive ductal breast carcinoma

Note

Transcript analysis indicated an upregulation of CPM compared to healthy tissue (Overall et al., 2004).

Clear cell ovarian cancer

Note

Transcript analysis indicated an upregulation of CPM compared to healthy tissue (Schwartz et al., 2002).

Primary cutaneous squamous cell carcinoma

Note

Transcript analysis indicated an upregulation of CPM (Haider et al., 2006).

Soft tissue carcinomas (synovial sarcoma, gastrointestinal stromal tumors, dedifferentiated-pleomorphic liposarcomas)

Note

Transcript analysis indicated an upregulation of CPM (Francis et al., 2007).

Lung cancer

Note

CPM activity was increased in bronchoalveolar lavage fluid of lung cancer patients (Dragovic et al., 1995).

Rapidly growing hepatoma

Note

CPM activity was increased (Deddish et al., 1990).

Pancreatic ductal adenocarcinoma

Note

Transcript analysis indicated an upregulation of CPM (Johnson et al., 2006).

Small cell lung cancer

Note

Transcript analysis indicated a downregulation of CPM (Cohen et al., 1997).

Leukemic mantle cell lymphoma

Note

Transcript analysis indicated a downregulation of CPM (Rizzatti et al., 2005).

Primary breast cancer cells with complete response to therapy with gemcitabine, epirubicin and docetaxel

Note

Transcript analysis showed that these cells were positive for CPM (Thuerigen et al., 2006).

Breakpoints

Note

The chromosome 12q13-15 bands were associated with a variety of benign and malignant solid tumor types by cytogenetic studies. Among the benign tumors, uterine leiomyoma, pleomorphic adenoma of the salivary gland, and lipoma all cluster to the 12q13-15 chromosomal region, which is also involved in hemangiopericytoma, endometrial polyps, chondromatous tumors, pulmonary chondroid hamartoma, and in a number of cases of benign epithelial breast tumors, diffuse astrocytomas, and a giant-cell bone tumor. Recurrent aberrations in 12q13-15 also have been detected in malignancies such as myxoid liposarcoma, soft tissue clear-cell sarcoma, chronic idiopathic myelofibrosis, and primary diffuse large B cell lymphomas. Using directional chromosome walking and uterine leiomyoma-derived cell lines, a breakpoint hot spot region was found at 12q13-15 (named Uterine Leiomyoma Cluster Region on chromosome 12, ULCR12) (Schoenmakers et al., 1994). Another breakpoint cluster region of 1.7 Mb was detected on chromosome 12q15 comprising the breakpoints of uterine leiomyoma, lipoma, and salivary gland adenoma cells (Van de Ven et al., 1995). This multiple-aberration region contains essentially all breakpoints of chromosome 12 (Wanshura et al., 1995). CPM was localized in the 12q15 region at one of the chromosomal breakpoints in radiation-transformed epithelial breast cell lines. Complex translocations were detected at this breakpoint. Since these gene rearrangements could alter CPM gene expression, CPM likely represents a breast cancer-involved candidate gene (Unger et al., 2010). EST analysis identified CPM as a putative fusion gene resulting from chromosome rearrangement. The ChimerDB database contains one instance where CPM acts as the 5' partner in a fusion gene (C7ORF64 7q21.2) and two instances where it is the 3' fusion partner (CYP19A1 15q21.1 and KIAA1737 14q24.3).

The clinical consequences of these fusions are not known.

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This article should be referenced as such:

Lambeir AM. CPM (carboxypeptidase M). Atlas Genet Cytogenet Oncol Haematol. 2014; 18(2):82-89.