EMP3 (epithelial membrane protein 3)

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Abstract

Epithelial membrane protein 3 (EMP3) has recently been proposed as a candidate tumor suppressor gene (TSG) for some kinds of solid tumors. EMP3 down-regulation has been explained by its epigenetic silencing through aberrant hypermethylation of the promoter region. EMP3 repression in cancer seems to be an organ-specific phenomenon, common in neuroblastoma and gliomas, relatively common in breast cancer, and rare in esophageal squamous cell carcinoma (ESCC). Among cancer-derived cell lines, it prevails in neuroblastoma, breast cancer and ESCC whereas it is rare in glioma, non-small cell lung carcinoma (NSCLC), gastric and colon cancer-derived cell lines. EMP3 expression level is associated with clinical prognosis in neuroblastoma, ESCC, NSCLC and upper urinary tract urothelial carcinoma. In contrast, EMP3 expression may be a novel marker of tumor aggressiveness in breast cancer whereas in gliomas, EMP3 repression by aberrant hypermethylation has a prognostic significance. In both tumor types, however, alternative mechanisms to the EMP3 epigenetic silencing may exist to explain EMP3 down-regulation. Moreover, EMP3 may be involved in the prostate cancer susceptibility.

Keywords

Epithelial membrane protein 3 (EMP3), tumor suppressor gene, solid tumors, promoter hypermethylation, prognosis.

Identity

Other names: YMP
HGNC (Hugo): EMP3
Location: 19q13.33
Local order
EMP3 is located centromeric to TMEM143 (transmembrane protein 143) and telomeric to CCDC114 (coiled-coil domain-containing protein 114).

Note

EMP3 is a hydrophobic membrane glycoprotein belonging to the PMP22 protein family. It displays a high degree of cross-species conservation in its nucleotide and protein sequence.
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DNA/RNA

Note
A human EMP3 cDNA was first identified by homology screening of databases (Ben-Porath and Benvenisty, 1996; Taylor and Suter, 1996). EMP3 belongs to the peripheral myelin protein 22-kDa (PMP22) gene family of small hydrophobic membrane glycoproteins (Taylor et al., 1995). It includes four closely related members (PMP22, EMP1, EMP2 and EMP3), as well as the additional and more distant member MP20. The amino acid sequence homology with PMP22, EMP1, EMP2 and MP20 is 41, 33, 38 and 23%, respectively, with the highest homology in the transmembrane domains (TMDs). The genomic structure, as well as the putative four TMD structure (included a PMP22 Claudin domain) are highly conserved among family members.

Functionally, the PMP22 gene family may control cell proliferation, cell differentiation and cell death. Remarkable, mutations in the PMP22 gene are responsible for various hereditary peripheral neuropathies in both humans and mice (Leal et al., 2001).

The human EMP3 gene maps on chromosome 19q13.33 (Lieher et al., 1999). The homologous gene in mouse maps on chromosome 7 (Ben-Porath et al., 1998).

Description
The genomic size of the human EMP3 gene is of 5.183 Kb, localized from 48325372 to 48330553. The 5'-UTR region contains a CpG island (62 CpG dimers) localized around the transcription start site (from -13 to +241 bp) (GenBank reference sequence NM_001425) (Alaminos et al., 2005). Regulatory transcription factor binding sites in the promoter region are COUP-TF1, STAT1, Bach2, Rel4, HNF-4alpha1, E47, AREB6, RORalpha1, HEN1 and COUP-TF.

Transcription
The gene is composed of five exons, including a non-coding exon 1, and produces at least nine different alternative splicing isoforms.

Pseudogene
No known pseudogenes.

Protein
EMP3 is a 163-amino acid membrane glycoprotein.

Description
EMP3 belongs to the PMP22 protein family and shares with its members structural and functional homologies.

Expression
Prominently expressed in fetal lung, liver and kidney, but relatively weakly expressed in both fetal and adult brain. In adult, it is ubiquitarily expressed in various normal tissues including lung, liver, ovary, small intenstine, colon, thymus, kidney, pancreas, heart and placenta with the highest expression in peripheral blood leukocytes (Taylor and Suter, 1996).

Localisation
Localised in the cell-membrane and cytoplasm.

Function
The function of the EMP3 protein is largely unknown but it may be involved in the following physiological processes.

On the basis of its sequence similarity to EMP1, it may be involved in the regulation of cell proliferation (Bolin et al., 1997).

The higher expression levels in fetal brain, lung and kidney compared to the respective adult counterparts suggest a role in the developmental regulation, especially in neuronal development (Bolin et al., 1997).
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Schematic view of the predicted structure of the multi-pass human EMP3 protein in a lipid bilayer. The Y-shape symbol indicates the putative N-linked carbohydrate sites in the first extracellular loop at Asn47 and Asn56 residues. The four hydrophobic TMDs (from 4 to 24, 66 to 86, 100 to 120 and 139 to 159 amino acid residues) and the PMP22 Claudin domain (from 20 to 156 residues) are shown with respect to the intracellular and extracellular sides of the membrane (Jetten and Suter, 2000). The molecular weight is of 18.429 kDa.

It may control the regulation of cell growth, differentiation and death, since its overexpression results in cell blebbing in embryonic kidney cell cultures and in the activation of the apoptosis pathway (Wilson et al., 2002).

In peripheral nervous system, it may regulate Schwann cell proliferation after injury and cell-cell interactions in active myelination (Bolin et al., 1997).

It may have possible roles in hematopoietic system (Bolin et al., 1997).

**Homology**

Comparative sequence analysis revealed the remarkable conservation of the EMP3 primary sequence. The EMP3 gene is present in the common ancestor of chordates and it is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, zebrafish and frog.

The PMP22 gene family probably evolved as result of a chromosome duplication event and divergence (Ben-Porath et al., 1998). Paralogs are PMP22, EMP1 and EMP2. Seventy-four organisms have orthologues with the human EMP3 gene.

**Mutations**

**Note**

Neither causative nor functional mutations reported. Eighteen human genomic variants from 12 studies described, three of which (nsv531627, nsv531628 and nsv531629, all copy number gains) with pathogenic clinical significance since associated to global developmental delay and seizure (Miller et al., 2010; Kaminsky et al., 2011).

In mouse, a single nucleotide polymorphism (SNP) is responsible for the reciprocal H4 minor histocompatibility alloantigens in the MHC-bound peptide derived from EMP3 and presented by the MHC class I molecule. The C>T nucleotide change results in the amino acid substitution from Thr (H4a, SGTVYIHL) to Ile (H4b, SGIVYIHL) in the minimal antigenic epitope SGIVYIHL (SYL8) derived from H4(b) (Yadav et al., 2003; Luedtke et al., 2003).

**Germinal**

No germinal mutations described.
**Somatic**


**Implicated in**

**Neuroblastoma / phaeochromocytoma**

By methylation-specific PCR (MS-PCR) and direct bisulphate DNA sequencing, EMP3 hypermethylation is common in both tumor tissue (24-68.4%) and neuroblastoma cell lines (33.3%). It occurs with concomitant downregulation of EMP3 protein expression in all clinical samples and in only 33.3% of neuroblastoma cell lines (Alaminos et al., 2005; Margets et al., 2008). EMP3 hypermethylation is associated with poor survival at two-year follow-up and with an high mortality rate (Alaminos et al., 2005).

In contrast, it is a rare event in sporadic (7.1%) and adult VHL-associated (6.1%) phaeochromocytomas (Margetts et al., 2008).

**Brain tumors / gliomas**

By MS-PCR, EMP3 hypermethylation is an early epigenetic event in gliomagenesis. It is common in pure (63%) and mixed (70%) oligodendroglial tumors in comparison to astrocytic ones (18%). It prevails in grade II (71.4%) upon grade III (44.7%) gliomas, and in secondary (89%) upon primary GBMs (17%) (Alaminos et al., 2005; Li et al., 2007; Kunitz et al., 2007; Mellai et al., 2013). Not found in GBM cell lines (Ernst et al., 2009).

Aberrant hypermethylation correlates with reduced mRNA expression and lack of EMP3 protein expression. It is strongly associated with IDH1/IDH2 somatic mutations in astrocytic and oligodendroglial tumors and inversely correlated with EGFR gene amplification. In oligodendrogliomas, it is also associated with loss of the 19q13.3 locus and with total 1p/19q co-deletion (Tews et al., 2006; Mellai et al., 2013), with prognostic significance on patient overall survival (Kunitz et al., 2007; Mellai et al., 2013).

The EMP3 gene belongs to the glioma CpG island methylator phenotype (G-CIMP) (Noushmehr et al., 2010), that identifies a distinct molecular glioma subclass, prevalent in low-grade tumors and associated with IDH1/2 mutations and with improved patient survival (Laffaire et al., 2011).

No tumor-specific mutations identified on 132 glioma patients, except for the SNPs rs4893 (p.Ile125Val, exon 5) and rs11671746 (3'-UTR) in four patients (Kunitz et al., 2007).

**Esophageal squamous cell carcinoma (ESCC)**

By MS-PCR, EMP3 hypermethylation is rare in tumor tissue (6%) but frequent in ESCC cell lines (75%), with an inverse correlation with mRNA expression levels (Fumoto et al., 2009a). Low EMP3 expression is associated with poor prognosis after recurrence, suggesting that EMP3 inactivation may confer an advantage for tumor growth only at late stage of disease.

**Breast cancer**

By RT-PCR, EMP3 mRNA expression is significantly higher in primary tumors than in normal breast tissue.

It correlates with the histologic grade III, lymph node metastasis and Her-2 expression in human mammary luminal epithelial cells (Mackey et al., 2003; Zhou et al., 2009). It may be a novel marker of tumor aggressiveness (Zhou et al., 2009).

By MS-PCR, EMP3 hypermethylation occurs occasionally in primary tumor tissue (36.5%) without association with mRNA expression levels. In breast cancer cell lines, EMP3 mRNA is frequently repressed in both invasive (70%) and non-invasive phenotype (75%). Promoter hypermethylation may explain mRNA repression in almost all the non-invasive phenotype and in only a part of the invasive phenotype (Evtimova et al., 2003).

**Non-small cell lung cancer (NSCLC)**

By Western blotting, EMP3 expression in tumor tissue is significantly lower than in normal lung tissue, correlates with the p-TNM stage and negatively with the proliferation index Ki-67. EMP3 may be a TSG at late stage of disease and a potential marker of prognosis in lung patients (Xue et al., 2013).

In lung cell lines, EMP3 is repressed with partial CpG hypermethylation in 11.1% of cases (Fumoto et al, 2009a).

**Upper urinary tract urothelial carcinoma**

At mRNA and protein level, EMP3 overexpression promotes in vitro tumor cell proliferation and migration by activation of the ErbB2-PI3K-AKT pathway. It suppresses cell adhesion. EMP3 and ErbB2 co-expression is the most important marker of
progression-free and metastasis-free patient survival (Wang et al., 2013).

**Prostate cancer**

By a case-control study in 275 multiplex sibships on candidate genes and genomic regions with linkage to tumor susceptibility and/or aggressiveness, the rs4893 variant displays a highly significant association, confirmed in a age-matched subsample. The EMP3 association, together with HPN: gene (19q11-q13.2), suggests the involvement of multiple genes within this genomic region in the prostate cancer susceptibility. The rs4893 allelic variant is significantly more frequent in prostate cancer patients compared to controls (Burmeister et al., 2004).

**Other malignancies**

By RT-PCR, EMP3 displays high mRNA expression in gastric and colon cancer-derived cell lines (Fumoto et al., 2009b).

**Keratoconus (KC)**

By RT-PCR, EMP3 is significantly upregulated (2.5-fold) in keratoconus patients compared to a reference control group (Nielsen et al., 2005). EMP3 may have a potential role in the epithelial changes of the disease in agreement with the finding of blebs on the surface of KC corneas (Pfister and Burstein, 1977).

**Breakpoints**

Unknown fusion proteins..

**To be noted**

No genetic variants in the regulatory or coding regions responsible for EMP3 repression in cancer-derived cell lines without EMP3 hypermethylation or for EMP3 overexpression in other cancer-derived cell lines. An exception is the finding of the rs4893 allelic variant in the Caucasian A549 NSCLC cell line (Fumoto et al., 2009a) within a panel of 45 representative cancer cell lines. A Japanese- or Asian-population specific haplotype of three SNPs (rs8102349, rs8355 and rs11665) in non-coding regions is reported without association with the EMP3 expression levels (Fumoto et al., 2009a).

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