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Review

CD147 and its interacting proteins in cellular functions

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Abstract: CD147 (basigin, EMMPRIN, neurothelin, M6, HAb18G, *etc*.), a transmembrane glycoprotein, has a broad expression pattern on various epithelial cells with some differences between species, e.g. rat, mouse, chicken and human, but is highly enriched on the surface of cancer cells of epithelial origin such as lung cancer, breast cancer and hepatoma cells. The CD147 antigen consists of two IgSF domains, a transmembrane sequence containing a charged residue (Glu) and a cytoplasmic domain of 40 residues. The particular structural features suggest that it is involved in protein-protein interactions. Although the interacting molecules are still not well known due to unavailability of the 3D structure of CD147, adhesion, coimmunoprecipitation and other studies recently suggest that several proteins, including integrins, cyclophilins, MCT, *etc*., interact with CD147 as its ligand or receptor candidates to mediate a wide range of cellular functions.

Key words: CD147; EMMPRIN; HAb18G; integrin; monocarboxylic acid transporter; cyclophilin; caveolin-1; βig-h3

CD147 相互作用蛋白及其细胞生物学功能

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摘 要：CD147 (basigin、EMMPRIN、neurothelin、M6、HAb18G 等)是一个跨膜糖蛋白家族，广泛表达于各种上皮细胞，但其表达在大鼠、小鼠、鸡和人等不同种属间存在很大差异性。CD147 高表达于上皮来源的肿瘤细胞表面，如肺癌、乳腺癌和肝癌等。CD147 抗原胞外段有 2 个 IgSF 结构域，跨膜区有一个带电谷氨酸(Glu)残基，胞内段含有 40 个氨基酸。CD147 的结构特点提示其可能参与蛋白 - 蛋白相互作用。由于 CD147 分子的 3D 结构信息还没有获得，与其相互作用的分子还没有完全明确，但近来应用黏附、免疫共沉淀等实验方法，一些研究报道提示，CD147 可与整合素(integrin)、环亲合素(cyclophilins)、单羧酸转运器(monocarboxylate transporter, MCT)等蛋白相互作用，而这些蛋白可能作为 CD147 分子的候选配体或受体，通过蛋白 - 蛋白相互作用，介导广泛的上皮细胞生物学功能。

关键词：CD147；EMMPRIN；HAb18G；整合素；单羧酸转运器；环亲合素；小窝蛋白 -1；βig-h3
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1 Introduction

Homeostasis in organized tissue structures is achieved by a dynamic interplay between the extracellular stroma and the epithelia involving many cellular adhesion molecules (CAMs). Disturbances in this relationship may be involved in the pathogenesis of a variety of epithelial-derived malignancies. CD147 is a widely expressed membrane protein that has been implicated in a variety of physiological and pathological processes. It is a highly glycosylated transmembrane protein with an ectodomain consisting of two regions exhibiting the characteristics of the immunoglobulin (Ig) superfamily which is the largest family of CAMs[1-4]. A well-known protein extracellular matrix metalloproteinase (MMP) inducer (EMMPRIN) forms the CD147 family along with a variety of other proteins, such as OX-47[2] and CE9[5]

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in rats, gp42[6] and basigin[1] in mice, HT7[3], neurothelin[7] and 5A11[8] in chickens, hBasigin, M6[9] and HAb18G[10] in human. As an adhesion molecule, CD147 has been reported to be expressed at varying levels in many epithelial cell types, and to interact with a variety of stroma cells including endothelial cells and fibroblasts, as well as the extracellular matrix[11].

CD147 has an extracellular region with two Ig domains and an N-terminal with several enzyme catalytic sites. The intracellular domain of CD147 is well conserved between species (70% and 60% in mouse *vs* human and chicken, respectively)[4]. The transmembrane domain of CD147 contains a glutamic acid residue, a charged residue which could be involved in the protein association on the plasma membrane. Similar to the leucine zipper motif, 3 leucines are repeated every seventh amino acid residue in the CD147 transmembrane domain[2,3]. This motif may be involved in the association between membrane proteins. As the transmembrane domain is highly conserved between species (96% between mouse and human or chicken[4]), it may serve critical biological functions. These structural features suggest that CD147 may form a complex with other membrane proteins, intracellular enzymes/factors as well as extracellular factors thereby being responsible for many interactions of CD147 with its partners. However, substrates or ligands for CD147 are still not identified. It is not clear whether CD147 is directly involved in signal transduction and cell adhesion as a signal transmitting adhesion molecule or as a regulator of adhesion in the interactions between epithelial cells and the component of extracellular matrix. This review concentrates on recent advances on several molecules which may interact with CD147 as ligand or receptor candidates.

2 Homo-oligomer formation by CD147

CD147 belongs to the Ig superfamily with homology to both the Ig variable (V) domain and MHC class II β chains[1-4]. Proteins with these characteristics form supramolecular structures, such as oligomer, which are crucial to the exertion of their characteristic functions.

Several evidences indicate that CD147 forms homo-oligmers which represent the formation of a macromolecular complex on or within the plasma membrane[12]. It is proposed that such homo-oligmers occur through association with a ligand on an opposing cell surface. It is known that N-terminal Ig domain of CD147 is required for stimulation of fibroblast MMP production[13-15]. By cotransfection of basigin (a member of CD147 family) expression vectors with two different tags, Yoshida *et al*. clarified that basigin forms homo-oligomers in a *cis*-dependent manner on the plasma membrane, and the molecules associate with each other probably via hydrophobic interactions between their N-terminal Ig-like domains. The N-terminal Ig domain of basigin is necessary and sufficient for basigin homo-oligomer formation[16]. Sun *et al*. used CD147 transfectants and immobilized recombinant CD147-Fc fusion protein to show that CD147/EMMPRIN engages in a homophilic interaction, predominantly through the first Ig domain. They also suggested that homophilic CD147-binding may occur in the context of both heterotypic and homotypic cell-cell interactions and may play a key role in MMP-2 production and tumor cell invasion[14].

Nevertheless, monomer form of CD147 with strong intensity does exist in some tissues. These monomers may be involved in other supramolecular structures via heterophilic association with other molecules[16] as discussed below.

3 Association of monocarboxylic acid transporters (MCTs) with CD147

Monocarboxylic acids play an important role in the metabolism of all cells. Some tissues, such as skeletal muscle, red blood cells and many cancer cells, rely on this pathway to produce most of their ATP. Metabolism of glucose via glycolysis results in the production of large quantities of lactate that must be transported out of the cell if high rates of glycolysis are to be maintained. MCTs catalyze proton-coupled transport of monocarboxylic acid, among which lactate is especially important.

Chemical cross-linking, coexpression, coimmunoprecipitation and colocalization studies have identified MCT1, MCT3 and MCT4 to be specifically associated with CD147 in the plasma membrane[17-19]. The association facilitates the expressions of both MCTs and CD147[18-20]. siRNA-mediated silencing of MCT4 impaired the maturation and trafficking of CD147 to the cell surface, resulting in an accumulation of CD147 in the endoplasmic reticulum. Knockdown of CD147 resulted in loss of MCT4 in the plasma membrane and accumulation of the transporter in the endolysosomes[20]. Similar results were also obtained in CD147-null mice, which showed the normal levels of transcribed MCT1, MCT3 and MCT4 mRNA, but severely reduced protein levels[21,22]. By using the fluorescence resonance energy transfer (FRET), Wilson *et al*. revealed that a dimer of CD147 binds to two molecules of MCT1[23]. Studies using CD147 chimeras indicated that the cytoplasmic tail and/or transmembrane regions of CD147 may be particularly important for association with MCT1[23]. All the data imply that CD147 acts as a chaperone for MCT1 and MCT4 translocation to the plasma membrane.

4 CD147 and cyclophilins

CD147-cyclophilin interactions have been well reviewed recently by Yurchenko *et al*[24]. Cyclophilin A (CyPA) is a ubiquitously expressed intracellular protein and is best known as the principal ligand for the potent immunosuppressive drug, cyclosporin (CsA)[25-27]. CyPA also possesses peptidylprolyl *cis-trans* isomerase activity and is thought to assist protein folding as a chaperon[28]. Recent experiments revealed that CD147 interacts with cyclophilins as a signaling receptor and mediate the signaling and chemotactic activities of extarcellular CyPA[29] and CyPB[30].

We recently obtained consistent results in identifying the function of CD147 in the invasion of host cells by severe acute respiratory syndrome (SARS) coronavirus (CoV)[31]. The protein-protein interactions among CD147, CyPA, and SARS-CoV structural proteins were analyzed by coimmunoprecipitation and surface plasmon resonance analysis. The results confirmed the interaction between CD147 and CyPA which were coimmunoprecipitated and colocalized on the plasma membrane and intracellular unit membranes. Although none of the SARS-CoV proteins was found to be directly bound to CD147, the nucleocapsid (N) protein of SARS-CoV was bound to CyPA, which interacts with CD147. Mediated by CyPA bound to SARS-CoV N protein, CD147 plays a functional role in facilitating invasion of host cells by SARS-CoV.

Although studies have shown that CypA binds to CD147 and transmits a signal to downstream cascades, the precise mechanism is still not clear. Previous study has shown that CypA serves as a secreted growth factor induced by oxidative stress and promotes cell proliferation in the vascular smooth muscle cells (VSMCs) through the ERK1/2 pathway[32]. Current studies indeed provide evidences that CypA stimulates proliferation of human pancreatic cancer Panc-1 cells through CD147 by activating the ERK1/2[33] and p38 pathways, and that CyPA can protect neurons from oxidative stress and *in vitro* ischemia via CD147 activation of ERK1/2 pathways[34].

5 CD147 and integrins

Integrins are cell surface adhesive receptors composed of α- and β-chain heterocomplexes, which mediate the physical and functional interactions between cell and its surrounding ertracellular matrix. Integrins thus serve as bidirectional transducers of extracellular and intracellular signals in the processes of cells adhesion, proliferation, differentiation, apoptosis and tumor progression.

Considering the structural and functional features of CD147 and integrins, these two molecules may interact with each other perfectly. Indeed, after CD147 cDNA was introduced into L cell, cell-substratum adhesion activity was enhanced. This enhanced cell-substratum adhesion was inhibited by an arginine-glycine-aspartic acid (RGD) peptide, which competitively inhibits integrins, and also by anti-integrin antiserum demonstrating a role of CD147 in promoting the integrin-mediated cell-substratum adhesion[35]. The following experiment showed that CD147, as a carrier of Lewis X antigen, promotes cell adhesion to substratum which is also mediated by integrin.

The direct physical association of integrin with CD147 was demonstrated by coimmunoprecipitation, cell-surface cross-linking and immunofluorescence colocalization experiments[36]. The CD147 protein was found to be associated with integrin α3β1 and α6β1, but not α2β1 nor α5β1.

CD98 is another transmembrane protein, of which few of its antibodies have been shown to induce homotypic aggregation of U937 promonocyte cells. Both anti-integrin and anti-CD147 inhibit the inducing effect of anti-CD98[37]. CD98 can form a dimer with amino acid transporters which are similar to MCTs, thus suggesting a possible role for CD147-integrin-CD98-MCT within a multimolecular unit on the plasma membrane that regulates cell aggregation.

Activation of the signaling pathway of integrin plays a central role in the maintaining and reconstructing of cell architecture. In *Drosophila melanogaster*, CD147 promotes cytoskeletal rearrangements and the formation of lamellipodia[38]. CD147 and integrin colocalize in cultured insect cells and in the visual system. The effect of CD147 is integrin-dependent as shown by the inhibition with RGD peptides and mutation study. CD147-mediated changes in the internal cell architecture, both *in vitro* and *in vivo*, require integrin binding activity.

6 CD147 and caveolin-1

Caveolin-1 was first identified as a tyrosine-phosphorylated protein in Rous sarcoma transformed cells[39] and is known primarily as an integral membrane protein, which functions in intracellular and extracellular lipid transport[40]. Caveolin-1 has also been reported to interact with a variety of signaling molecules including growth factor receptors, G proteins, Src family kinases, *etc*[40].

Recently, Tang *et al*. revealed an important association between CD147 and caveolin-1 based on coimmunoprecipitation in different cell types[41]. The CD147-caveolin-1 complex appears on the cell surface involving the Ig domain 2 of CD147 as shown by extensive CD147 mutagenesis experiments. This association is quite distinct from CD147-integrin complexes which require Ig domain 1 instead of Ig domain 2. Interestingly, this interaction results in decreased CD147 cell surface clustering and CD147-dependent MMP induction. Knockdown of caveolin-1 levels by RNAi leads to a shift in CD147 toward its more active, more highly glycosylated and clustered form which triggers MMP production. These results give a partial explanation why caveolin-1 can suppress cell proliferation, tumor cell invasion, soft agar growth and MMP production[42,43].

Further studies have demonstrated that caveolin-1 selectively associates with less glycosylated (LG)-CD147, and restricts the biosynthetic conversion of LG-CD147 to high glycosylated (HG)-CD147, thereby leading to diminished self-aggregation of CD147 on the cell surface and MMP induction[44].

On the contrary, Barth *et al*. reported inconsistent results[45]. In the bleomycin-induced lung injury system, both CD147 and MMPs (MMP-2 and -9) expressions were upregulated in conjunction with downregulation of caveolin-1 in the lung epithelial cell line and in retrospective samples of bleomycin-induced fibrosis and caveolin-1 knockout mice. Colocalization experiments, however, excluded any direct interaction between caveolin-1 and CD147 in the normal and bleomycin-treated cells. The real features of CD147-caveolin-1 interrelationship therefore remain unclear, and further investigations are required.

7 βig-h3, a new molecule candidate associated with CD147

The network of CD147-interacting molecules is not fully understood yet. With the extensive and effective research being carried out, new candidate molecules are likely to come forth. We have recently demonstrated that expression levels of βig-h3 (also known as TGFBI, betaigh3, BIGH3), a secretary ertracellular matrix protein, is positively correlated to the expression of CD147 by cDNA microarray, quantitative real-time PCR, Western blot and siRNA assay[46].

βig-h3 was first identified from A549 lung adenocarcinoma cell line after long-term treatment by TGF-β1[47]. βig-h3, is involved in cell growth, migration, apoptosis, wound healing and tumorigenesis[48-53], and might function as either a promoter or inhibitor of carcinogenesis depending on cells and tumor types.

Results obtained from cell adhesion, invasion and gelatin zymography assay indicated that βig-h3 enhances hepatoma cell invasion and metastasis potential[46]. βig-h3, containing an RGD (Arg-Gly-Asp) motif, may interact with integrins[51,54,55]. CD147 is known to form complexes with integrins (see above “CD147 and integrins” section). Referring to our recent results that βig-h3 was coimmunoprecipitated with CD147 and integrin α3β1 (authors’ unpublished data), these findings shed new insight into the possibility of integrin (especially for α3β1) acting as a bridge between CD147 and βig-h3 to form a trimer, and thereof regulating CD147-induced invasion and metastasis of tumor cells. The detailed investigation is currently underway in our laboratory.

8 Conclusions

As a widely expressed transmembrane glycosylated adhesion molecule in the epithelial cells, the structural features of CD147 imply that it may interact with a variety of other proteins to play important roles in cell proliferation, energy metabolism, migration, adhesion and motion, especially in cancer metastasis. CD147 may induce several malignant properties associated with cancer, including migration, invasiveness and angiogenesis. It is of great significance to further explore the interacting molecules or ligands of CD147, not only for elucidating its action mechanism but also as targets for development of diagnosis and treatment methods for CD147-associated diseases. Indeed, Licartin (^{131}I mAb specific for HAb18G/CD147) was developed in our laboratory and has been applied safely and effectively in treating hepatocellular carcinoma patients[10,56,57].

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