Published in final edited form as:

Exp Mol Pathol. 2007 December ; 83(3): 283–295.

CD147 Immunoglobulin Superfamily Receptor Function and Role in Pathology

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Abstract

The immunoglobulin superfamily member CD147 plays an important role in fetal, neuronal, lymphocyte and extracellular matrix development. Here we review the current understanding of CD147 expression and protein interactions with regard to CD147 function and its role in pathologic conditions including heart disease, Alzheimer's disease, stroke and cancer. A model linking hypoxic conditions found within the tumor microenvironment to up-regulation of CD147 expression and tumor progression is introduced.

Keywords

CD147; EMMPRIN; MMP; MCT; immunoglobulin superfamily; integrin; tumor; metastasis

1. Introduction

CD147, a member of the immunoglobulin superfamily, was discovered twenty five years ago (Biswas 1982), however, very little is known about its regulation and function *in vivo*. Originally identified as a tumor surface protein capable of inducing matrix metalloproteinase (MMP) expression in fibroblasts, the protein was initially termed tumor cell-derived collagenase stimulatory factor (TCSF) (Biswas et al. 1987; Ellis et al. 1989). Following its cloning, TCSF was determined to be a transmembrane glycoprotein that was highly homologous with proteins of the immunoglobulin (Ig) superfamily (Fossum et al. 1991; Miyauchi et al. 1991; Kasinrer et al. 1992; Biswas et al. 1995) and was able to induce the production of several MMPs (Kataoka et al. 1993; Biswas et al. 1995; Guo et al. 1997). These findings resulted in the renaming of the protein as CD147/EMMPRIN (extracellular matrix metalloproteinase inducer) (Biswas et al. 1995; Guo et al. 1997). While increased expression of CD147 occurs in many tumors, its expression is not limited to tumor cells (Ellis et al. 1989; Muraoka et al. 1993; Polette et al. 1997; van den Oord et al. 1997; Bordador et al. 2000; Sameshima et al. 2000; Jiang et al. 2001). CD147 is a pleiotropic molecule that is critical in fetal development and retinal function and has been shown to play a role in thymic T cell development, as well as many neurological processes ranging from the development of the nervous system to involvement in spatial learning and plaque formation within Alzheimer's stricken brains (Naruhashi et al. 1997; Muramatsu et al. 2003; Zhou et al. 2005). Because of the ubiquitous expression and pleiotropic nature of this molecule, understanding the protein-protein interactions and regulation of CD147 expression is essential for therapeutic intervention

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strategies. Here we will review the functional consequences of CD147 expression under physiologic and pathologic conditions as well as the body of literature on CD147 structure and associated proteins.

2. Structural Organization

CD147 is a transmembrane glycoprotein that was categorized as a member of the immunoglobulin superfamily (IgSF) of receptors (Fossum et al. 1991; Miyauchi et al. 1991; Kasinrerker et al. 1992; Biswas et al. 1995). CD147 was identified independently in various species and are referenced throughout the literature as EMMPRIN (Extracellular Matrix Metalloproteinase-Inducer), M6 (Human) (Kasinrerker et al. 1992), Neurothelin, 5A11 and HT7 (chicken) (Seulberger et al. 1992; Fadool et al. 1993; Schlosshauer et al. 1995), OX47 and CE9 (rat) (Fossum et al. 1991; Nehme et al. 1995), and Basigin, gp42 (human and mouse) (Altruda et al. 1989; Miyauchi et al. 1991; Miyauchi et al. 1995). The CD147 gene, designated BSG for basigin, is located on chromosome 19p13.3 and encodes a 29 kD protein, though migration on SDS-PAGE usually occurs between 35–65 kD, depending on the degree of glycosylation (Kasinrerker et al. 1992; Kirsch et al. 1997; Kasinrerker et al. 1999). Treatment of the protein with endoglycosidase F demonstrated that almost half of CD147's molecular weight was due to the addition of N-linked carbohydrates (Kasinrerker et al. 1992). The protein is composed of an extracellular domain of 187 residues, a 24 residue transmembrane domain and a 40 amino acid cytoplasmic region (Biswas et al. 1995). CD147 is classified as a member of a small family of related proteins, including the teratocarcinoma antigen GP70 and the synaptic glycoprotein SDR1, that share the features of two Ig-like extracellular domains, a short cytoplasmic tail, and a single transmembrane domain (Fossum et al. 1991; Shirozu et al. 1996). Three glycosylation sites have been identified within the CD147 Ig like domains: two within the membrane proximal Ig domain and one within the distal Ig domain (Hakomori 1996; Sun et al. 2001; Tang et al. 2004). N-linked glycosylation is critical to CD147 and is postulated to serve as a regulatory mechanism of CD147 function.

Recently, a distinct CD147 transcript that encodes for three Ig domains was identified in mouse retina (Hanna et al. 2003; Ochrietor et al. 2003). While this variant has not been fully characterized as of yet, it is believed to aid in the alignment of CD147 associated lactate transporters to sites of cell-cell contact via homophilic CD147 interactions.

3. CD147-Associated Proteins

A single charged glutamic acid residue resides within the hydrophobic transmembrane domain of CD147 (Fossum et al. 1991). This feature is atypical of transmembrane domains and was first described for the neu oncoprotein as a way to promote oligomerization (Weiner et al. 1989) or to potentiate protein-protein interactions. Sequence comparison of the various species-specific CD147 isoforms have demonstrated a high degree of conservation within both the cytoplasmic and transmembrane domains, implying a high degree of functional importance associated with these regions (Miyauchi et al. 1991). Studies performed with a CD2-CD147 chimera implicate the transmembrane and cytoplasmic domains of CD147 as being critical for protein-protein interactions within the plasma membrane (Kirk et al. 2000). Two members of the monocarboxylate transporter (MCT) family of proteins, MCT1 and MCT4, were found to require CD147 as a chaperone for their expression at the plasma membrane (Kirk et al. 2000). Additionally, experimental evidence exists for CD147's association with integrin (Berdichevski et al. 1997; Curtin et al. 2005) caveolin-1 (Cav-1) (Tang et al. 2004), and cyclophilins (CyP) (Yurchenko et al. 2001; Pushkarsky et al. 2005; Yurchenko et al. 2005). These protein interactions are critical to CD147's function and explain the complexity of CD147 behavior.

MCT

Monocarboxylate transporter proteins catalyze the proton-linked transport of monocarboxylates, including lactate and pyruvate: elements essential for the maintenance of metabolic homeostasis within most cells (Halestrap et al. 1999). All MCT proteins share the same basic structure, having 12 transmembrane domains and cytosolically-exposed C and N termini, as well as a large loop region between transmembrane domains 6 and 7 (Halestrap et al. 1999). Despite the structural similarities between the fourteen members that comprise this family, experimental evidence of proton-linked transport exists only for the first four isoforms (MCT1-MCT4).

CD147 has been shown to interact and co-immunoprecipitate with two members of the proton-linked MCT family, MCT1 and MCT4 (Kirk et al. 2000). In all tissues expressing MCT1 or MCT4, CD147 expression was consistently found co-localized in the same regions (Kirk et al. 2000). MCT1 and MCT4 require direct association with CD147 within the cell for their transport to the plasma membrane (Kirk et al. 2000). CD147 was initially thought to serve solely as a chaperone in this instance, yet their association persists once the proteins localize within the plasma membrane, intimating another function to this complex. While the significance of this continued association is not yet clear, recent evidence suggests that CD147 association with MCT1 or MCT4 within the plasma membrane is essential for MCT mediated lactate transport (Wilson et al. 2005). Fluorescence resonance energy transfer analyses suggest that the minimal complex consists of a dimer of CD147 interacting with two MCT1 molecules (Wilson et al. 2002). Aggressive tumors were found to express higher than usual levels of CD147, which corresponded with up-regulated levels of MCT1 (Froberg et al. 2001; Jin et al. 2006; Jin et al. 2006; Nabeshima et al. 2006; Zhang et al. 2006); an event potentially necessary to meet the high glycolytic needs of transformed cells. Recently, expression of MCT4 was shown to control plasma membrane localization of CD147 in a metastatic breast cancer cell line (Gallagher et al. 2007). The increased expression of MCTs observed in many forms of cancer is important to tumor viability. Tumor cells thrive under hypoxic conditions, yet their high glycolytic nature results in the production of excess lactic acid, which, in turn, has to be regulated by MCT for tumor survival. Increased expression of MCTs could serve as an indicator of the transition from normalcy to malignancy. Indeed, recently, MCT inhibitors have been proposed as anti-cancer agents (Wahl et al. 2002; Coss et al. 2003; Mathupala et al. 2004; Fang et al. 2006).

Integrin

Integrins constitute a superfamily of membrane proteins that allow individual cells to communicate with their environment. Through their interactions with the extracellular matrix (ECM), external stimuli are transmitted internally through the activation of various signaling cascades, thus allowing cells to adapt to environmental changes. Two types of integrin signaling exist: direct, whereby an extracellular ligand binds to integrin and induces intracellular signaling and indirect, whereby changes in integrin-mediated cell anchorage result from altered mitogen signaling (Keely et al. 1998; Springer et al. 2004). Most integrins are non-covalently linked heterodimers composed of both an alpha and beta subunit with functional specificity defined by the pairing of these subunits.

Originally thought to function independently, a growing body of evidence has demonstrated that broader functions for integrins exist through their ability to interact with other membrane-bound proteins in *cis* (Porter et al. 1998); CD147 is one such protein. Immunoprecipitation and immunofluorescent co-localization experiments identified two integrin isoforms, $\alpha_3\beta_1$ and $\alpha_6\beta_1$, that associate with CD147 at points of cell-cell contact (Berdichevski et al. 1997). These integrins, which were shown to preferentially bind to laminins, non-collagenous glycoproteins that serve as the major constituent of the basement membrane (Delwel et al. 1994; Kikkawa

et al. 1998), have been implicated in several processes critical to metastasis, including the promotion of cell adhesion (Malinda et al. 1996; Engbring et al. 2003), angiogenesis (Malinda et al. 1999; Engbring et al. 2003), signaling, which includes MMP induction (Reich et al. 1995; Morini et al. 2000) and chemotaxis and proliferation (Engbring et al. 2003). Through the association of CD147 with integrin, it is possible that CD147 may regulate the integrin/laminin association, and in so doing, regulate such diverse processes as basement membrane formation (Malinda et al. 1996), fetal development (Ryan et al. 1996; Ekblom et al. 2003), the promotion of cell adhesion (Malinda et al. 1996; Engbring et al. 2003), angiogenesis (Malinda et al. 1999; Engbring et al. 2003), signaling, MMP induction, chemotaxis and proliferation.

The interaction of CD147 with integrin is conserved in *Drosophila* and is proposed to play a role in dorsal closure and extraembryonic membrane apposition (Reed et al. 2004), as well as in maintenance of cellular architecture through cytoskeletal rearrangement (Curtin et al. 2005). Within cultured insect cells, CD147/integrin interactions are essential for lamellipodia formation and within retinal cells disruption of the CD147-integrin interaction results in aberrant distribution of organelles, including mitochondria, nuclei, and rough endoplasmic reticulum (Curtin et al. 2005).

Cyclophilins

Cyclophilins (CyP) are members of the immunophilin family of peptidyl-prolyl cis-trans isomerases having proposed functions as chaperones and mediators of protein folding (Galat 1993). The notion of cyclophilin A functioning as a chaperone comes from several lines of evidence, including its association with protein transport complexes as well as its ability to regulate the surface expression of the asialoglycoprotein receptor in human cells (Huang et al. 2002) and the rhodopsin photoreceptor in *Drosophila* (Colley et al. 1991). Recently, several reports implicated cyclophilins as regulators of CD147 surface expression following the observation that cyclosporine A (CsA), which binds CyP, adversely affected CD147 surface expression (Yurchenko et al. 2001; Pushkarsky et al. 2005; Yurchenko et al. 2005). Peptide binding studies identified proline 211 (P211) within the CD147 transmembrane domain as being essential for CyP associated transport of CD147 to the plasma membrane (Yurchenko et al. 2005). In a subsequent study by this group, the lesser-characterized CyP60 was identified as the chaperone of CD147 (Pushkarsky et al. 2005).

Aside from their functioning as protein chaperones, cyclophilins also mediate chemotaxis of neutrophils, eosinophils and T cells when secreted from cells in response to inflammatory stimuli (Sherry et al. 1992; Xu et al. 1992; Allain et al. 2002; Yurchenko et al. 2002). Cell surface heparans are the primary receptors for secreted CyP (Denys et al. 1998; Saphire et al. 1999). Recently, however, CD147 has been identified as being essential for cyclophilin-mediated signaling (Yurchenko et al. 2002; Arora et al. 2005). Binding of extracellular CyPA to CD147 via heparans resulted in Erk activation and chemotaxis. Two amino acids, proline 180 and glycine 181, were identified within the extracellular domain of CD147 as being crucial for CD147 mediated signaling and chemotaxis. Additionally, through the use of CyPA mutants, the rotamase activity of CyPA was found to be important for this CD147 mediated signaling (Yurchenko et al. 2002). Interestingly, the association of CyPA and CD147 is further supported by findings that increased levels of CyPA in synovial fluid and increased CD147 levels on reactive neutrophils in rheumatoid arthritis patients correlated with the severity of disease (Tegeder et al. 1997; Konttinen et al. 2000). Furthermore, CyPA is incorporated into HIV-1 virions and has been shown to play a role in early viral infection (Braaten et al. 1996; Sherry et al. 1998). CD147 has been shown to facilitate HIV-1 infection through its interaction with viral associated CyPA (Pushkarsky et al. 2001).

In a mouse model of induced asthma where elevated airway levels of cyclophilins have been observed, targeting the cyclophilin-CD147 interaction using anti-CD147 mAb decreased

recruitment of activated Th2 effector cells into inflamed lung tissues, resulting in decreased cytokine production and eosinophil recruitment and therefore greatly decreased lung inflammation and pathology (Gwinn et al. 2006). Clearly, cyclophilins are capable of modulating the immune response through their specific association with cellular proteins including CD147.

Caveolin-1

Caveolin proteins serve as the major constituents of caveolae, cholesterol- and glycosphingolipid-rich moieties present within the plasma membranes of most cells that mediate the transcytosis of macromolecules in a clathrin-independent manner (Williams et al. 2005). Since their initial characterization, many other functions have been ascribed to these structures, including cholesterol homeostasis, the organization and retention of cellular receptors and signal transducing elements reviewed in (Williams et al. 2004) and, most recently, as a regulator of transformation and tumorigenesis (Williams et al. 2004; Williams et al. 2005; Williams et al. 2005). While the caveolin family of proteins is comprised of three isoforms (caveolins 1, 2 and 3), only caveolin-1 has been shown to directly associate with CD147. This association apparently begins within the Golgi apparatus, with caveolin-1 specifically binding to and escorting the lower glycosylated forms of CD147 to the plasma membrane; thus preventing the formation of the self-aggregating, highly glycosylated species of CD147 which is responsible for MMP production (Tang et al. 2004). Caveolin-1 is proposed to serve as a negative regulator of CD147; the direct association of cav-1 with the second Ig domain of CD147 was found to decrease CD147 clustering (Tang et al. 2004). This hypothesis was supported by the generation of a CD147 mutant lacking the second Ig domain, which was incapable of associating with caveolin-1, as well as following the RNAi knockdown of caveolin-1, both of which resulted in impaired MMP production (Tang et al. 2004).

Recently, studies using murine hepatocarcinoma cell lines demonstrated an opposite effect of caveolin-1, namely that increased caveolin -1 expression results in an increased proportion of highly glycosylated CD147 relative to the lower glycosylated form and increased production of MMP-11 and higher invasiveness. In these studies down regulation of caveolin -1 resulted in a decrease in highly glycosylated CD147 (Jia et al. 2006). Regardless of the outcome of these studies, it is clear that the expression of CD147 glycosylation forms is functionally linked with caveolin -1 expression.

4. CD147 Function: clues from CD147 null mice

Just as CD147 has been found in association with several proteins and has been shown to be expressed on many cell types, the functions ascribed to CD147 are varied and are evidenced in the phenotype observed in the CD147 null mouse. One of the first observations regarding the CD147 null mouse was that implantation of the null fetus was severely impaired (Igakura et al. 1996; Naruhashi et al. 1997; Igakura et al. 1998). Although CD147 null embryos developed normally during the early stages of preimplantation, fewer than 8% of null embryos successfully implanted in the uterus of CD147 heterozygous females mated to heterozygous males (CD147 +/-) (Igakura et al. 1998). Increased expression of CD147 within the uterus of wildtype mice was observed at the stage of blastocyst implantation in the endometrium (Igakura et al. 1998; Kuno et al. 1998). Additionally, during the time of implantation increased levels of CD147 expression was detected in the trophectoderm of the wildtype embryo indicating the possibility that CD147 function, with respect to fetal development, is incumbent upon the induction of MMP production (Igakura et al. 1998); evidence in support of this notion was found in both mice and humans. Within human placentas, it is believed that CD147, through the induction of MMP production, may induce fetal membrane rupture and detachment from the uterus at the time of parturition (Li et al. 2004). Interestingly, CD147 null females were capable of supporting gestation of implanted CD147 wildtype embryos although with severely

reduced efficiency (Igakura et al. 1998). Male CD147 null mice are sterile due to arrest of spermatogenesis at the metaphase of the first meiosis (Igakura et al. 1998). Together these observations indicate that CD147 expression within both the uterus and the embryo are required for successful implantation and suggest a functional interaction of CD147 with cell membrane proteins.

CD147 mediated transport of MCT1 and MCT4 to the plasma membrane is crucial to many processes. CD147 null mice were found to be deficient for MCT1, MCT3 and MCT4 within the retinal pigment epithelia, leading to blindness as a result of abnormal photoreceptor function (Hori et al. 2000; Ochrietor et al. 2002; Philp et al. 2003). Retinal development requires the coordinated shuttling of lactate between photoreceptor cells and Muller cells. Muller cells metabolize glucose as their main source of energy and, in the process, produce lactate as a major end product, while this lactate can be used to fuel oxidative phosphorylation within neighboring photoreceptor cells. MCT1, whose expression within the plasma membrane is incumbent upon its association with CD147, transports the lactate between these cells; therefore, the metabolic potential of both cell types are coupled to one another in an MCT1 dependent manner. The importance of this coupling is most evident in CD147 null mice. Absence of CD147 results in impaired surface expression of MCT1, which in turn results in the death of photoreceptor cells and ultimately blindness due to the lack of lactate transport (Philp et al. 2003). Retinal specific expression of the three Ig domain isoform of CD147, (Ochrietor et al. 2003) suggests that the homophillic interaction of this CD147 isoform may direct MCT1 specifically to areas of cell-cell contact (Hanna et al. 2003).

CD147 Function: an inducer of matrix metalloproteinases

CD147 was initially identified following the observation that interstitial collagenase (MMP-1) production was induced during the co-culturing of tumor cells and fibroblasts (Biswas 1982; Biswas 1984). Further studies revealed that CD147 is capable of inducing the expression of several MMPs other than MMP-1, including MMP-2, MMP-3, MMP-9 and MMP-11 and as such was renamed EMMPRIN/CD147 (Kataoka et al. 1993; Biswas et al. 1995; Guo et al. 1997). It was determined that either CD147 expressing tumor cells or conditioned media from the same cells were equally capable of inducing MMP production in co-cultured fibroblast cells (Biswas 1982; Biswas 1984). Increased MMP expression was obtained following the exogenous treatment of fibroblasts with recombinant CD147 protein as well as the adenoviral transduction of fibroblasts with CD147 in the absence of tumor cells (Li et al. 2001). These studies indicated that membrane bound and soluble CD147 are equally capable of inducing MMP production from fibroblast cells. The soluble form of CD147 has been detected in conditioned media as full length protein (Taylor et al. 2002) or as part of shed microvesicles (Sidhu et al. 2004), as well as in forms lacking the transmembrane and cytoplasmic domain derived from MMP mediated cleavage of CD147 from the cell surface (Haug et al. 2004; Tang et al. 2004; Egawa et al. 2006; Maatta et al. 2006).

Recent studies have addressed whether CD147 expressed on tumor cells induces production of MMP from surrounding peritumoral fibroblasts and whether CD147 could induce MMP production from tumor cells themselves. Other features that have been resolved include the fact that CD147, like other Ig containing molecules, interact homotypically. Sun and Hemler produced recombinant soluble CD147 fusion proteins and, using CD147 transfectants, determined that CD147 can interact homotypically via the D1 Ig domain. Additionally, soluble CD147 was shown to induce MMP production from fibroblasts expressing CD147 as well as from tumor cells themselves (Sun et al. 2001). These experiments do not rule out the possibility of a distinct receptor for CD147, however. Transfection of human breast cancer cells with CD147 cDNA followed by injection into mammary tissue of nude mice resulted in an enhancement of tumor growth and increase in metastatic incidences, both of which were

directly correlated with high levels of tumor-derived MMP-2 and MMP-9 (Zucker et al. 2001). The induction of MMP-2 transcription was found to be directly linked to the glycosylation status of CD147 (Sun et al. 2001). Treatment of CD147 expressing MDA-435 breast carcinoma cells with either anti-CD147 antibody or purified, deglycosylated CD147 did not lead to the induction of MMP-1 and MMP-2 expression and treatment with deglycosylated CD147 antagonized the MMP induction capabilities of purified, native CD147, as well (Sun et al. 2001). Clearly there is a requirement for the N-linked glycosylation of CD147 in MMP induction.

Further evaluation of CD147 glycosylation demonstrated a link between the complexity of the attached sugars, CD147 function and cancer; whereby the CD147 expressed on cancer cells were found to contain the more complex β 1–6 branched poly lactosamine sugars as opposed to the lower glycosylated species which typically contain mannose (Tang et al. 2004). The degree of glycosylation, the complexity of the associated sugars and their link to cancer is thought to occur at the level of cellular association with the extracellular matrix (ECM). It has been postulated that CD147 glycosylation allows for greater association with the ECM; this, coupled with the fact that glycosylation is required for the induction of MMP expression, suggest this process may serve as a regulatory mechanism of CD147 function as well as a possible therapeutic strategy (Hakomori 1996; Sun et al. 2001; Tang et al. 2004).

Role in lymphocyte migration and activation

Thymocyte maturation occurs through a series of distinct stages and is thought to require two distinct signals: one that regulates survival / selection of the population and one that initiates expansion of the population. While the pre-TCR signaling complex, comprised of TCR β chain, pT α and a functional CD3 complex, was found to regulate selection / survival, evidence suggests that CD147 ligation can serve as the second signal necessary for expansion (Renno et al. 2002). Within the thymus, CD147 expression is highest on late stage, immature thymocytes, which correlates with transition to the next maturational level. The requirement of CD147 in T cell maturation was illustrated following the treatment of immature fetal lymphocytes with an anti-CD147 monoclonal antibody, which arrested any further development (Renno et al. 2002).

Within circulating immune cell populations, CD147 is highly expressed on activated T and B lymphocytes, as well as dendritic cells, monocytes and macrophage (Koch et al. 1999). CD147 was identified as an activation associated antigen on PHA activated T cells (Kasinerk et al. 1992). Analysis of mRNA levels in both naïve and activated T cells revealed a 3.75-fold increase in CD147 transcription in the activated population (Zhang et al. 2002). Recently, increased expression of CD147 was observed on CD3+ T cells from systemic lupus erythematosus patients compared to healthy donor T cells, likely indicating their increased activation (Pistol et al. 2007). Engagement of CD147 with the MEM-M6/6 anti-CD147 monoclonal antibody was found to inhibit anti-CD3 induced T cell activation (Koch et al. 1999), presumably by inhibiting the reorganization and clustering of GPI-anchored co-receptors within lipid rafts which in turn alters down-stream signaling events (Staffler et al. 2003). For T cells, the level of CD147 expression also correlates with the state of differentiation, whereby immature thymocytes express higher CD147 levels than do mature resting T cells (Kirsch et al. 1997).

Blocking CD147 expressed on antigen presenting cells inhibits T cell activation. Studies on antibody pre-pulsed monoblastoid cells or peripheral blood dendritic cells co-cultured with T cells revealed inhibition of anti-CD3 induced T cell proliferation as well as inhibition of alloantigen induced T cell responses, suggesting that CD147-dependent T cell activation occurs at the level of the antigen presenting cell (APC) rather than the T cell (Stonehouse et al. 1999; Woodhead et al. 2000). This may be attributable to CD147's function as an adhesion

molecule. Studies performed with anti-CD147 treated human monoblastoid U937 cells demonstrated the importance of CD147-induced cellular adhesion and highlighted the involvement of the LFA-1/ICAM-1 pathway in this process (Kasinrerk et al. 1999). These findings, coupled with the fact that CD147 is expressed on both APCs and T cells, suggests a more general function for CD147 as a mediator of cell-cell interaction and regulator of antigen presentation (Woodhead et al. 2000).

The specific targeting of CD147 has proven efficacious in the treatment of steroid-refractory acute graft-versus-host disease (GVHD) (Deeg et al. 2001). GVHD is a T cell mediated disorder whereby donor lymphocytes recognize host tissues as foreign and initiate immune responses against them. As a result, acute GVHD is a major complication following hematopoietic stem cell transplantations. Because CD147 is primarily expressed on activated T cell populations, those cells that would mediate GVHD can be selectively targeted without disrupting/depleting the entire complement of T cells. Administration of the anti-CD147 antibody ABX-CBL, an immunoglobulin M murine monoclonal antibody, extended the median survival time from 20 days post-transplantation to 117 days with little to no adverse side effects reported (Deeg et al. 2001).

5. CD147 in Disease: Cancer

The metastatic potential of cancerous cells is dependent upon their ability to disengage themselves from environmental cues that serve to regulate and constrain them. Typically, successful metastasis requires alterations in cytoskeletal architecture, expression of surface adhesion molecules and penetration of the basement membrane; phenomena that have been allied with known CD147 function. While the sequence of events leading to unregulated growth has yet to be elucidated, the induction of MMP activity has been shown to mediate the degradation of the ECM, thus alleviating the physical constraint to cell movement *in vivo*. The fact that CD147 is found over-expressed in a number of cancerous specimens, coupled with its ability to induce MMP expression, suggests that it serves as a key regulator of oncogenesis and that it is linked with one or more signaling pathways.

Evaluation of several signaling pathways has demonstrated a link between CD147 and the MAPK cascade (Lim et al. 1998). In metastatic ovarian carcinoma, the activities of the extracellular signal-regulated kinase (ERK), p38 and c-Jun N-terminal kinase (JNK) were found to be elevated concomitantly with increased MMP-2 production (Davidson et al. 2003). Further evaluation of these signaling pathways demonstrated that a distinct pattern existed between these signaling proteins and the protein expression patterns they subsequently induced. MMP-2 expression was found to correlate with activation of both ERK and p38 kinases, MMP-9 correlated positively with p38 activation and inversely with ERK expression and activation, while CD147 expression strongly correlated only with activated ERK (Davidson et al. 2003). While fibroblasts normally constitutively express MMPs at low levels, dysregulated MMP expression and activation aids in cancer cell migration. It has been widely documented that tumorigenic cells expressing CD147 induce MMP expression by neighboring fibroblasts (Biswas 1982; Kataoka et al. 1993; Biswas et al. 1995; Guo et al. 1997). Analyses of both tumor and peritumoral fibroblasts in breast, colon, lung, skin and head/neck tumors by *in situ* hybridization revealed that CD147 expression is primarily tumor associated, while MMP expression is fibroblast associated (Pyke et al. 1992; Majmudar et al. 1994; Noel et al. 1994; Heppner et al. 1996; Polette et al. 1997). Of the MMPs induced by CD147, malignant progression has been most closely correlated with the expression of MMP-2 in several forms of cancer (Sameshima et al. 2000; Ishikawa et al. 2004; Kawamura et al. 2004; Pasioka et al. 2004; Morgia et al. 2005; Redondo et al. 2005) and these increased levels are typically indicative of poor prognostic outcome (Vaisanen et al. 1996; Ishibashi et al. 2004; Morgia et al. 2005). Antibodies to CD147 have potential anti-cancer therapeutic utility and have been

shown to decrease MMP expression leading to an inhibition of tumor cell invasion (Bordador et al. 2000; Sun et al. 2001; Kanekura et al. 2002).

Aside from stimulating MMP production in neighboring stromal cells, recent evidence suggests CD147 stimulates its own expression through a positive feedback mechanism and induces the production of vascular endothelial growth factor (VEGF) (Tang et al. 2005) as well as a soluble form of CD147 (Tang et al. 2004). The result of proteolytic cleavage of the carboxy terminus, the generation of a soluble form of CD147 increases the potential for stimulation of MMP expression from adjacent stromal cells to distal ones and is thought to aid metastasis to distant sites (Tang et al. 2004). Furthering the metastatic potential of CD147 expressing tumor cells is their ability to regulate the angiogenic process through the induction of VEGF (Tang et al. 2005). VEGF serves as a major regulator of the angiogenic process in a wide variety of circumstances, including tumor formation. *In vitro* and *in vivo* analyses demonstrate the inextricable link between CD147 expression and the induction of VEGF. In human breast cancer and glioblastoma cell lines, suppression of CD147 by antisense RNA not only reduced the production of MMP-2 and MMP-9 but also downregulated VEGF secretion (Liang et al. 2005; Tang et al. 2005). *In vivo*, tumor growth and angiogenesis were stimulated by the over-expression of CD147 and this phenomenon was inhibited following the antisense suppression of CD147 (Tang et al. 2005).

CD147 is associated with the $\alpha 3\beta 1$ and $\alpha 6\beta 1$ integrins which interact with laminins (Berdichevski et al. 1997). Integrins serve as the major receptors for cellular attachment to the ECM, therefore, it is not surprising that their interaction with laminin, the major component of the basement membrane, serves as a key event in the metastatic process (Engbring et al. 2003). The elevated expression levels of both $\alpha 3\beta 1$ and $\alpha 6\beta 1$ integrins has been witnessed in most metastatic and primary cancers (Bartolazzi et al. 1994; Demetriou et al. 2004). Comparison of normal prostate cells to cancerous cells showed a preferential pairing of $\alpha 6$ with $\beta 4$ that transitioned to $\alpha 6\beta 1$ in cancer cells (Demetriou et al. 2004). The significance of this transition, while still speculated, is most likely related to alterations in downstream signaling events.

Recent evidence suggests that stimulation of $\alpha 3\beta 1$ activates signaling mechanisms that specifically promote tumor cell growth and progression (Choma et al. 2004; Manohar et al. 2004; Wang et al. 2004). The aberrant expression of $\alpha 3\beta 1$ and $\alpha 6\beta 1$ integrin species in many forms of cancer coupled with the fact that they are capable of associating with CD147 suggest these proteins work in concert to mediate ECM breakdown for tumor cell invasion to occur.

Tissue Repair/Remodeling

A delicate balance exists between MMP-induced stromal remodeling/restoration of homeostasis and stromal destruction; intuitively, MMP production must be a tightly regulated process. CD147 has been postulated to mediate this balance directly via a feed-back mechanism that links the affected epithelial cells with neighboring fibroblasts (Gabison et al. 2005). Within the eye, corneal ulcerations predominantly occur as a result of the breakdown of the protective epithelial barrier of the eye, leaving it susceptible to infection by bacteria, viruses and fungi and, if left untreated, they can result in blindness. CD147 has been identified in both healthy and ulcerated corneas, but was found at much greater levels within diseased corneas and its expression was found localized to areas of greater MMP expression (Gabison et al. 2005).

Within the cardiovascular system, this delicate balance is even more evident. MMP expression is critical for the prevention of hypertension and, at the same time, implicated in the progression of congestive heart failure (CHF) (Spinale et al. 2000; Ergul et al. 2004). Remodeling of the human vasculature for the maintenance of pliable vessels occurs through the constant degradation and regeneration of the ECM. Analyses of hypertensive patients identified a deficit

in MMP production concomitant with decreased CD147 expression and increased production of collagen that could contribute to target organ damage, stroke, left ventricular hypertrophy and coronary artery disease (Ergul et al. 2004). Interestingly, greatly decreased CD147 expression and MMP levels were found in diabetic arteries implicating deregulation of CD147 in the diabetic vasculature where pathologic vascular remodeling is characterized by increased collagen deposition (Portik-Dobos et al. 2002).

End-stage CHF is typified by increased wall stress that leads to dysfunctional pumping of the heart resulting from tissue remodeling of the left ventricle. Evaluation of diseased and normal myocardium demonstrated CD147 expression in both populations; however, the diseased samples showed significantly higher levels as well as increased MMP expression (Spinale et al. 2000). Therefore, it is believed that the left ventricular problems associated with CHF are the direct result of dysregulated CD147 expression and MMP activity.

Ischemic disease

Low oxygen conditions exist in the brain during stroke and in the heart during myocardial infarction. During these conditions of hypoxia and ischemia cells within the tissues become dependent upon glycolysis for their energy metabolism. Transport of lactic acid that is produced as a byproduct of glycolysis is required for continued cell viability and is accomplished by the CD147 associated lactate transporters MCT-1 and MCT-4 (Halestrap et al. 1999; Kirk et al. 2000). Upregulation of MCT and CD147 expression is reported under ischemic conditions in neuronal and cardiac cells (Zhang et al. 2005; Han et al. 2006). The up-regulation of MCTs serves to protect cells from lactic acid buildup due to low oxygen levels, however, the coordinated up-regulation of CD147 expression has other effects on the cells and tissues as a result of CD147 interactions with other proteins.

CD147, in conjunction with CyPA, has been reported to protect neurons from oxidative stress and ischemia (Boulos et al. 2007). CD147 has been shown to serve as a receptor for CyPA (Yurchenko et al. 2002). The addition of CyPA to neuronal cultures resulted in activation of ERK1/2 (Boulos et al. 2007), similar to the downstream signaling events observed upon CD147/CyPA association (Yurchenko et al. 2002). CyPA levels are higher in the brain than they are in any other organ, predominantly localizing to neurons. Interestingly, CyPA was found to be released from cardiac myocytes upon hypoxia / reoxygenation in vitro or ischemia / reperfusion in vivo and was accompanied by upregulation of CD147 (Seko et al. 2004). The addition of rhCyPA to cardiac myocyte cultures led to the activation of ERK1/2, p38MAPK, SAPK and Akt. Cardiac myocytes may increase the secretion of CyPA and expression of CD147 in response to hypoxia/reoxygenation as a means to initiate pro-survival signaling in an autocrine fashion thus limiting the amount of cell death (Seko et al. 2004).

Although the CD147 / CyPA association and related signaling may provide protection to neurons and cardiac myocytes from ischemic damage, the induction of matrix metalloproteinases through increased CD147 expression may promote ischemic related pathology by increasing tissue destruction. Increased levels of CD147 within the basal ganglia and cortexes of ischemic brains correlated with increased MMP-2 and MMP-9 levels potentially resulting in destruction of the brain microvasculature following an ischemic event (Burggraf et al. 2005). In cardiac disease CD147, MT-MMP-1, MMP-2 and MMP-9 levels are increased in patients suffering from acute myocardial infarction (MI) but not those with stable angina (Schmidt et al. 2006). MIs are induced by the rupturing of atherosclerotic plaques; a process that is mediated by MMPs, all of which have been detected within vulnerable plaques.

Alzheimer's disease

Alzheimer's Disease is a neurodegenerative disease characterized by progressive cognitive deficiency that is manifested by impaired spatial reasoning, motor commands and language skills. It is the errant production of amyloid β peptides that is believed to lead to the formation of the characteristic amyloid plaques and neurofibrillary tangles within the neocortical and subcortical regions of the brain resulting in disease pathology. The γ secretase complex regulates production of these amyloid β peptides reviewed in (Caltagareone et al. 2006; Zhou et al. 2007). Recently CD147 was observed to be a regulatory component of the γ secretase complex (Zhou et al. 2005). Depletion of CD147 from the γ secretase complex through RNA interference in cell lines resulted in an increase in amyloid β peptide production but had no effect on the expression levels of other complex components or complex substrates suggesting that CD147 may regulate γ secretase activity (Zhou et al. 2005). Interestingly, neurological abnormalities observed in CD147 null mice including spatial learning and memory deficits (Naruhashi et al. 1997) are similar to those observed in mouse models of Alzheimer's disease (Higgins et al. 2003; Richardson et al. 2003). Although the mechanism by which CD147 attenuates the production of amyloid β peptides is unknown, further study of CD147 function within the γ secretase complex may aid Alzheimer's disease therapy. Interestingly, CD147 associated $\alpha 6 \beta 1$ integrins bind amyloid β peptides initiating a signal transduction cascade in microglial cells (Bamberger et al. 2003) indicating the potential for another level of regulation influenced by CD147 expression in Alzheimer's disease.

6. Hypoxic induction of MCT and CD147 expression promotes tumor progression

As tumor size increases hypoxic conditions arise within the tumor microenvironment resulting in the induction of hypoxia inducible factor, HIF-1 α , a transcription factor that has been shown to induce MCT-4 gene expression in cells (Moeller et al. 2005; Moeller et al. 2006). Upregulation of MCTs in tumor cells is advantageous to tumor survival. Rapid tumor proliferation under hypoxic conditions is mediated by glycolysis which produces increased levels of intracellular lactic acid requiring export via MCTs (Figure 1A). Due to the action of upregulated MCTs the concentration of lactic acid increases in the extracellular tumor microenvironment as well. This excess lactic acid has been determined to inhibit peritumoral cytotoxic T cell function, thus permitting continued unchecked growth of the tumor (Fischer et al. 2007). Since MCT surface expression is linked to CD147 due to the requirement for interaction between the two proteins for successful cell surface expression (Kirk et al. 2000), a coordinate upregulation of CD147 is observed on tumor cells. Indeed, screening of numerous clinical tumor specimens consistently reveals a link between the most aggressive tumors and the highest expression levels of CD147 (Davidson et al. 2003; Rosenthal et al. 2003; Ishibashi et al. 2004; Reimers et al. 2004; Li et al. 2005; Cheng et al. 2006; Jin et al. 2006; Jin et al. 2006; Nabeshima et al. 2006; Riethdorf et al. 2006; Vigneswaran et al. 2006; Zhang et al. 2006; Zheng et al. 2006). Increased expression of CD147 results in induction of increased MMP production by peritumoral fibroblasts resulting in degradation of the extracellular matrix and a favorable environment for tumor metastasis (Figure 1B). Inhibition of CD147, MCT, or HIF-1 α within tumor cells would coordinately decrease metastatic potential and tumor progression.

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Figure 1. The CD147-MCT complex promotes tumor progression

A.) Under hypoxic conditions within the tumor microenvironment rapid tumor proliferation is achieved by anaerobic glycolysis, the byproduct of which is lactic acid. Coordinate upregulation of hypoxia inducible factor, HIF-1 α , results in increased transcription of MCT (Moeller et al. 2005; Moeller et al. 2006) and increased cell surface expression of the CD147-MCT complex after their assembly in the Golgi apparatus. Tumor viability is maintained by the MCT facilitated transport of lactic acid into the peritumoral space thus regulating intracellular pH. B) Peritumoral cytotoxic T cell (Tc) function is inhibited by increased lactic acid in the tumor microenvironment (Fischer et al. 2007) enabling unchecked tumor growth. Increased CD147 expression induces MMP production by neighboring fibroblasts (Kataoka et al. 1993; Biswas et al. 1995; Guo et al. 1997; Sun et al. 2001) resulting in breakdown of the extracellular matrix and metastasis of CD147 expressing tumor cells.