

Gene Section

Review

CD97 (CD97 molecule)

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Identity

Hugo: CD97

Other names: TM7LN1

Location: 19p13

DNA/RNA

Description

DNA contains 27.322 kb composed of 20 coding exons. Exons 1-2 encode the 5' untranslated region and the signal peptide, exons 3-7 the five EGF domains, exons 8-13 the extracellular stalk, exons 14-18 the seven-span transmembrane (TM7) domains and exons 19-20 the intracellular part and the 3' untranslated region.

Transcription

3247 bp mRNA transcribed in telomeric to centromeric

orientation; 2508 bp open reading frame. Human CD97 exists in three isoforms that result from alternative splicing of exons 5 and 6 and thus contain different numbers of EGF domains in the extracellular part of the molecule. The isoforms are designated as CD97 (EGF1,2,5), CD97 (EGF1,2,3,5) and CD97 (EGF1-5) in human.

Pseudogene

No pseudogenes reported.

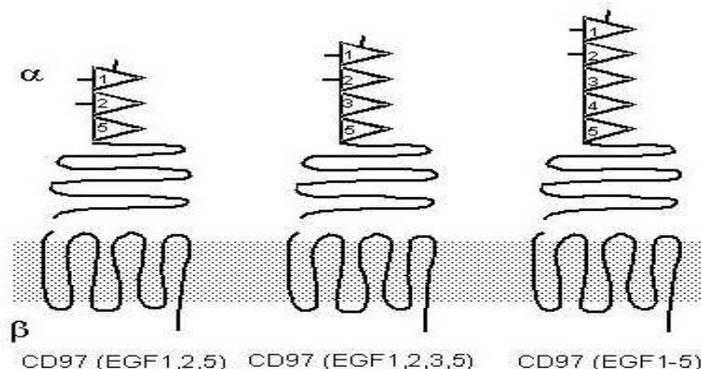
Protein

Description

CD97 belongs to the B family of G protein-coupled receptors (GPCRs). Subfamily B2 contains cell surface molecules with long extracellular N-termini (LNB-TM7) known also as adhesion class of heptahelical receptors.



Genomic organization of CD97 (drawn to scale), boxes represent exons.



Structure of CD97. Three isoforms containing 3, 4, or 5 EGF domains exist. N-glycosylation sites in the EGF domains are indicated.

CD97 is the founding member of a small subfamily within the adhesion class called EGF-TM7 family. All EGF-TM7 receptors (CD97, EMR1, EMR2, EMR3, EMR4) consist of extracellular tandemly arranged EGF domains, a stalk, the seven-span transmembrane (TM7) and a short intracellular part. They are expressed as heterodimers of a non-covalently bound alpha- and beta-chain resulting from intracellular autocatalytic cleavage at a conserved GPCR proteolytic site (GPS). The alpha-chain represents the extracellular region with the varying numbers of EGF domains and the main part of the stalk and the beta-chain consists of the stalk residue, the TM7 and intracellular part.

Three CD97 isoforms containing 3, 4 or 5 EGF domains are described. The mature full length proteins contain either 722, 766 or 815 amino acids (aa). After cleavage the (secretory) alpha-chains contain 420, 464, or 513 aa. The beta-chain theoretically contains 305 aa with a molecular weight of 34.3 kDa. However, immunoprecipitation of the beta-chain yielded a molecular weight of approximately 28 kDa. The discrepancy between the theoretical and actual molecular weight of the beta-chain is not yet clarified. Depending on the cell type and transformation status of the cell, CD97 is completely or partly N-glycosylated or naked. In normal muscle cells CD97 is not or only slightly N-glycosylated. The molecular weight for the respective naked alpha-chain of the various CD97 isoforms are 45.6, 50.5 and 55.8 kDa. In hematopoietic cells CD97 is N-glycosylated at the EGF domains resulting in molecular weights of 74-78, 80-82, and 86-89 kDa for the alpha-chains of the respective isoform. During tumor transformation CD97 may get N-glycosylated. Although the CD97 stalk contains many Ser or Thr residues the molecule seems not to be O-glycosylated.

Expression

Broad, not cell-type specific.

- Hematopoietic system: strong in peripheral blood myeloid cells and activated lymphocytes, moderately in subsets of tissue-derived leukocytes;
- Strong in smooth muscle cells (except for arterial vascular smooth muscle cells), skeletal muscle cells (stronger in slow-twitch fibers), heart muscle cells;
- Fat cells;
- Low in normal intestinal, thyroidal epithelial cells, moderately in duct cells of the pancreas, parotis gland and in bile duct cells of the liver.

Localisation

Usually at the cell membrane; soluble CD97 (sCD97) representing the CD97 alpha-chain in body fluids;
Skeletal muscle cells: at the sarcolemm and intracellularly in the sacroendoplasmatic reticulum (SR).

Function

CD97 has the ability to bind cellular and extracellular matrix ligands. The first two EGF domains of CD97 bind CD55 (decay accelerating factor). The fourth EGF domain of CD97 and thus only the longest CD97 isoform interacts with the glycosaminoglycan chondroitin sulfate B. CD97 binds to alpha5beta1 and alphavbeta3 integrins through interaction with the CD97 stalk region.

- Hematopoietic cells: Functional studies indicate a role of CD97 in leukocyte trafficking. CD97 antibodies block tissue localization of immune cells in vivo leading to impaired protection against bacteria and amelioration of autoimmune pathology.

- Tumor cells: In vitro CD97 increases single cell random motility and directed migration and invasion of tumor cells in 2D and 3D matrices. CD97 enhances proteolytic activity of matrix metalloproteinases (MMPs) and secretion of chemokines in an isoform-specific manner. CD97 (EGF 1,2,5) overexpression promotes tumor growth in scid mice.

The alpha-chain of the longest CD97 (EGF1-5) isoform (sCD97) enhances angiogenesis in in vivo tumor models.

- Muscle, fat, duct cells: function unknown.

Homology

H. sapiens: CD97

P. troglodytes: CD97

B. taurus: CD97

S. scrofa: CD97

C. lupus: CD97

M. musculus: CD97

R. norvegicus: CD97

Exists only in mammals.

Mutations

Note: unknown.

Implicated in

Note: Note for all tumors:

Antibodies to various epitopes of CD97 vary strongly in their staining pattern and cross-reactivity to other EGF-TM7 molecules. The first group of monoclonal antibodies, which includes BL-Ac/F2, VIM-3b and CLB-CD97/1, binds to the EGF domains of CD97 (CD97^{EGF}/ antibodies). These antibodies also detect EMR2, another member of the EGF-TM7 family. In most cases, this cross-reactivity will not influence the results obtained for CD97 staining in tumors since EMR2 is strongly restricted to myeloid cells. CD97 antibodies MEM-180 and CLB-CD97/3 bind to the stalk region of CD97 (CD97^{stalk}) and do not bind EMR2.

CD97^{EGF} epitope accessibility depends on cell type-specific N-glycosylation (see above). CD97^{EGF} antibodies detect only N-glycosylated CD97. During tumor transformation, not only the CD97 protein expression level but also the degree of CD97 N-glycosylation varies. Thus, the selection of the CD97 antibody strongly influences the result in immunohistological studies focused on the correlation between CD97 and histopathological subtypes, diagnosis, progression, or prognosis of tumors. CD97 in tumors is strongly regulated at the post-transcriptional level.

Thyroid cancer

Note: In normal thyroid tissue, no or low immunoreactivity of CD97 is found. In differentiated follicular thyroid carcinoma or papillary thyroid carcinoma, CD97 expression is also either lacking or low. Most undifferentiated anaplastic carcinomas reveal high CD97 presentation. CD97 is absent or only weakly present in patients with postoperative T1 tumors but increased greatly with the progression to postoperative T4 tumors. Until now, only antibodies against CD97 EGF domains (CD97^{EGF} antibodies, see above) have been used in studies of thyroid carcinomas.

Prognosis

Not determined.

Cytogenetics

Not determined.

Oncogenesis

Overexpression of CD97 might be important for the progression of thyroid cancer.

Colorectal cancer

Note: Normal human colorectal epithelium is slightly CD97-positive. Most colorectal carcinomas express CD97. The strongest staining for CD97 occurs in scattered tumor cells at the invasion front compared to cells located within solid tumor formations of the same tumor. Carcinomas with more strongly CD97-stained scattered tumor cells show a poorer clinical stage as well as increased lymph vessel invasion compared to cases with uniform CD97 staining.

Prognosis

Not determined.

Cytogenetics

Not determined.

Oncogenesis

Overexpression of CD97 might be important for invasion and metastasis of colorectal cancer.

Gastric cancer

Note: CD97 is present in normal parietal cells of

gastric mucosa. It is stronger expressed by most gastric carcinomas. Half of the tumors show scattered tumor cells at the invasion front with stronger CD97 expression than tumor cells located in solid tumor formations.

Prognosis

Not determined.

Cytogenetics

Not determined.

Leiomyosarcoma

Note: Normal smooth muscle cells are CD97-positive. In this cell type CD97 is not N-glycosylated. Thus, monoclonal antibodies that detect an N-glycosylation dependent epitope of CD97 do not react with normal smooth muscle cells (CD97^{EGF} antibodies). During transformation CD97 get partly N-glycosylated in most uterine leiomyoma and or completely N-glycosylated in nearly 25% of the leiomyosarcomas. These tumors are now positive for CD97^{EGF} antibodies. However, one third of leiomyosarcomas are completely devoid of CD97.

Prognosis

Not determined.

Cytogenetics

Not determined.

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