Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

CD248 (CD248 molecule, endosialin)

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Published in Atlas Database: December 2008

Online updated version : http://AtlasGeneticsOncology.org/Genes/CD248ID968ch11q13.html
DOI: 10.4267/2042/44605

Identity

Other names: 2610111G01Rik; CD164L1; MGC119478; MGC119479; TEM1; endosialin

HGNC (Hugo): CD248

Location: 11q13.1

Note: The endosialin gene is localized on the minus strand.

DNA/RNA

Description

Endosialin was identified to be transcribed from a 2557 bp single-exon gene localized on chromosome 11q13 (Rettig et al., 1992; Christian et al., 2001), a region containing genes for a number of cell surface antigens (Rettig et al., 1992; Rettig and Old, 1989).

Transcription

The 2580 bp mRNA of Endosialin consist of a 17 bp 5' UTR, an ORF of 2274 bp (AF279142), and a 289 bp 3' UTR (Christian et al., 2001).

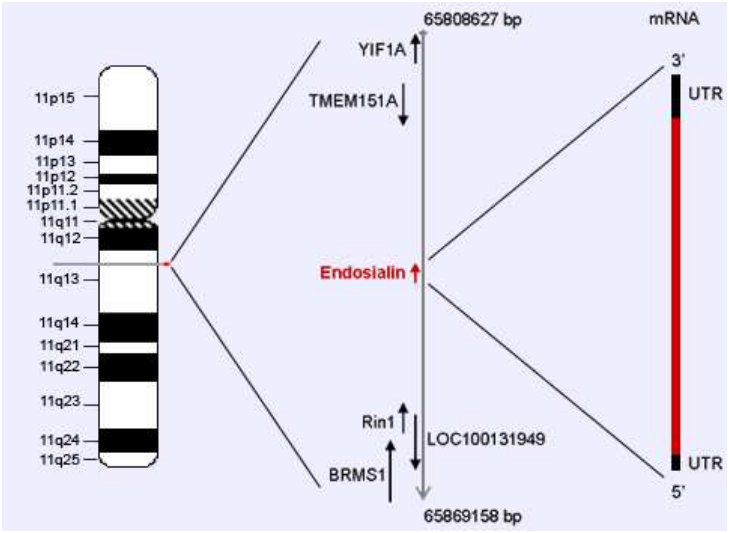
Pseudogene

No.

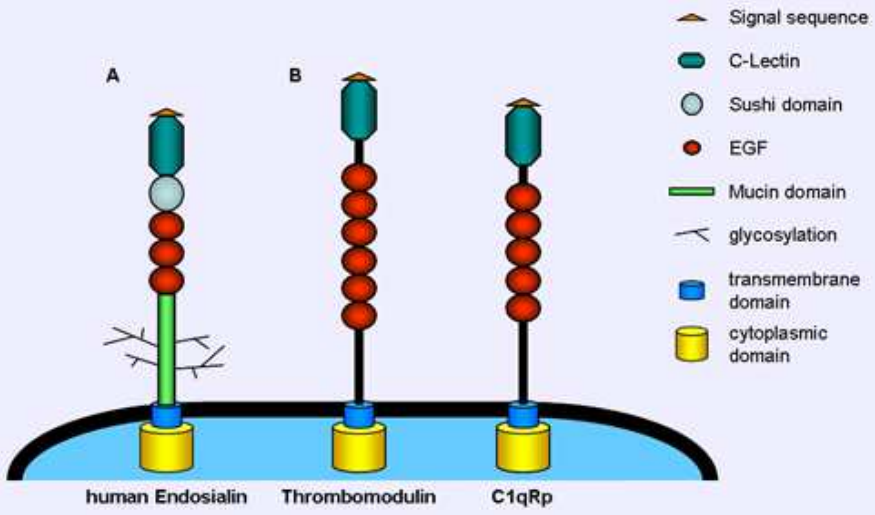
Protein

Note

Although Endosialin was originally described as tumor endothelial marker (Rettig et al., 1992; Seaman et al., 2007; St Croix et al., 2000), it turned out that Endosialin is a marker for activated mesenchymal cells, including myofibroblasts, pericytes and smooth muscle cells (SMC) (MacFadyen et al., 2005; Christian et al., 2008).



The endosialin gene is localized on the q arm of chromosome 11. The single-exon gene is transcribed from the minus strand (modified from Entrez Gene).



Structure of Endosialin and its homologues Thrombomodulin and C1qRp.
A: The extracellular domain of Endosialin consists of a signal sequence (orange triangle), a C-lectin like domain (dark green octagon), a Sushi/CCP/scr domain (grey circle), 3 EGF-like domains (red circles), and a negatively charged, O-glycosylated mucin-like domain (light green rectangle). The single transmembrane domain (blue cylinder) is followed by a short cytoplasmic tail (yellow cylinder).
B: The globular domains of Endosialin are homologue to thrombomodulin, containing 6 EGF repeats and the complement receptor C1qRp, demonstrating 5 EGF repeats.

Description

Endosialin is a 757 amino acid (aa) type I C-type lectin-like transmembrane protein (Christian et al., 2001). The core protein has a molecular weight of 95 kDa (Rettig et al., 1992; Christian et al., 2001). The distinct extracellular domain (aa 1-685) consists of a signal leader peptide (aa 1-20) and 5 globular domains followed by a mucin-like region (Figure A) (Christian et al., 2001). The single hydrophobic transmembrane domain spans the aa 686-706, followed by a short intracellular domain of 50 aa (aa 707-757). The 5 globular domains are well defined as C-type lectin-like domain (aa 20-157), a Sushi/CCP/scr like domain (aa 176-230) and 3 EGF repeats (aa 235-271, aa 274-311, aa 316-350). The EGF repeats 2 and 3 are predicted to have a Ca^{2+} binding function. In contrast, in the C-terminal part (aa 360-757) specific binding sites or catalytic domains were not identified (Christian et al., 2001; Carson-Walter et al., 2001). The glycosylation and sialic acid modification of more than 30 possible O-glycosylation sites, but only N-glycosylation Asn-Xaa-(Ser/Thr) consensus sequence on Asn-628 results in a shift of the molecular weight from 95 kDa to 165 kDa (Rettig et al., 1992; Christian et al., 2001). Additionally, a 120 kDa asialo form of Endosialin was identified (Rettig et al., 1992; Christian et al., 2001). A ~150 kDa form of Endosialin was detectable in the LA1-5s neuroblastoma cell supernatant (Rettig et al., 1992; Christian et al., 2001).

Expression

Endosialin is expressed in the majority of human carcinomas, sarcomas and neuroectodermal tumors (Rettig et al., 1992; St Croix et al., 2000; Brady et al., 2004; Huber et al., 2006; Madden et al., 2004; Davies et al., 2004; Rmali et al., 2005; Christian et al., 2008) as well as during physiological processes, such as corpus luteum formation and wound healing (Carson-Walter et al., 2001; St Croix et al., 2000). In contrast, Endosialin is not or weakly expressed in the mesenchymal compartment of corresponding normal human tissues (MacFadyen et al., 2007; MacFadyen et al., 2005; Carson-Walter et al., 2001). Endosialin-positive cells in the tumors were identified as myofibroblasts, tumor vessel-associated pericytes and smooth muscle cells (MacFadyen et al., 2005; Huber et al., 2006; Christian et al., 2008; MacFadyen et al., 2007; Bagley et al., 2008a; Virgintino et al., 2007; Simonavicius et al., 2008), although Endosialin was described as tumor endothelial marker (Rettig et al., 1992; St Croix et al., 2000). In addition, recent publications identified Endosialin expressing CD45+ VE-cadherin+ CD146+ CD34+ CD31+ TEM1+ Tem7+ vascular leukocytes (VLC) (Conejo-Garcia et al., 2005), as well as Endosialin-positive VEGFR 2+ CD31+ CD45- VE-cadherin+ endothelial precursor cells (EPC) (Bagley et al., 2008b). During neovascularization of the human fetal telencephalon, Endosialin is expressed by vessel-associated pericytes (Virgintino et al., 2007).

In vitro, Endosialin is expressed by fibroblasts, pericytes, smooth muscle cells and preadipocytes (Christian et al., 2008). Some neuroblastoma cell lines including LA1-5s, IMR-32 and SMS-SAN express Endosialin (Rettig et al., 1992).

The mouse homologue of Endosialin is strongly and heterogeneously expressed in almost all tissues during embryonic development (Opavsky et al., 2001; Rupp et al., 2006; MacFadyen et al., 2007). The expression is decreased in new-born mice and almost undetectable in

tissues of adult mice (Carson-Walter et al., 2001; MacFadyen et al., 2007; Lax et al., 2007; Rupp et al., 2006).

Localisation

Endosialin is localized on the cell surface (Christian et al., 2001; Christian et al., 2008; MacFadyen et al., 2005). Some staining of the Golgi can also be observed, since Endosialin is a Typ-I transmembrane protein (MacFadyen et al., 2005).

Function

A role of Endosialin in tumor progression and metastasis was demonstrated by experiments with Endosialin knock-out mice. In abdominal xenograft transplantations, tumor volume and the incidence of distant metastases were significantly reduced in knock-out mice compared to wild type mice, resulting in an increased survival rate of Endosialin-deficient mice (Nanda et al., 2006). Nevertheless, the molecular function of Endosialin is far from being understood. Recent publications demonstrated a role of Endosialin in the proliferation and migration of myofibroblasts (Christian et al., 2008). The tube-formation and migration of Endosialin expressing pericytes could be blocked by anti-Endosialin antibodies (Bagley et al., 2008a). Additionally, Endosialin overexpressing CHO cells demonstrated increased adhesion to fibronectin, migration though Matrigel and MMP-9 activity (Tomkowicz et al., 2007).
It is not clarified yet, how these functions of Endosialin result in tumor progression and metastasis. However, these findings indicate a role of Endosialin in early angiogenic stages (Bagley et al., 2008b) and vessel maturation, as well as a function of Endosialin in tumor stroma formation and reorganization of the tumor stroma including tumor blood vessels in tissues where areas of stable blood supply are in close proximity to regions of necrosis, hypoxia and excessive growth (Christian et al., 2001). Interestingly, recent findings described the induction of Endosialin expression by hypoxia, mediated by HIF-2a (Ohradanova et al., 2008).
Additionally, Endosialin functions as receptor for extracellular matrix components (Tomkowicz et al., 2007) and tumor cell expressed ligands like Mac-2 Binding Protein. The Endosialin-Mac-2 Binding Protein interaction results in a decreased adhesion between tumor cells and the surrounding myofibroblasts (Becker et al., 2008). However, this mechanism is not analyzed in detail.

Homology

Whereas the C terminal part of human Endosialin (aa 361-757) showed no sequence homology to other proteins (Christian et al., 2001), the globular N-terminal extracellular part (aa 30-360) demonstrated 39% homology to thrombomodulin precursor protein and 33% homology to the complement receptor C1qRp (Figure B) (Christian et al., 2001). Although there is only moderate sequence identity, cysteine residues predicted to form disulfide bridges and a WIGL consensus motive found in endocytosis regulating proteins (Dean et al., 2000; Nepomuceno et al., 1997) localized in the C-type lectin-like domain are conserved in all three proteins.
Mouse Endosialin (mEn) shows 77.5% homology to human Endosialin (Opavsky et al., 2001; Carson-Walter et al., 2001). Like its human counterpart, mEn is a 765 aa type I transmembrane protein with a 17 aa signal peptide, a C-type lectin-like domain (aa 22-157), a Sushi domain (aa 164-230) and 3 EGF-like repeats (aa 234-272, aa 274-311 and aa 315-351), followed by a sialomucin-like region, a single membrane spanning domain (22 aa), and a 51 aa long cytoplasmatic tail. mEn is also transcribed from a single copy, intron-less gene, located on mouse chromosome 19, a region homologue to human chromosome region 11q. The 82 kDa core protein has multiple O- glycosylation sites in the extracellular domain but only one predicted N-glycosylation site on position aa 636, resulting in a glycosylated protein of 92 kDa. Whereas the mucine-like domain of mEn (aa 478-610) and human Endosialin are hardly conserved, the transmembrane domains are identical and only 4 aa are substituted in the cytoplasmatic tails (Carson-Walter et al., 2001; Opavsky et al., 2001). Additionally, possible phosphorylation and N-myristoylation sites as well as a PDZ binding sequence (Carson-Walter et al., 2001) were identified in the intracellular domain, indicating an evolutionary conserved function between mouse and human Endosialin.

Mutations

Note

In one publication, a single base pare substitution at bp 717 (aa 239) was detected (Brady et al., 2004). A resulting change in the function of Endosialin caused by this mutation has not been referred yet.

Implicated in

Tumors

Disease

Endosialin is poorly detectable in normal tissues. In contrast, it is highly expressed in human carcinomas, sarcomas and neuroectodermal tumors (Rettig et al., 1992; Christian et al., 2008).

Brain tumors

Disease

Endosialin expression was detected in 40% of analyzed benign meningioma (grade I) and less invasive grade II astrocytoma specimens, whereas Endosialin is undetectable in normal brain. In higher grade brain tumors Endosialin expression was detectable in 67%

and 100% of grade III anaplastic astrocytoma and highly invasive glioblastoma multiforme specimens, respectively (Brady et al., 2004).

Prognosis

Endosialin expression correlates with high tumor grade and aggressive histological behavior in human brain tumors (Brady et al., 2004; Simonavicius et al., 2008).

Breast carcinomas

Disease

Endosialin is significantly upregulated in breast carcinoma samples of patients with nodal involvement, as well as in specimens of patients with recurrent disease or death caused by breast cancer (Davies et al., 2004).

Malignant melanoma

Disease

Endosialin expression was detectable in benign melanocytic nevi, cutaneous melanoma metastases, lymph node metastases, basal cell carcinomas and squamous cell carcinomas. Whereas Endosialin expression is restricted to scattered fibroblasts in the normal human skin, the Endosialin expression pattern is heterogeneous (reactive fibroblasts and vessel-like structures) in the different stages of malignant melanoma progression (Huber et al., 2006; Christian et al., 2008).

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This article should be referenced as such:

Becker R, Augustin HG. CD248 (CD248 molecule, endosialin). Atlas Genet Cytogenet Oncol Haematol. 2009; 13(11):799-803.