Gene Section

OPCML (opioid binding protein/cell adhesion molecule-like)

Artur Czekierdowski, Sylwia Czekierdowska

Ist Dept. of Gynecologic Oncology and Gynecology, Medical University in Lublin, Poland (AC, SC)

Published in Atlas Database: January 2009
Online updated version: http://AtlasGeneticsOncology.org/Genes/OPCMLID44423ch11q25.html
DOI: 10.4267/2042/44641
This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2009 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: OBCAM; OPCM
HGNC (Hugo): OPCML
Location: 11q25

Note: OPCML belongs to the IgLON family of immunoglobulin domain containing glycosylphosphatidylinositol (GPI)-anchored cell adhesion molecules, which includes OPCML, LSAMP, NEGR1 and HNT. The protein is localized in the plasma membrane and may have an accessory role in opioid receptor function.

DNA/RNA

Note
OPCML comprises 7 exons, spans approximately 600 kb and is transcribed from telomere to centromere. Sequence analysis of the OPCML promoter revealed a GC-rich region spanning 900 bp approximate 500 bp upstream of the translational start site.

Protein

Description
OPCML consisted of one half beta-sheets and one fourth alpha-helices. Hydropathy analysis suggested that hydrophobic and hydrophilic regions were evenly distributed along the sequence, but the NH2- and COOH-termini were hydrophobic. Hydrophobic moments and Fourier-transform amphipathic analyses further suggest that residues 23-30 and 83-93 were amphipathic beta-sheets. Structural elements include three, with the first and third being full C2 domains and the middle domain being a truncated C2 domain, and a GPI anchor. Protein is extensively glycosylated with six potential N-linked sites.

Expression
OPCML is highly expressed in the nervous system and involved in cell adhesion and cell-cell recognition. During the first postnatal week, protein is prominent within cerebral cortex, developing hippocampus, pyriform cortex, and the mitral cell layer of the olfactory bulb. At later ages, OPCML is expressed prominently within all regions of Ammon's horn and in the mitral cell layer of the olfactory bulb and the pyriform cortex. OPCML is localized preferentially to dendrites compared with somata and terminals of hypothalamic vasopressin-secreting magnocellular neurons. This localization indicates that protein is one of the dendrite-associated cell adhesion molecules. It is synthesized within the somata, attached to vasopressin neurosecretory granules via the glycosylphosphatidylinositol anchor, and transported to the dendrites. Moreover, the subcellular localization of OPCML is changed in an activity-dependent manner. Recently published data suggested that OPCML-v1 was widely expressed in all normal adult and fetal tissues except for placenta and peripheral blood mononuclear cells, though at varying levels (highly expressed in brain, kidney, spleen, stomach, trachea, testis, cervix, ovary and prostate, and weakly in lung, breast, and bone marrow). Compared to v1, OPCML-v2 displayed a more tissue-specific expression pattern in adult tissues, with expression absent or barely detectable in kidney, spleen, pancreas, breast, testis, lung, colon, liver, testis and bone marrow. In contrast to its expression in adult tissues, OPCML-v2 was expressed at moderate to high levels in all fetal tissues except for placenta.
**Function**

OPCML was originally isolated as a potential microtype opiate receptor. Subsequent studies have shown that the physiologic opiate receptors belong to the G-protein-coupled receptor family, however, they do not promote direct binding of opioids when transfected into heterologous cells. IgLONs have been suggested to play an important role in cell adhesion and cell-cell recognition, through both homo- and heterophilic interactions within the family. Recently, it has been proposed that IgLONs function mainly as heterodimers called Diglons. OPCML may contribute to the diversity at the surface of different populations of neurons during development. Some latest evidences also suggest that OPCML is a synaptic cell adhesion molecule concerning synaptogenesis and its surface localization is dynamically regulated in response to neuronal activity. Recently, it has been shown that IgLONs are expressed outside the nervous system, and OPCML might act as a tumor suppressor. As a cell adhesion molecule, OPCML comprises several protein-protein interaction domains, commonly found in cell surface-adshesion and receptor molecules. Through these domains, OPCML may bind directly to growth promoting or inhibitory molecules and modulate their functions in tumor cells.

New findings suggested that OPCML is an excellent candidate for tumor suppressor gene (TSG). OPCML is frequently somatically inactivated in cancer by allele loss and by CpG island methylation. OPCML has functional characteristics consistent with TSG properties both in vitro and in vivo. It has been found existence somatic missense mutation in individual with epithelial ovarian cancer and it shows clear evidence of loss of function. Another data showed that OPCML gene promoter methylation may play an important role in the carcinogenesis of cervical and lung carcinoma. OPCML probably functions as a tumor suppressor through interacting with other IgLONs to form heterodimeric complex involved in signal transduction. Among the IgLON family, OPCML was the first member reported to possess tumor suppressor functions in epithelial ovarian cancer, being frequently silenced genetically and epigenetically at the early step of ovarian carcinogenesis. This inactivation is due to its promoter methylation, which further impairs its response to environmental stresses. Loss of OPCML reduces the intercellular adhesion and heterodimeric complex formation and thus impairs the corresponding signaling pathways, thereby promoting the progress of carcinogenesis. Latest evidences of Cui et al (2008) suggested that OPCML is frequently inactivated epigenetically in multiple tumor cell line including nasopharyngeal, esophageal, lung, gastric, hepatocellular, colorectal, breast, cervical and prostate carcinomas. Authors showed that OPCML is a stress-responsive and p53-regulated gene, with the response abrogated when the promoter becomes methylated.

Ectopic expression of OPCML in tumor cell lines with endogenous silencing led to strong inhibition of cell colony formation, dramatic anchorage-dependent and - independent growth inhibition demonstrating that OPCML acts as a broad tumor suppressor. The role of OPCML in DNA damage repair, apoptosis and cell cycle arrest with respect to stress response remains to be further investigated.

**Homology**

Two alternative splice transcripts of OPCML, variant 1 (v1) and variant 2 (v2), were previously identified in human, which differ only in their 59 exons but encode an identical mature protein. Among the four IgLON family members, OPCML shares the highest homology to HNT that lies approximately 80 kb centromeric to OPCML in the opposite orientation. Notably, the coding region in exon 1 of OPCML-v1 and HNT is identical, and so is the exon 2 except for only several bases. The first Ig domains of these two proteins share 92% identity, while the second and third Ig domains share 70% and 66% identity, respectively. This raises the possibility that OPCML and HNT may originate from the same ancestor by gene conversion during evolution.

**Implicated in**

**Epithelial ovarian cancer (EOC)**

**Oncogenesis**

OPCML is frequently somatically inactivated in EOC by allele loss and by CpG island methylation (Sellar et al., 2003).

Hypermethylation of OPCML was not correlated to FIGO stage, however, in 80% of cases with methylated OPCML early clinical stage was also present. Tumor grading and histological type had no significant influence on the presence of hypermethylation of OPCML gene. In a group of OPCML mRNA-negative tumors there were 75% of cases with hypermethylated exon of OPCML and the correlation between these variables was statistically significant. No promoter hypermethylation of the studied gene was found in normal ovaries (Czekierdowski et al., 2006).

Methylation-sensitive PCR analysis showed that the OPCML promoter was hypermethylated in RAS-transformed human ovarian epithelial cells (T29H) and that treatment with the DNA methyltransferase inhibitor 5'-aza-2'-deoxycytidine promoted demethylation of the OPCML promoter and restored OPCML expression in T29H cells. Suppression of oncogenic RAS activity by stable siRNA specific for HRAS(V12) led to the demethylation and re-expression of OPCML in T29H cells, demonstrating that oncogenic RAS activity is directly responsible for the observed OPCML promoter hypermethylation and epigenetic gene silencing of OPCML. RAS signaling pathway may play an important role in epigenetic
inactivation of OPCML in human epithelial ovarian cancer (Mei et al., 2006).
Expression of OPCML mRNA in ovarian epithelial carcinoma was significantly lower than those of normal and benign tumors. Methylation were detected in 44.4% of cancer cells promoter, while 0% in normal ovarian tissue and benign ovarian tumors. The ratio of methylation of ovarian epithelial carcinoma was significantly higher than those of normal and benign tumors (Zhang et al., 2006). The relationship between gene expression and promoter methylation was significantly correlated (OPCML expression in ovarian serous carcinomas was significantly higher than in ovarian adenomas and normal tissues. CpG island methylation and LOH are probably two mechanisms of OPCML inactivation. LOH at D11S4085 was also correlated with loss of OPCML expression. The LOH rate at D11S4085 in carcinomas was significantly higher than that for adenomas and normal tissues. Abnormal methylation of OPCML was found in 53.4% of the carcinomas, while in none of the adenomas or normal tissues (Chen et al., 2007).

**Invasive cervical carcinoma**

**Oncogenesis**

OPCML gene promoter methylation may play an important role in the carcinogenesis of cervical carcinoma and OPCML gene may be a cervical carcinoma-associated candidate tumor suppressor gene (Ye et al., 2008).

**Squamous cell lung carcinoma**

**Oncogenesis**

OPCML hypermethylation did not differ significantly based on gender, race, age or tumor stage, indicating their wide applicability as potential lung adenocarcinoma markers (Tsou et al., 2007).

**Gastric cancer**

**Oncogenesis**

OPCML could play a key role in the tumorigenesis and metastasis of gastric cancer. The expression level of this gene was the highest in normal gastric epithelium, which was decreased in primary carcinoma, and further decreased in metastatic lymph nodes (Wang et al., 2007).

**Hepatocellular carcinoma**

**Oncogenesis**

Hypermethylation rates of OPCML was higher in HCC than in pericancer tissues (70.0% vs. 64.6%). Promoter methylation of OPCML gene may play an important role in hepatocarcinogenesis (Liu et al., 2006).

**Gliomas**

**Oncogenesis**

OPCML was significantly reduced or absent in 83% of brain tumours and all cell lines compared with nonneoplastic whole brain. Two OPCML splice variants have been identified in humans, termed alpha1 and alpha2, but the latter has not been demonstrated in human neural tissues. Hypermethylation of the alpha1 OPCML promoter, associated did not correlate with expression levels in the subset of brain tumours tested, implying transcription of OPCML from an alternative promoter or a different mechanism of down-regulation (Reed et al., 2007).

**Phaeochromocytoma**

**Oncogenesis**

OPCML was methylated in 12% of phaeochromocytomas (Margetts et al., 2008).

**References**


Shark KB, Lee NM. Cloning, sequencing and localization to chromosome 11 of a cDNA encoding a human opioid-binding cell adhesion molecule (OBCAM). Gene. 1995 Apr 3;155(2):213-7


Reed J, McNamee C, Rackstraw S, Jenkins J, Moss D, Diglons are heterodimeric proteins composed of IgLON subunits, and Diglon-CO inhibits neurite outgrowth from cerebellar granule cells. J Cell Sci. 2004 Aug 1;117(Pt 17):3961-73


Yamada M, Hashimoto T, Hayashi N, Higuchi M, Murakami A, Nakashima T, Maekawa S, Miyata S. Synaptic adhesion molecule OBCAM; synaptogenesis and dynamic internalization. Brain Res. 2007 Aug 24;1165:5-14


This article should be referenced as such: