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Review

Cancer-related Issues of CD147

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Abstract. *CD147 is involved in many physiological functions, such as lymphocyte responsiveness, spermatogenesis, implantation, fertilization and neurological functions at early stages of development. Here we specifically review the role of CD147 in cancer. We focus on the following aspects: expression of CD147 in malignant versus normal tissues and its possible impact on prognosis, interaction of tumor cell-expressed CD147 with stroma cells and induction of matrix metalloproteinases, as well as the role of CD147 in tumor angiogenesis. The function of CD147 in supercomplexes with monocarboxylate transporters (MCT) and amino acid transporters such as CD98hc and large neutral amino acid transporter 1 (LAT1), as well as the functional contribution of CD147 in complexes with caveolin-1 and integrins, is discussed. Target validation experiments making use of CD147-directed RNAi and monoclonal antibodies are summarized. Finally, the relevance of CD147 as a target for therapeutic intervention in cancer patients is discussed.*

CD147 is a member of the immunoglobulin family of receptors. Members of this family play a role in intercellular communication involved in many immune-related functions, differentiation and development. CD147 plays a role in spermatogenesis, lymphocyte activation, expression of monocarboxylate transporters (MCT) and has been identified as a regulatory subunit of the γ-secretase complex in Alzheimer's disease amyloid β-peptide production (1-5). Some of these insights were obtained from the study of *cd147*$^{-/-}$ mice. These animals are defective in matrix metalloproteinase (MMP) regulation, spermatogenesis, lymphocyte responsiveness and neurological functions at the early stages of development. Such female mice are infertile due to failure of implantation and fertilization (5). CD147 is involved in the transport of the MCT-1 and MCT-3 to the plasma membrane since reduced accumulation of these transporters has been observed in the retina of *cd147* knock-out mice. A functional role of CD147 in cell adhesion is supported by its involvement in the blood-brain barrier and its interactions with integrins. CD147 has been implicated in many pathological processes, such as rheumatoid arthritis, experimental lung injury, atherosclerosis, chronic liver disease induced by hepatitis C virus, ischemic myocardial injury and heart failure (4). Treatment of transplant patients with a CD147 antibody was effective due to inhibition of T-cell activation (6). In the following pages, we review the expression and the functional role of CD147 in human cancer and discuss its possible role as a target for therapeutic intervention.

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General Features of CD147

CD147, a transmembrane protein of the immunoglobulin (Ig) superfamily was identified independently in different species and has many designations across different species such as M6, Neurothelin, 5A11, HT7, OX-47, CE9, EMMPRIN, Basigin, and gp42 (7-11).The most prevalent standard isoform is a single-chain type I transmembrane molecule composed of a 21 amino acid signal sequence, a 186 residues-long extracellular domain consisting of two Ig-like domains, a transmembrane domain of 21 amino acids and a cytoplasmic domain of 41 residues. The topology of CD147 and a rarely occurring splice variant as well as the corresponding amino acid sequences are shown in Figures 1 and 2. The transmembrane region harbors a leucine zipper and a charged residue (glutamic acid). The corresponding

gene is located on chromosome 19p13.3 and encodes a 29 kDa backbone protein. Three *N* glycosylation sites have been identified and migration on sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE) occurs between 39 and 65 kDa depending on the degree of glycosylation. A CD147 transcript as a new alternative splice variant composed of three Ig-like domains has been identified in the retina of the mouse (12). This isoform, Figure 1 right, results from the translation of a region within the first intron of CD147 as indicated in Figure 2 for human CD147. This splice variant was shown to interact homophilically and might function in alignment of lactate transporters in the retina where lactate is an important metabolite.

CD147 has a broad expression pattern on hematopoietic and non-hematopoietic cells such as monocytes, granulocytes, epithelial and endothelial cells. Weak expression has been noted on resting T lymphocytes, whereas expression is increased on activated T lymphocytes and monocytes (7-11, 13). Amino acid-based sequence comparisons of the CD147 orthologs of chicken, mouse, rat, rhesus monkey, chimpanzee and human are shown in Figure 3. The amino acid sequence homology of the human protein *versus* that of chimpanzee, rhesus monkey, rat, mouse and chicken is 96%, 88%, 65%, 65% and 53%, respectively. The perfect conservation of the amino acid sequences of the transmembrane sequences across all listed species (2) as described above is a remarkable feature, which includes the presence of a conserved glutamic acid residue. This finding indicates the involvement of transmembrane amino acids in protein protein interactions within the plasma membrane. The cytoplasmic domains are more conserved than the extracellular domains pointing to similar considerations with respect to conserved protein protein interactions with proteins located in the cytoplasm.

CD147 paralogs are embigin, a developmentally expressed protein (14), and neuroplastin, which acts as a synaptic glycoprotein (15). The amino acid sequence alignment of CD147 with its paralogs is shown in Figure 4, indicating amino acid sequence homology between human CD147, embigin and neuroplastin as 22% and 36% respectively. It is again noteworthy that the strongest amino acid conservation among the paralogs is observed in the transmembrane domains, including the charged glutamic acid.

Induction of MMP Is a Cancer-related Feature of CD147

It has been shown that CD147-positive tumor cells and their supernatants induce expression of MMPs such as MMP-1, MMP-2, MMP-3, MMP-9 and MMP-11, in cultured fibroblasts (16-18). Therefore, CD147 is also designated as extracellular MMP inducer (EMMPRIN). It was shown that MMP induction can also be mediated by soluble CD147, which was found in tissue culture supernatants as full-length protein or as a protein containing the extracellular domain only generated by MMP-mediated shedding (19-21). Soluble CD147 also has been detected in microvesicles (exosomes) (22, 23). Homotypic interactions may play an important role regarding the mode of action of MMP induction since it has been shown that recombinant CD147 fusion proteins can interact homotypically (24). However, interaction of CD147 with an as yet unidentified receptor might also be responsible for the phenomena as described above. CD147 can also be induced in tumor cells by epidermal growth factor receptor (EGFR)-mediated signaling (autocrine mechanism) (25). Controlled degradation of the extracellular matrix is a prerequisite for tumor invasion and metastasis. Transfection of breast cancer cells with *CD147* resulted in increased tumor growth and metastasis after implantation into the mammary gland and correlated with high levels of MMP-2 and MMP-9 (26). The molecular mechanisms of these phenomena have been poorly resolved. Glycosylated CD147 was shown to be a prerequisite for MMP induction at the transcriptional level (25). Induction of MMPs by CD147 was prevented with a monoclonal antibody directed against CD147 (25).

CD147 Mediates MMP-dependent and -independent Angiogenesis

It was found that CD147 expression was significantly up-regulated in activated human umbilical venule endothelial cells (HUVEC's) (27). Inhibition of CD147 expression by RNAi led to significantly decreased angiogenesis *in vitro*. CD147 may regulate angiogenesis by several mechanisms including proliferation, survival, MMP secretion and phosphoinositide 3 kinase/protein kinase B (PI3K/Akt) activation. Modulation of remodeling of the extracellular matrix by MMPs and its impact on angiogenesis is a well-known phenomenon. In addition, it was shown that CD147 is involved in the induction of vascular endothelial growth factor (VEGF) (28). In the B16 melanoma model, MMP-2/MMP-9 expression occurs independently of CD147 (28). Knock-down of *CD147* caused reduced VEGF production *in vivo* accompanied by reduced blood vessel formation, supporting the notion that CD147 promotes MMP-independent angiogenesis in this model. CD147 stimulates VEGF production in tumor and stromal compartments and VEGF induction involves the PI3K/Akt pathway. CD147 was shown to be required for responses to bevacizumab therapy in head-and-neck squamous cell carcinoma models (29). Bevacizumab therapy was effective in FaDu xenografts expressing CD147, but not in tumors with silenced CD147 expression. Tumor vesicle-associated CD147 was shown to modulate the angiogenic activity of HUVECs. This was

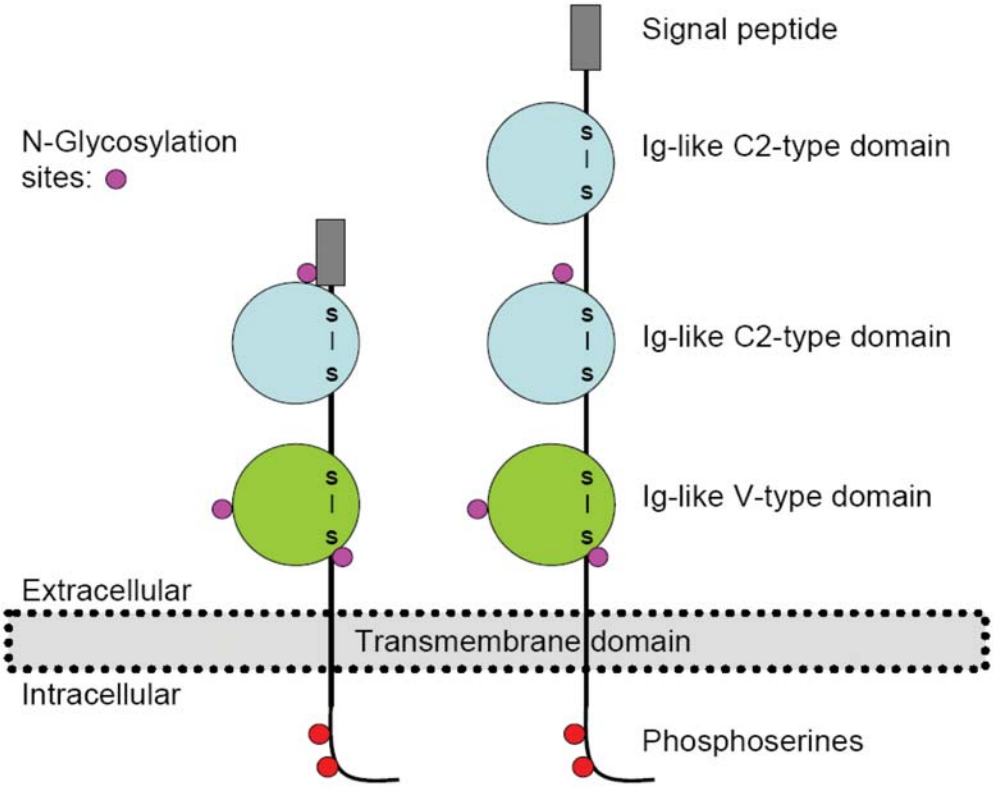

Figure 1. *Topology of human CD147 isoforms. The most frequently expressed variant of CD147 (2 Ig-like domain form) is shown on the left, the rarely expressed CD147 variant (3 Ig-like domain form) is shown on the right. Modules, N-glycosylation sites, phosphoserine residues and isoform-specific amino acids are highlighted according to the Swissprot entry BASI_HUMAN.*

Figure 2. *Amino acid sequence and functional motifs of human CD147. Domains and motifs are highlighted by a color code as outlined. The positions of the Ig-like domains are labeled according to Interpro Prosite PROFILE PS50835, that of the first Ig-like domain and the disulfide bridges according to Interpro SMART SM00408. All other annotations are based on the Swissprot entry BASI_HUMAN.*

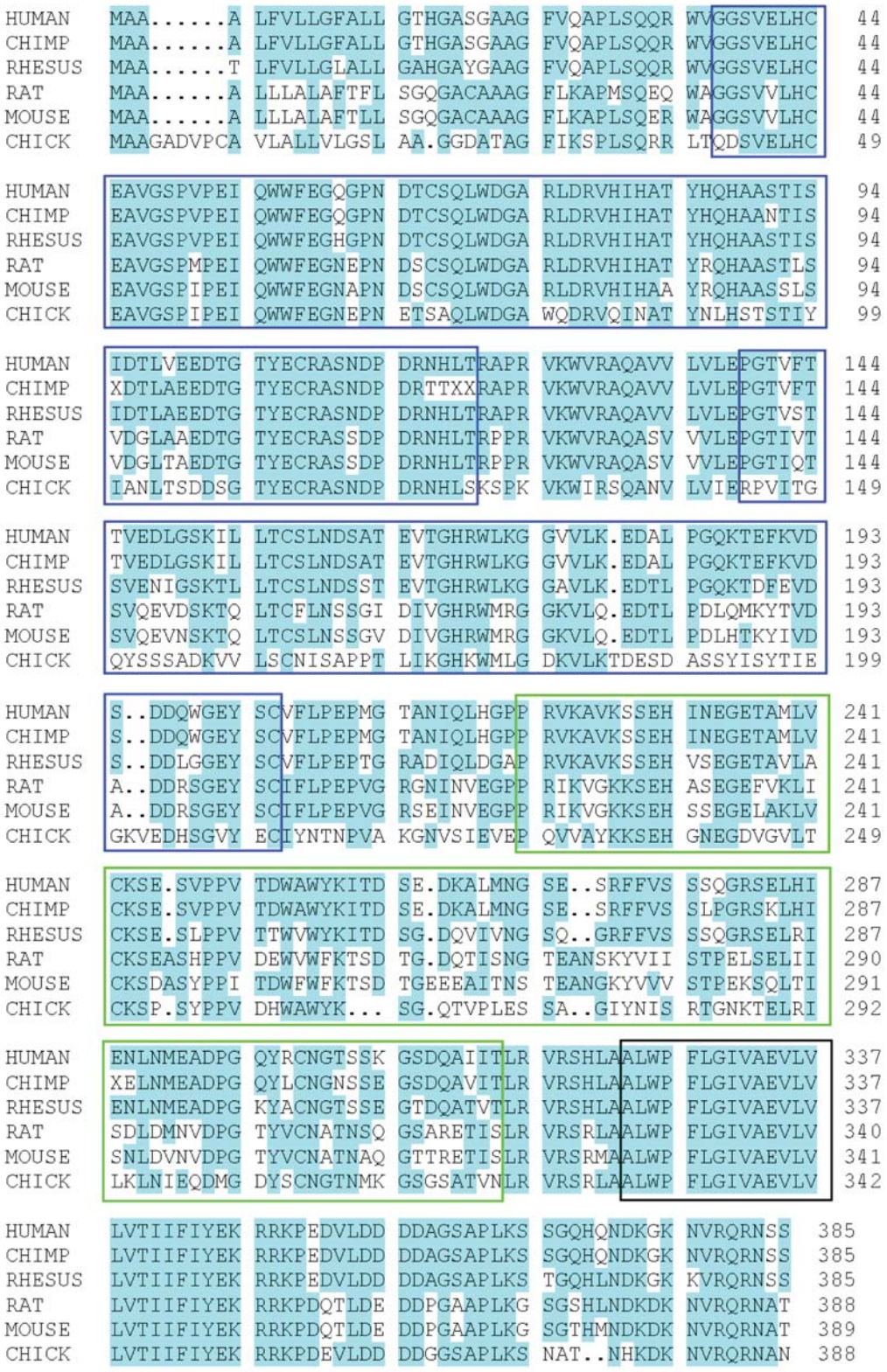

Figure 3. *Amino acid sequence alignment of CD147 from different species (orthologs). Identical amino acids are indicated by a light blue background, Ig-like C2-type domains, Ig-like V-type domains and the transmembrane domains are boxed by dark blue, green and black colors, respectively. Chimp and rhesus sequences are predicted based on their genome sequences, the other sequences were derived from the Swissprot dada base (BASI_X).*

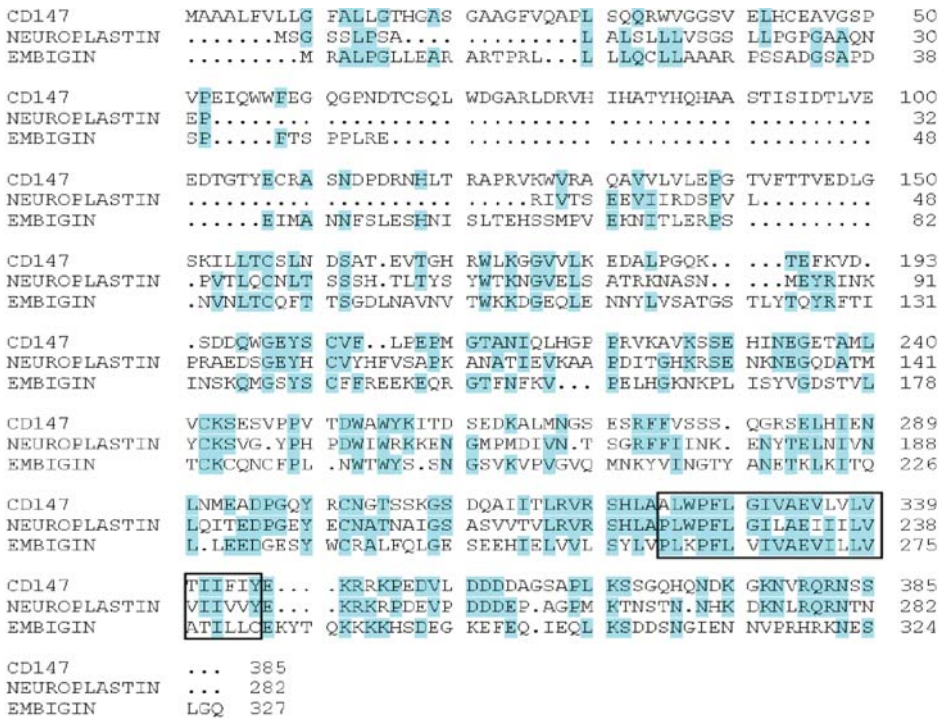

Figure 4. *Amino acid sequences of human CD147 and its paralogs Neuroplastin and Embigin. Identical amino acids are indicated by light blue color and the transmembrane domains are highlighted by a black box. The sequences are derived from the Swissprot databases: BASI_HUMAN, NPTN_HUMAN, EMB_HUMAN.*

shown for vesicles derived from ovarian carcinoma cell lines OVCAR3, SKOV3 and A2780 (22). Treatment of OVCAR3 cells with RNAi directed against CD147 suppressed the angiogenic potential of OVCAR-3 derived microvesicles.

CD147 Association with Cyclophilins (Cyps)

Cyps are a family of proteins that share peptidyl-prolyl *cis-trans* isomerase activity which is involved in their chaperone function. However, there is also evidence that Cyps are involved in intracellular communication (30). Cyps are located intracellularly as well as extracellularly. It was shown that extracellular CypB might be involved in recruitment of $CD4^+$ T-cells into infected tissue (31). Competition experiments have shown that CypA and CypB share a common receptor at the cell surface (32) which was identified as CD147 (33). CypA and CypB are able to transduce signals in several types of cells (34). Few reports covering cancer-related aspects of CD147/Cyp interaction are available. Expression of CD147 and CypA in pancreatic adenocarcinoma tissue are substantially higher than in corresponding normal tissues. Exogenous CypA significantly stimulated cancer cell proliferation in a dose-dependent manner and this effect was blocked by pretreatment with anti-CD147 antibody. In addition, CypA stimulated extracellular signal-related kinase 1 and 2 (ERK1/2) and p38 mitogen-activated protein kinase (MAPK) signaling pathways and increased the secretion of cytokines (IL5 and IL17) in Panc-1 cells. Several studies have shown the involvement of inflammatory or proinflammatory mediators in oncogenesis. IL5 is involved in the pathogenesis of atopic diseases and regulates production, activation and localization of eosinophils causing tissue damage in atopic diseases. IL17 stimulates secretion of chemokines containing nuclear factor κB (NFκB) binding sites in their promoter regions, including IL8 and monocyte chemoattractant protein-1 (MCP-1). A role of CypA in cancer is supported by the finding that CypA and macrophage inhibitory factor (MIF) are the most dominantly expressed proteins in non-small cell lung carcinoma (35) and a novel cyclophilin similar to CypA has been associated with metastasis and shown to be overexpressed in bladder cancer, hepatocellular carcinoma, sarcoma and breast carcinoma (36).

Target Validation Experiments with RNAi Reveal Functional CD147/MCT Interactions

CD147 has been described as an ancillary protein for function and expression of monocarboxylate transporters MCT1 (SLCT16A1), MCT3 (SLC16A3) and MCT4 (SLC16A4) (37-

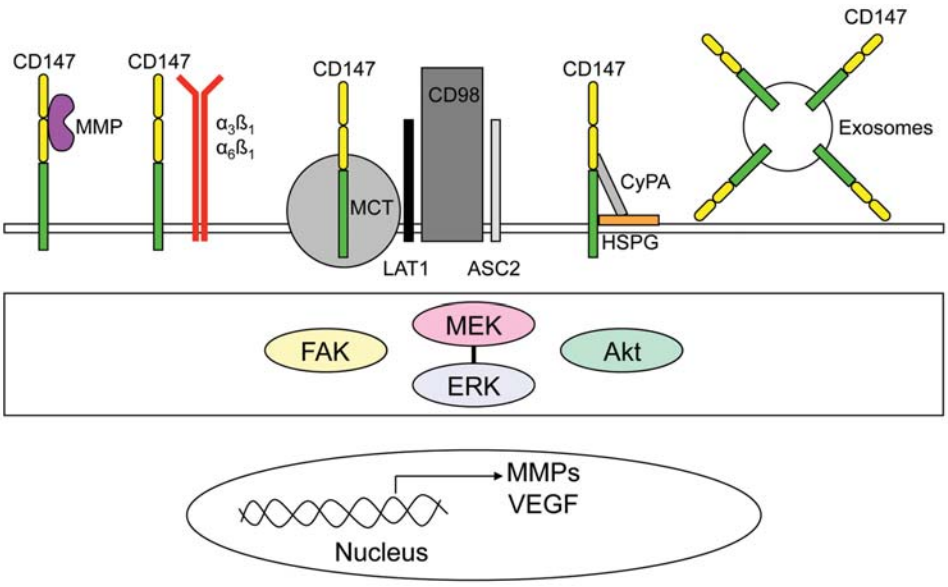

Figure 5. *Schematic overview of CD147-associated proteins, mediators of signaling and transcriptionally induced genes. Details are given in the text. HSPG, Heparan-sulfate proteoglycan; FAK, focal adhesion kinase; MEK, Map-Erk kinase; ERK, extracellular signal-related kinases; Akt, serine-threonine kinase; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor; α3β1 and α6β1, integrins; MCT, monocarbocylate transporter; LAT1, large neutral amino acid transporter; CD98, subunit of LAT1; ASC2, Asc-type amino acid transporter-2.*

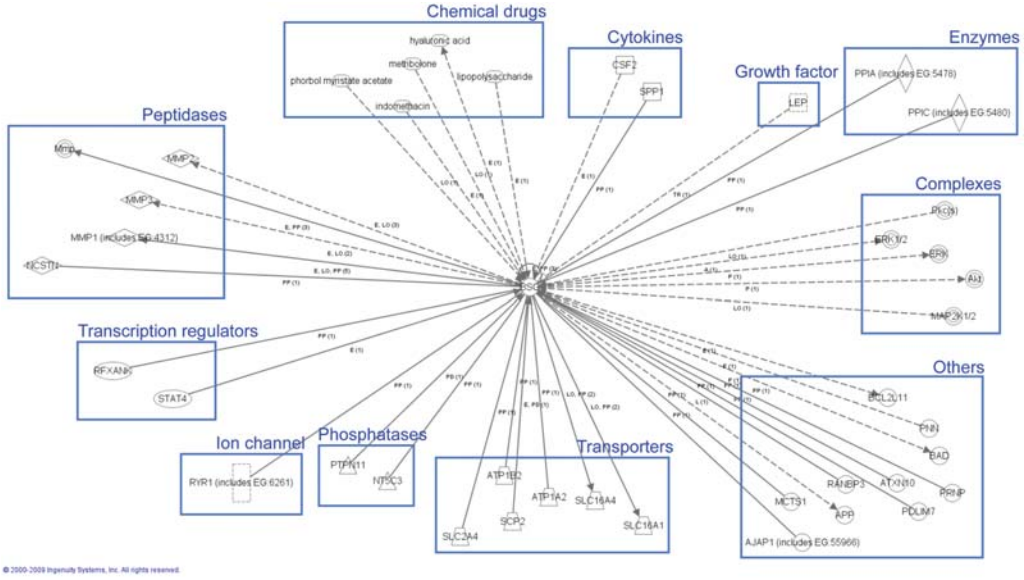

Figure 6. *CD147 neighbourhood analysis. Ingenuity pathway analysis (IPA) was used to create the neighborhood of genes for CD147. Shown are all molecules with a direct relationship to CD147. Edges are annotated by the relationship type of two molecules: PP, protein-protein interaction; E expression; P, phosphorylation; LO, location; PD, protein DNA interaction; TR, translocation; A, activation. All neighboring molecules of CD147 were manually grouped and annotated according to their molecular type. MMP1/2/3, matrix metalloproteinases 1/2/3; NCSTN, nicastrin; Mmp, group of matrix metalloproteinases; RFXANK, regulatory factor X-associated ankyrin-containing protein; STAT4, signal transducer and activator of transcription; RYR1, ryanodine receptor 1; PTPN11, protein tyrosine phosphatase, non-receptor type 11; NT5C3, 5'-nucleotidase, cytosolic III; SLC2A4, solute carrier family 2, member 4; SLC16A4, solute carrier family 16, member 4; SLC16A1, solute carrier family 16, member 1; ATP1B2, ATPase, Na^+/K^+ transporting, beta 2 polypeptide; ATP1A2, ATPase, Na^+/K^+ transporting, alpha 2 (+) polypeptide; SCP2, sterol carrier protein 2; AJAP1, adherens junctions-associated protein 1; MCTS1, malignant T-cell amplified sequence 1; APP, amyloid beta (A4) precursor protein; RANBP3, RAN binding protein 3; ATXN10, ataxin 10; PDLIM7, PDZ and LIM domain 7; PRNP, prion protein; BAD, BCL2-associated agonist of cell death; PNN, pinin, desmosome-associated protein; BCL2L11, BCL2-like 11; PPIA/PPIC, peptidylprolyl isomerase A/C (cyclophilin A/C); LEP, leptin; CSF2, colony-stimulating factor 2; SPP1, secreted phosphoprotein 1; Pkc(s), group of protein kinases c; ERK1/2, group of ERKs; ERK, group of ERKs; Akt, group of Akts; MAP2K1/2, mitogen-activated protein kinase kinase group of kinases.*

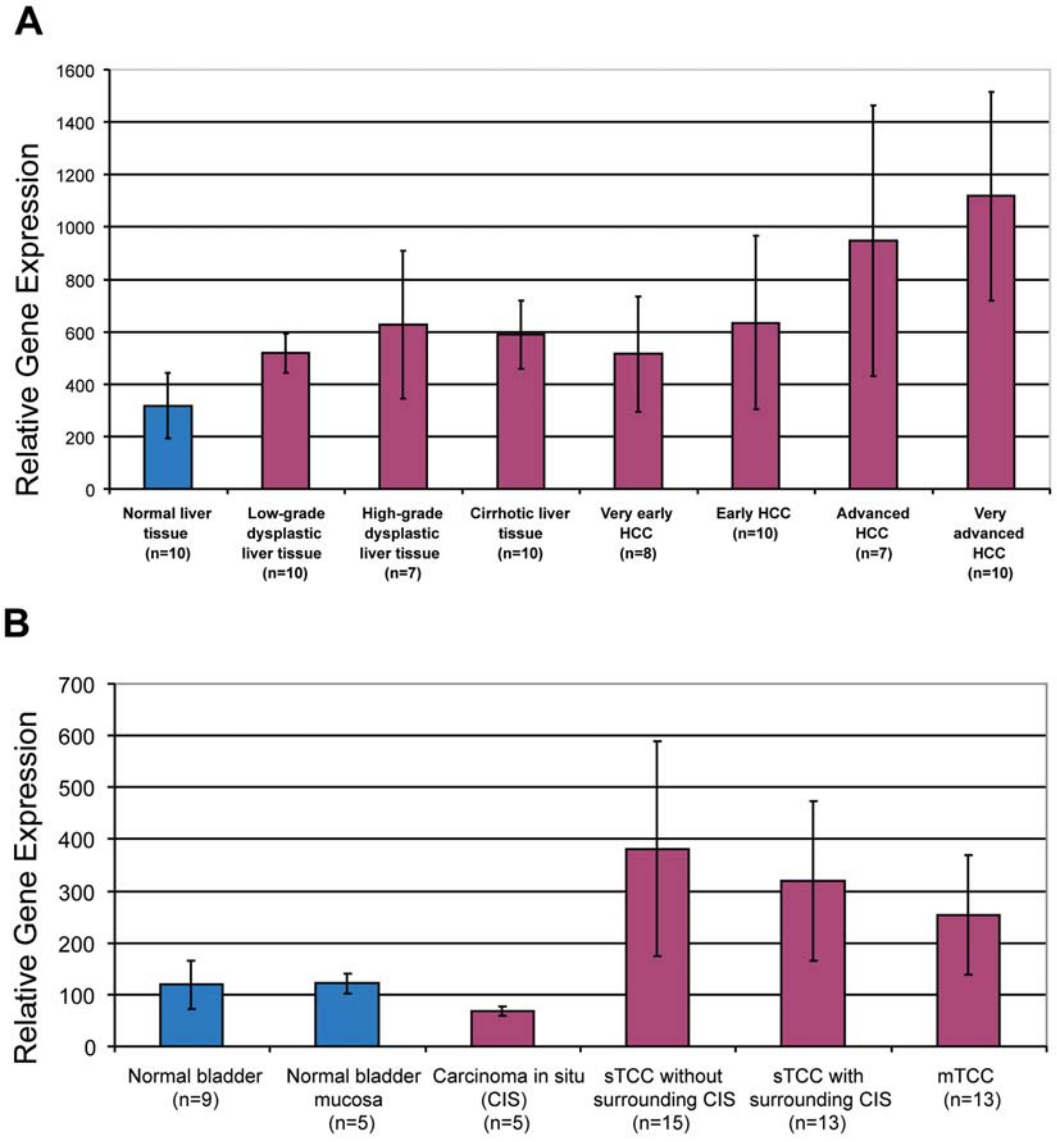

Figure 7. *RNA-based CD147 expression in liver cancer and bladder cancer in comparison to corresponding normal tissues. Comparison of CD147 expression signals between tumor-related and normal tissues for (A) liver and (B) bladder. Gene expression data were derived from the GEO database [liver (GSE6764), bladder (GSE3167)]. These relative units of expression sets exemplify results obtained from several distinct studies (GSE1898, GSE6222, GSE5364 for liver and GSE7476, E-TABM-147 for bladder); n depicts the number of biological samples within each group. HCC, Hepatocellular carcinoma; CIS, carcinoma in situ; sTCC, superficial transitional cell carcinoma; mTCC, muscle invasive transitional cell carcinoma.*

40). Expression of MCT3 seems to be restricted to the retina, whereas MCT1 and MCT4 are broadly expressed in many tissues. Functional transporters are heteromers composed of CD147 and MCT1 or MCT4 and are involved in transport of lactate from the cytoplasm to the outside of the cell (41). Tumor cells are characterized by excessive anaerobic glycolysis resulting in deregulated lactate production, a phenomenon referred to as the Warburg effect (42).

Several groups have shown the impact of CD147 and its linkage to MCT with respect to cell viability, migration and proliferation by neutralization of CD147 function *via* knock down of its RNA or by inhibition of the protein with monoclonal antibodies. Blocking of CD147 with monoclonal antibody MEM-M6/1 (43) induces cell death in LoVo, HT-29, WiDr and SW620 colon cancer cells, and A2058 melanoma cells, but not in WI-38 and TIG-113 normal fibroblasts. MEM-M6/1 inhibits lactate release and lowered the intracellular pH. Induction of acidification correlated with inhibition of glycolytic flux and a decrease in intracellular ATP levels. In A375 human melanoma

cells, a CD147-targeting siRNA was shown to inhibit proliferation, invasiveness, VEGF production and down-regulation of glycolysis (27). CD147 RNAi knockdown in a human Jurkat T-lymphoma cell line (44) resulted in reduced proliferation, migration and reduced adhesion to the extracellular matrix protein fibronectin *in vitro*. Silencing of CD147 by RNAi reduced the proliferation rate of MiaPaCa2 and Panc1 pancreatic carcinoma cell lines (45). CD147 silencing reduced invasiveness through the chorioallantoic membrane of chick embryos (CAM assay) and inhibited tumorigenicity in a xenograft model in nude mice (45). These observations can be explained by an increase in intracellular lactate concentration resulting in cell death since lactate has been shown to lower pyruvate reduction to lactate by lactate dehydrogenase (LDH) and inhibition of LDH was shown to reduce the Warburg effect and to inhibit proliferation of tumor cells (46). The role of CD147 in stroma tumor interactions was studied with SW620 colon cancer cells (47). Experiments *in vitro* indicated that colon cancer stromal cell interactions mediated by CD147 led to increased MMP-2 expression in fibroblasts, but not in macrophages. CD147 RNAi targeting stroma cell CD147 was able to significantly down-regulate *CD147* mRNA levels in mice bearing human colon cancer xenografts and suppress growth of the xenografts. These observations suggest that CD147 expressed on stroma cells plays an important role in growth of the SW620 colon cancer xenograft. Blockage of tumor expressed CD147 by RNAi did not result in inhibition of tumor growth. Proteomics-based analysis revealed further interaction partners of CD147 in addition to MCT: CD98 heavy chain (CD98hc), large neutral amino transporter 1 (LAT1) and Asc-type amino acid transporter 2 (ASCT2), all of which are L-type amino acid transporters (48). These interactions were revealed by covalent cross-linking and mass spectrometry. The data reveal the existence of a CD147-CD98 cell surface supercomplex that plays a role in energy metabolism, likely by coordinating transport of lactate and amino acids. CD98hc is a multifunctional glycoprotein with a single transmembrane domain, is highly expressed on proliferating cells and functions as a chaperone for transporters. It has been shown that CD98hc forms disulfide-bridged heterodimers with at least six types of L-type amino transporters (48). Co-regulation of cell surface CD98hc/LAT1 and CD147/MCT protein complexes support their physical interactions. In addition, interactions of CD98hc with integrin β1 and epithelial cell adhesion molecule (EpCAM) have been described (48, 49). Altogether, the identified interactions point to the existence of a CD147-based supercomplex. Interactions of CD147 with other proteins are summarized in Figures 5 and 6.

Association of CD147 with Caveolin and Integrins

CD147 associates with caveolin-1, thereby diminishing both CD147 clustering and CD147-dependent MMP-1-inducing activity (50). Highly specific association on the surface of several types of cells has been observed. Complex formation is temperature and cholesterol dependent, reminiscent of associations seen with caveolae/lipid rafts. Overexpression of CD147 caused a specific decrease in clustering of cell surface CD147. It was shown that caveolin interacts with low glycoforms of CD147 and inhibits their conversion to high glycoforms which are the isoforms which self-aggregate and stimulate MMP production (51). Interaction of CD147 with integrins α6β1 and α3β1 is responsible for the invasion potential of human hepatoma cells (52). α6β1 and CD147 co-localize on human hepatoma cells. The enhancing effect of CD147 on invasion capacity and secretion of MMPs was partially blocked by α6β1 antibodies. Wortmannin, a PI3K inhibitor that reverses the effect of CD147 on the regulation of intracellular Ca^{2+} mobilization, significantly reduced cell invasion potential and secretion of MMPs in human hepatoma cells. Based on these data, α6β1 interacts with CD147 to mediate tumor invasion and metastasis through the PI3K pathway. In addition, it was shown that in human hepatoma cell overexpression of CD147 promotes invasion and metastasis *via* α3β1 integrin-fokal adhesion kinase (FAK)-paxillin and FAK-PI3K- Ca^{2+} pathways. α3β1 and CD147 co-localize on human 7721 hepatoma cells. The enhancing effect of CD147 on adhesion, invasion and MMP secretion was reduced by integrin α3β1 antibodies. Expression of integrin downstream molecules including FAK, phospho-FAK, paxillin and phospho-paxillin were increased in human hepatoma cells overexpressing CD147. Wortmannin and LY294002, specific PI3K inhibitors, reversed the effect of CD147 on the regulation of intracellular Ca^{2+} mobilization and reduced cell adhesion, invasion and MMP secretion. In *Drosophila melanogaster*, CD147 promotes cytoskeletal rearrangements and the formation of lamellopodia. CD147 and integrin co-localize in cultured insect cells and in the visual system. The effect of CD147 is integrin-dependent as shown with argine-glycine-aspartate (RGD) peptides and mutation analysis (53, 54). In leukocytes, CD147 has also been shown to interact with the sialoglycoprotein CD43 and thereby regulates adhesiveness of leukocyte function antigen 1 (LFA-1), the broadly expressed β2 integrin of leukocytes (55).

Function of CD147 as an Anti-apoptotic Protein and Mediator of Chemoresistance

In several cancer cell lines, CD147 has been identified as a mediator of anti-apoptotic function and chemoresistance. In HO-8910 ovarian carcinoma cells, *CD147* RNAi reduces

tumor cell invasion, tumorigenicity and chemosensitivity to paclitaxel (56). Up-regulation of CD147 has been observed in several multidrug-resistant cancer cell lines (57). Independently, involvement of CD147 in resistance of cancer cells to a variety of chemotherapeutic agents was reported (58). In addition, CD147 was identified as a receptor which promotes androgen-independent growth of tumor cells in a hyaluronan-dependent manner (59). In human oral squamous carcinoma cells (SCC), CD147-directed RNAi reduced X-chromosome linked inhibitor of apoptosis protein (XIAP) expression and increased chemosensitivity to 5 fluorouracil (60). In breast cancer cell lines, it was shown that CD147 confers resistance to anoikis as demonstrated by activation of caspase 3, increased DNA fragmentation and lower cellular viability. Silencing of CD147 resulted in elevation of Bim protein levels (61). Treatment of cells with a MAP/ERK kinase (MEK) inhibitor (UO126) or a proteasome inhibitor (epoximycin) also induced Bim-1 accumulation and rendered cells sensitive to anoikis. These results suggest that CD147 protects cancer cells from anoikis and that this effect is mediated at least in part by a MAP kinase-dependent reduction of Bim. It has been shown that expression of CD147 leads to activation of ERK which phosphorylates proapoptotic Bim, resulting in degradation of Bim by the proteasome. Down-regulation of Bim suppresses anoikis and promotes survival of tumor cells detached from matrices as a prerequisite for cancer cell invasion and metastasis. CD147 was shown to stimulate hyaluronan production (59). Hyaluronan-tumor cell interaction is implicated in multidrug resistance due to activation of the PI3K/Akt pathway. Furthermore, it was demonstrated that CD147 is a mediator of multidrug resistance through hyaluronan-mediated up-regulation of ErbB2 signaling and cell survival pathways (62-64).

Expression of CD147 in Cancer

High incidence of expression of CD147 in different cancer entities making use of tissue microarrays and monoclonal antibodies (mAb) MEM-M6/1 and HIM6 (65) was noted in a systematic investigation (65). A lot of 2348 and 608 tissue samples covering 129 distinct tumor types and 76 different normal tissues, respectively, were investigated for their CD147 status with these antibodies. CD147 expression was found in 112 out of 129 tumor entities with the following incidences: squamous cell carcinomas (60-100%), pancreatic (87%), chromophobic kidney (83%), hepatocellular (83%), medullary breast (83%) and glioblastoma multiforme (79%). Homogeneous expression of CD147 was found in tumor types such as squamous cell carcinoma of different types of organs and mesotheliomas. The following normal tissues scored positively for CD147 expression: proliferatively active and differentiating epithelial cells, myocardial cells in the left heart ventricle and vascular endothelial cells of the brain. Interestingly, CD147 isoforms differing in presence or absence of Lewis X glycan structures were found on breast cancer cells.

Another investigation of expression and function of CD147 as a cancer-associated biomarker made use of mAb HAb18 (IgG1) (66). A lot of 28 tissue microarrays and 1117 pathological sections of breast tissue samples were analyzed. The incidence of CD147 expression was: cancer of the liver 80% (n=20), lung 62% (n=90), stomach 66% (n=44), colon 58% (n=19), rectum 59% (n=17), breast 64% (n=1055), cancer 80% (n=10), brain 90% (n=52), oesophagus 87% (n=16), ovary 75% (n=40), urinary bladder 85% (n=41), skin (squamous cell carcinoma) 58% (n=41), larynx 85% (n=63) and kidney 73% (n=33), and 30% of sarcomas such as osteo, chondro- and fibrosarcoma (n=102). Staining was ranked as weak, moderate and strong. Strong staining was observed in 20% of breast, ovarian and brain tumors. In a retrospective study of 106 patients with infiltrating ductal carcinoma of the breast, the level of CD147 expression was correlated with survival of the patients (66).

Up-regulation of CD147 also has been noted in glioma, laryngeal squamous cell, ovarian, renal cell and skin carcinoma (67-71). CD147 was described as a marker of poor diagnosis in serous ovarian and bladder carcinomas (72, 73).

We have analyzed RNA-based CD147 expression in liver and bladder cancer in comparison to corresponding normal tissues based on GEO database expression data (74). As shown in Figure 7A, which includes normal liver, low- and high-grade dysplastic liver tissue, cirrhotic liver as well as early and advanced hepatocellular carcinoma, RNA levels of CD147 in the liver pathologies are significantly higher in comparison to normal liver tissue and correlate with pathogenicity. Analogous findings are presented for bladder carcinoma in Figure 7B. Steady-state RNA levels of *CD147* are increased in transitional bladder carcinoma compared to normal bladder tissue and carcinoma *in situ*.

Antibodies Directed against CD147

Many mAbs directed against CD147 interacting with distinct epitopes have been established (75). Most of the antibodies only bind to phytohemagglutinin (PHA) stimulated T-cells, not to resting T-cells. This phenomenon was explained by bivalent binding of the low-affinity antibodies to clustered CD147 molecules on activated T-cells and not by neo-epitopes specifically displayed on activated T-cells. High affinity antibodies were able to bind in a monovalent fashion to resting T-cells, which are low expressors of CD147. Induction of dimerisation by the low-affinity antibodies resulted in inhibition of CD3-mediated T-cell activation. High-affinity mAb MEM-M6/6, recognizing a unique epitope, inhibits T cell activation by 80% and as outlined in

a previous section also proliferation of colon cancer and melanoma cells and not non-transformed fibroblasts (43). Triggering of CD147 by mAbs was shown to cause displacement of glycosylphosphatidylinositol (GPI)-anchored co-receptors CD48 and CD59 from microdomains in human T-lymphocytes (76). Perturbation of microdomains is responsible for inhibition of T-cell proliferation. Making use of COS-7 transfectants and mAbs covering different CD147 epitopes, it was shown that CD147 contains different epitopes involved in regulation of cell adhesion (homotypic cell aggregation) and lymphocyte activation (77).

A different set of CD147-directed mAbs were evaluated with respect to treatment of hepatocellular carcinoma (HCC) (78). mAb Hb18G and Licartin, a ^{131}I-labeled F(ab')$_2$ fragment of mAb Hb18G) mediate suppression of MMP secretion in co-cultured fibroblasts and inhibit invasion, and Licartin significantly inhibited the growth of HCC cells. mAb Hb18G and Licartin effectively reduced growth and metastasis as well as the expression of stromal factors such as MMPs, VEGF and fibroblast surface protein (78). Clinical studies were reported for targeted radioimmunotherapy of HCC patients with Licartin (79). Of the 73 patients completing two cycles in a phase II trial, 6 (8%) were noted to have a partial response, 14 (19%) a minor response and 43 (59%) had stable disease. The survival of progression-free patients was significantly higher than that of patients with progressive disease. Chimeric CD147 antibody (IgG1) referred to as CNTO 3899 was evaluated as an agent for potential treatment of head-and-neck squamous cell carcinoma (80). The antibody inhibited proliferation of SSC-1 and FaDu cells up to 57%. Inhibition of collagen degradation was noted as well. Significant tumor growth inhibition was noted in SSC-1 xenografts. CNTO 3899 augments radiation response of SSC-1 and FaDu cells *in vitro* and in xenografts. Furthermore, the same study showed that CD147 function is associated with cytokine production of proinflammatory and proangiogenic factors such as IL1β, IL6, IL8 and VEGF. Inhibition of cytokines, MMPs and VEGF seems to mediate the mechanism of action of this mAb. The studies as outlined would suggest that inhibition of proliferation of tumor cells by CD147 mAbs in the absence of immune effector cells is either cell-type-specific and/or might be dependent on distinct epitopes the mAbs are directed against. Inhibition of T-cell activation and/or depletion was not investigated with CNTO 3899, Hb18G or Licartin. Efficacy data with staged xenografts (≥100 mm^3) would be helpful to document the *in vivo* potency of therapeutic CD147 mAbs.

CD147 as a Target for Treatment of Cancer

Target validation experiments with mAbs and RNAi directed against CD147 have been summarized in the preceding sections of this review. Since the molecular interactions of CD147 with associated proteins are poorly defined, interference with small molecules is presently in the focus of drug development. The most obvious mode of intervention is to block CD147 function with mAbs. RNAi-mediated intervention would need more progress regarding the targeted delivery to cancer cells.

A critical issue is the broad expression of CD147, requiring toxicity studies for mAbs in a cross-reactive species. The function of CD147 as a mediator acros the blood brain barrier would call for appropriate experiments for a therapeutic mAb. Expression of CD147 on hematopoietic cells and its function as a lymphocyte activation antigen are also critical issues. On the other hand, dependence of tumor cells on energy supply by anaerobic glycolysis (Warburg effect) and inhibition of the latter by CD147 mAbs which disrupt interaction with MCT and amino acid transporters makes tumor cells vulnerable to modulation of CD147 function. Antibody-dependent cellular cytotoxicity positive and negative mAbs should be evaluated preclinically to define the optimal format of the mAb. Unfortunately, the possible immunosuppressive effects caused by modulation of CD147 function cannot be modeled appropriately in *in vivo* efficacy models. The impact of CD147 modulation and inhibition of MMPs is a controversial issue since pro- and antitumoral activities are associated with MMPs and the consequences of CD147 modulation regarding tumor stroma interactions have to be dissected in more detail. However, CD147 clearly impacts on invasion, proliferation, angiogenesis, tumor cell metabolism such as glycolysis, and mediates prosurvival signals, multi-drug resistance and PI3K/Akt signaling, which are all hallmarks of oncogenesis.

References

1 Huet E, Gabison EE and Mourah S: Role of emmprin/CD147 in tissue remodeling. Connect Tissue Res *49*: 175-179, 2008.

2 Iacono KT, Brown AL, Greene MI and Saouaf SJ: CD147 immunoglobulin superfamily receptor function and role in pathology. Exp Mol Pathol *83*: 283-295, 2007.

3 Nabeshima K, Iwasaki H, Koga K, Hojo H, Suzumiya J and Kikuchi M: Emmprin (basigin/CD147): matrix metalloproteinase modulator and multifunctional cell recognition molecule that plays a critical role in cancer progression. Pathol Int *56*: 359-367, 2006.

4 Gabison EE, Hoang-Xuan T, Mauviel A and Menashi S: EMMPRIN/CD147, an MMP modulator in cancer, development and tissue repair. Biochimie *87*: 361-368, 2005.

5 Muramatsu T and Miyauchi T: Basigin (CD147): a multifunctional transmembrane protein involved in reproduction, neural function, inflammation and tumor invasion. Histol Histopathol *18*: 981-987, 2003.

6 Deeg HJ, Blazar BR, Bolwell BJ, Long GD, Schuening F, Cunningham J, Rifkin RM, Abhyankar S, Briggs AD, Burt R, Lipani J, Roskos LK, White JM, Havrilla N, Schwab G and Heslop HE: Treatment of steroid-refractory acute graft-*versus*-host disease with anti-CD147 monoclonal antibody ABX-CBL. Blood *98*: 2052-2058, 2001.

7 Kasinrerk W, Fiebiger E, Stefanová I, Baumruker T, Knapp W and Stockinger H: Human leukocyte activation antigen M6, a member of the Ig superfamily, is the species homologue of rat OX-47, mouse basigin, and chicken HT7 molecule. J Immunol *149*: 847-854, 1992.

8 Altruda F, Cervella P, Gaeta ML, Daniele A, Giancotti F, Tarone G, Stefanuto G and Silengo L: Cloning of cDNA for a novel mouse membrane glycoprotein (gp42): shared identity to histocompatibility antigens, immunoglobulins and neural-cell adhesion molecules. Gene *85*: 445-451, 1989.

9 Miyauchi T, Kanekura T, Yamaoka A, Ozawa M, Miyazawa S and Muramatsu T: Basigin, a new, broadly distributed member of the immunoglobulin superfamily, has strong homology with both the immunoglobulin V domain and the beta-chain of major histocompatibility complex class II antigen. J Biochem *107*: 316-323, 1990.

10 Seulberger H, Lottspeich F and Risau W: The inducible blood rain barrier specific molecule HT7 is a novel immunoglobulin-like cell surface glycoprotein. EMBO J *9*: 2151-2158, 1990.

11 Fossum S, Mallett S and Barclay AN: The MRC OX-47 antigen is a member of the immunoglobulin superfamily with an unusual transmembrane sequence. Eur J Immunol *21*: 671-679, 1991.

12 Hanna SM, Kirk P, Holt OJ, Puklavec MJ, Brown MH and Barclay AN: A novel form of the membrane protein CD147 that contains an extra Ig-like domain and interacts homophilically. BMC Biochem *4*: 17, 2003.

13 Ochrietor JD, Moroz TP, van Ekeris L, Clamp MF, Jefferson SC, deCarvalho AC, Fadool JM, Wistow G, Muramatsu T and Linser PJ: Retina-specific expression of 5A11/Basigin-2, a member of the immunoglobulin gene superfamily. Invest Ophthalmol Vis Sci *44*: 4086-4096, 2003.

14 Lain E, Carnejac S, Escher P, Wilson MC, Lømo T, Gajendran N and Brenner HR: A novel role for embigin to promote sprouting of motor nerve terminals at the neuromuscular junction. J Biol Chem *284*: 8930-8939, 2009.

15 Smalla KH, Matthies H, Langnäse K, Shabir S, Böckers TM, Wyneken U, Staak S, Krug M, Beesley PW and Gundelfinger ED: The synaptic glycoprotein neuroplastin is involved in long-term potentiation at hippocampal CA1 synapses. Proc Natl Acad Sci USA *97*: 4327-4332, 2000.

16 Kataoka H, DeCastro R, Zucker S and Biswas C: Tumor cell-derived collagenase-stimulatory factor increases expression of interstitial collagenase, stromelysin, and 72-kDa gelatinase. Cancer Res *53*: 3154-3158, 1993.

17 Biswas C, Zhang Y, DeCastro R, Guo H, Nakamura T, Kataoka H and Nabeshima K: The human tumor cell-derived collagenase stimulatory factor (renamed EMMPRIN) is a member of the immunoglobulin superfamily. Cancer Res *55*: 434-439, 1995.

18 Guo H, Zucker S, Gordon MK, Toole BP and Biswas C: Stimulation of matrix metalloproteinase production by recombinant extracellular matrix metalloproteinase inducer from transfected Chinese hamster ovary cells. J Biol Chem *272*: 24-27, 1997.

19 Li R, Huang L, Guo H and Toole BP: Basigin (murine EMMPRIN) stimulates matrix metalloproteinase production by fibroblasts. J Cell Physiol *186*: 371-379, 2001.

20 Taylor PM, Woodfield RJ, Hodgkin MN, Pettitt TR, Martin A, Kerr DJ and Wakelam MJ: Breast cancer cell-derived EMMPRIN stimulates fibroblast MMP2 release through a phospholipase A(2) and 5-lipoxygenase catalyzed pathway. Oncogene *21*: 5765-5772, 2002.

21 Egawa N, Koshikawa N, Tomari T, Nabeshima K, Isobe T and Seiki M: Membrane type 1 matrix metalloproteinase (MT1-MMP/MMP-14) cleaves and releases a 22-kDa extracellular matrix metalloproteinase inducer (EMMPRIN) fragment from tumor cells. J Biol Chem *281*: 37576-37585, 2006.

22 Millimaggi D, Mari M, D'Ascenzo S, Carosa E, Jannini EA, Zucker S, Carta G, Pavan A and Dolo V: Tumor vesicle-associated CD147 modulates the angiogenic capability of endothelial cells. Neoplasia *9*: 349-357, 2007.

23 Simpson RJ, Jensen SS and Lim JW: Proteomic profiling of exosomes: current perspectives. Proteomics *8*: 4083-4099, 2008.

24 Sun J, Hemler ME: Regulation of MMP-1 and MMP-2 production through CD147/extracellular matrix metalloproteinase inducer interactions. Cancer Res *61*: 2276-2281, 2001.

25 Menashi S, Serova M, Ma L, Vignot S, Mourah S and Calvo F: Regulation of extracellular matrix metalloproteinase inducer and matrix metalloproteinase expression by amphiregulin in transformed human breast epithelial cells. Cancer Res *63*: 7575-7580, 2003.

26 Zucker S, Hymowitz M, Rollo EE, Mann R, Conner CE, Cao J, Foda HD, Tompkins DC and Toole BP: Tumorigenic potential of extracellular matrix metalloproteinase inducer. Am J Pathol *158*: 1921-1928, 2001.

27 Chen Y, Zhang H, Gou X, Horikawa Y, Xing J and Chen Z: Up-regulation of HAb18G/CD147 in activated human umbilical vein endothelial cells enhances angiogenesis. Cancer Lett *278*: 113-121, 2009.

28 Voigt H, Vetter-Kauczok CS, Schrama D, Hofmann UB, Becker JC and Houben R: CD147 impacts angiogenesis and metastasis formation. Cancer Invest *27*: 329-33, 2009.

29 Newman JR, Helman EE, Safavy S, Zhang W and Rosenthal EL: EMMPRIN expression is required for response to bevacizumab therapy in HNSCC xenografts. Cancer Lett *274*: 313-318, 2009.

30 Yurchenko V, Constant S and Bukrinsky M: Dealing with the family: CD147 interactions with cyclophilins. Immunology *117*: 301-309, 2006.

31 Bukrinsky MI: Cyclophilins: unexpected messengers in intercellular communications. Trends Immunol *23*: 323-325, 2002.

32 Yurchenko V, Zybarth G, O'Connor M, Dai WW, Franchin G, Hao T, Guo H, Hung HC, Toole B, Gallay P, Sherry B and Bukrinsky M: Active site residues of cyclophilin A are crucial for its signaling activity *via* CD147. J Biol Chem *277*: 22959-22965, 2002.

33 Yurchenko V, O'Connor M, Dai WW, Guo H, Toole B, Sherry B and Bukrinsky M: CD147 is a signaling receptor for cyclophilin B. Biochem Biophys Res Commun *288*: 786-788, 2001.

34 Rodriguez JA, Li M, Yao Q, Chen C and Fisher WE: Gene overexpression in pancreatic adenocarcinoma: diagnostic and therapeutic implications. World J Surg *29*: 297-305, 2005.

35 Campa MJ, Wang MZ, Howard B, Fitzgerald MC and Patz EF Jr: Protein expression profiling identifies macrophage migration inhibitory factor and cyclophilin A as potential molecular targets in non-small cell lung cancer. Cancer Res *63*: 1652-1656, 2003.

36 Meza-Zepeda LA, Forus A, Lygren B, Dahlberg AB, Godager LH, South AP, Marenholz I, Lioumi M, Flørenes VA, Maelandsmo GM, Serra M, Mischke D, Nizetic D, Ragoussis J, Tarkkanen M, Nesland JM, Knuutila S and Myklebost O: Positional cloning identifies a novel cyclophilin as a candidate amplified oncogene in 1q21. Oncogene *21*: 2261-2269, 2002.

37 Gallagher SM, Castorino JJ, Wang D and Philp NJ: Monocarboxylate transporter 4 regulates maturation and trafficking of CD147 to the plasma membrane in the metastatic breast cancer cell line MDA-MB-231. Cancer Res *67*: 4182-4189, 2007.

38 Philp NJ, Ochrietor JD, Rudoy C, Muramatsu T and Linser PJ: Loss of MCT1, MCT3, and MCT4 expression in the retinal pigment epithelium and neural retina of the 5A11/basigin-null mouse. Invest Ophthalmol Vis Sci *44*: 1305-1311, 2003.

39 Deora AA, Philp N, Hu J, Bok D and Rodriguez-Boulan E: Mechanisms regulating tissue-specific polarity of monocarboxylate transporters and their chaperone CD147 in kidney and retinal epithelia. Proc Natl Acad Sci USA *102*: 16245-16250, 2005.

40 Kirk P, Wilson MC, Heddle C, Brown MH, Barclay AN and Halestrap AP: CD147 is tightly associated with lactate transporters MCT1 and MCT4 and facilitates their cell surface expression. EMBO J *19*: 3896-3904, 2000.

41 Wilson MC, Meredith D, Fox JE, Manoharan C, Davies AJ and Halestrap AP: Basigin (CD147) is the target for organomercurial inhibition of monocarboxylate transporter isoforms 1 and 4: the ancillary protein for the insensitive MCT2 is EMBIGIN (gp70). J Biol Chem *280*: 27213-21, 2005.

42 Warburg O: On the origin of cancer cells. Science *123*: 309-314, 1956.

43 Baba M, Inoue M, Itoh K and Nishizawa Y: Blocking CD147 induces cell death in cancer cells through impairment of glycolytic energy metabolism. Biochem Biophys Res Commun *374*: 111-116, 2008.

44 Chen X, Su J, Chang J, Kanekura T, Li J, Kuang YH, Peng S, Yang F, Lu H and Zhang JL: Inhibition of CD147 gene expression *via* RNA interference reduces tumor cell proliferation, activation, adhesion, and migration activity in the human Jurkat T-lymphoma cell line. Cancer Invest *26*: 689-697, 2008.

45 Schneiderhan W, Scheler M, Holzmann KH, Marx M, Gschwend JE, Bucholz M, Gress TM, Seufferlein T, Adler G and Oswald F: CD147 silencing inhibits lactate transport and reduces malignant potential of pancreatic cancer cells in *in vivo* and *in vitro* models. Gut *58*: 1391-1398, 2009.

46 Holbrook JI, Liljas A, Steindl SJ and Rossmann MG: Lactate Dehydrogenase. *In*: Oxidation-Reduction Part A: Dehydrogenases (l); Electron transfer (l). Boyder PD (ed.). London: Academic Press, pp. 191-292, 1975.

47 Lucas T, Abraham D and Aharinejad S: Modulation of tumor associated macrophages in solid tumors. Front Biosci *13*: 5580-5588, 2008.

48 Xu D and Hemler ME: Metabolic activation-related CD147-CD98 complex. Mol Cell Proteomics *4*: 1061-1071, 2005.

49 Zent R, Fenczik CA, Calderwood DA, Liu S, Dellos M and Ginsberg MH: Class- and splice variant-specific association of CD98 with integrin beta cytoplasmic domains. J Biol Chem *275*: 5059-5064, 2000.

50 Tang W and Hemler ME: Caveolin-1 regulates matrix metalloproteinases-1 induction and CD147/EMMPRIN cell surface clustering. J Biol Chem *279*: 11112-11118, 2004.

51 Tang W, Chang SB and Hemler ME: Links between CD147 function, glycosylation, and caveolin-1. Mol Biol Cell *15*: 4043-4050, 2004.

52 Dai JY, Dou KF, Wang CH, Zhao P, Lau WB, Tao L, Wu YM, Tang J, Jiang JL and Chen ZN: The interaction of HAb18G/CD147 with integrin alpha6beta1 and its implications for the invasion potential of human hepatoma cells. BMC Cancer *9*: 337, 2009.

53 Curtin KD, Zhang Z and Wyman RJ: Gap junction proteins are not interchangeable in development of neural function in the *Drosophila* visual system. J Cell Sci *115*: 3379-3388, 2002.

54 Curtin KD, Meinertzhagen IA and Wyman RJ: Basigin (EMMPRIN/CD147) interacts with integrin to affect cellular architecture. J Cell Sci *118*: 2649-2660, 2005.

55 Khunkaewla P, Schiller HB, Paster W, Leksa V, Cermak L, Andera L, Horejsi V and Stockinger H: LFA-1-mediated leukocyte adhesion regulated by the interaction of CD43 with LFA-1 and CD147. Mol Immunol *45*: 1703-1711, 2008.

56 Zou W, Yang H, Hou X, Zhang W, Chen B and Xin X: Inhibition of CD147 gene expression *via* RNA interference reduces tumor cell invasion, tumorigenicity and increases chemosensitivity to paclitaxel in HO-8910pm cells. Cancer Lett *248*: 211-218, 2007.

57 Toole BP and Slomiany MG: Hyaluronan, CD44 and Emmprin: partners in cancer cell chemoresistance. Drug Resist Update *11*: 110-121, 2008.

58 Li QQ, Cao XX, Xu JD, Chen Q, Wang WJ, Tang F, Chen ZQ, Liu XP and Xu ZD: The role of P-glycoprotein/cellular prion protein interaction in multidrug-resistant breast cancer cells treated with paclitaxel. Cell Mol Life Sci *66*: 504-515, 2009.

59 Marieb EA, Zoltan-Jones A, Li R, Misra S, Ghatak S, Cao J, Zucker S and Toole BP: Emmprin promotes anchorage-independent growth in human mammary carcinoma cells by stimulating hyaluronan production. Cancer Res *64*: 1229-1232, 2004.

60 Kuang YH, Chen X, Su J, Wu LS, Liao LQ, Li D, Chen ZS and Kanekura T: RNA interference targeting CD147 induces apoptosis of multidrug-resistant cancer cells related to XIAP depletion. Cancer Lett *276*: 189-195, 2009.

61 Yang JM, O'Neill P, Jin W, Foty R, Medina DJ, Xu Z, Lomas M, Arndt GM, Tang Y, Nakada M, Yan L and Hait WN: Extracellular matrix metalloproteinase inducer (CD147) confers resistance of breast cancer cells to anoikis through inhibition of Bim. J Biol Chem *281*: 9719-9727, 2006.

62 Yang JM, Xu Z, Wu H, Zhu H, Wu X and Hait WN: Overexpression of extracellular matrix metalloproteinase inducer in multidrug resistant cancer cells. Mol Cancer Res *1*: 420-427, 2003.

63 Misra S, Ghatak S, Zoltan-Jones A and Toole BP: Regulation of multidrug resistance in cancer cells by hyaluronan. J Biol Chem *278*: 25285-25288, 2003.

64 Li QQ, Wang WJ, Xu JD, Cao XX, Chen Q, Yang JM and Xu ZD: Involvement of CD147 in regulation of multidrug resistance to P-gp substrate drugs and *in vitro* invasion in breast cancer cells. Cancer Sci *98*: 1064-1069, 2007.

65 Riethdorf S, Reimers N, Assmann V, Kornfeld JW, Terracciano L, Sauter G and Pantel K: High incidence of EMMPRIN expression in human tumors. Int J Cancer *119*: 1800-1810, 2006.

66 Li Y, Xu J, Chen L, Zhong WD, Zhang Z, Mi L, Zhang Y, Liao CG, Bian HJ, Jiang JL, Yang XM, Li XY, Fan CM, Zhu P, Fu L and Chen ZN: HAb18G (CD147), a cancer-associated biomarker and its role in cancer detection. Histopathology *54*: 677-687, 2009.

67 Sameshima T, Nabeshima K, Toole BP, Yokogami K, Okada Y, Goya T, Koono M and Wakisaka S: Expression of EMMPRIN (CD147), a cell surface inducer of matrix metalloproteinases, in normal human brain and gliomas. Int J Cancer *88*: 21-27, 2000.

68 Rosenthal EL, Shreenivas S, Peters GE, Grizzle WE, Desmond R and Gladson CL: Expression of extracellular matrix metalloprotease inducer in laryngeal squamous cell carcinoma. Laryngoscope *113*: 1406-1410, 2003.

69 Sillanpää S, Anttila M, Suhonen K, Hämäläinen K, Turpeenniemi-Hujanen T, Puistola U, Tammi M, Sironen R, Saarikoski S and Kosma VM: Prognostic significance of extracellular matrix metalloproteinase inducer and matrix metalloproteinase 2 in epithelial ovarian cancer. Tumour Biol *28*: 280-289, 2007.

70 Liang YX, He HC, Han ZD, Bi XC, Dai QS, Ye YK, Qin WJ, Zeng GH, Zhu G, Xu CL and Zhong WD: CD147 and VEGF expression in advanced renal cell carcinoma and their prognostic value. Cancer Invest *27*: 788-793, 2009.

71 Chen X, Kanekura T and Kanzaki T: Expression of Basigin in human fetal, infantile and adult skin and in basal cell carcinoma. J Cutan Pathol *28*: 184-190, 2001.

72 Davidson B, Goldberg I, Berner A, Kristensen GB and Reich R: EMMPRIN (extracellular matrix metalloproteinase inducer) is a novel marker of poor outcome in serous ovarian carcinoma. Clin Exp Metastasis *20*: 161-169, 2003.

73 Als AB, Dyrskjøt L, von der Maase H, Koed K, Mansilla F, Toldbod HE, Jensen JL, Ulhøi BP, Sengeløv L, Jensen KM and Orntoft TF: Emmprin and survivin predict response and survival following cisplatin-containing chemotherapy in patients with advanced bladder cancer. Clin Cancer Res *13*: 4407-4414, 2007.

74 Barrett T and Edgar R: Gene expression omnibus: microarray data storage, submission, retrieval and analysis. Meth Enzymol *411*: 352-369, 2006

75 Koch C, Staffler G, Hüttinger R, Hilgert I, Prager E, Cerný J, Steinlein P, Majdic O, Horejsí V and Stockinger H: T-Cell activation-associated epitopes of CD147 in regulation of the T-cell response, and their definition by antibody affinity and antigen density. Int Immunol *11*: 777-786, 1999.

76 Staffler G, Szekeres A, Schütz GJ, Säemann MD, Prager E, Zeyda M, Drbal K, Zlabinger GJ, Stulnig TM and Stockinger H: Selective inhibition of T-cell activation *via* CD147 through novel modulation of lipid rafts. J Immunol *171*: 1707-1714, 2003.

77 Chiampanichayakul S, Peng-in P, Khunkaewla P, Stockinger H and Kasinrerk W: CD147 contains different bioactive epitopes involving the regulation of cell adhesion and lymphocyte activation. Immunobiology *211*: 167-78, 2006.

78 Xu J, Xu HY, Zhang Q, Song F, Jiang JL, Yang XM, Mi L, Wen N, Tian R, Wang L, Yao H, Feng Q, Zhang Y, Xing JL, Zhu P and Chen ZN: HAb18G/CD147 functions in invasion and metastasis of hepatocellular carcinoma. Mol Cancer Res *5*: 605-614, 2007.

79 Xu J, Shen ZY, Chen XG, Zhang Q, Bian HJ, Zhu P, Xu HY, Song F, Yang XM, Mi L, Zhao QC, Tian R, Feng Q, Zhang SH, Li Y, Jiang JL, Li L, Yu XL, Zhang Z and Chen ZN: A randomized controlled trial of Licartin for preventing hepatoma recurrence after liver transplantation. Hepatology *45*: 269-276, 2007.

80 Dean NR, Newman JR, Helman EE, Zhang W, Safavy S, Weeks DM, Cunningham M, Snyder LA, Tang Y, Yan L, McNally LR, Buchsbaum DJ and Rosenthal EL: Anti-EMMPRIN monoclonal antibody as a novel agent for therapy of head and neck cancer. Clin Cancer Res *15*: 4058-4065, 2009.

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