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Review article

Structural insights on druggable hotspots in CD147: A bull's eye view

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ABSTRACT

CD147/Basigin/EMMPRIN (Extracellular Matrix Metalloproteinase inducer) is a single pass type1 transmembrane protein playing a central role in developmental process, wound healing, nutrient transport, inflammation, arthritis and also in microbial pathologies. It is also found to be a potent stimulator of MMP (matrix metalloproteinases) and has been considered as a prognostic marker in cancer. Dysregulation of CD147 is reported in several types of cancer. It activates cell proliferation, invasion, metastasis and inhibits tumor cell apoptosis under hypoxic condition. Thus, CD147 serves as a hub protein in cancer, as it is involved in several homophilic and heterophilic cellular interactions spanning the major hallmarks of cancer. Targeting these interactions is considered to be an efficient therapeutic modality in cancerous conditions. Hence, by this review we intend to collate the structure-function relationships of CD147, with an exclusive thrust on potential druggable hotspots based on its intra and inter molecular interactions.

1. Introduction - CD147 and cancer pathogenesis

Cell invasion, metastasis and angiogenesis are the key factors for carcinogenesis [1]. Cluster of differentiation 147 (CD147) protein is a member of immunoglobulin superfamily that is found to be over expressed in cancer cells, which leads to inhibition of tumor cell apoptosis, promotion of tumor growth and aids in the formation of malignant tumor [2]. It is reported to play a major role in tumor cell metastases [3] and also considered as potential drug target in many cancers, as it features as a hub protein in major hallmarks of cancer.

CD147 is indirectly involved in pH homeostasis by regulating monocarboxylate transporter (MCT) expression. MCT1 and MCT4 directly bind to the transmembrane and cytoplasmic regions of CD147. Further, CD147 transports MCT1 and MCT4 to the cell surface, thereby aiding in modulation of pH homeostasis in cancer cells [4]. The extracellular interactions of CD147 with integrin α6β and α3β are also found to regulate the downstream of FAK pathway, thereby aiding cell proliferation, migration and invasion [5]. CD147 also act as a signalling receptor for cyclophilins which are responsible for chemotaxis in many of the physiological and pathological processes like cell-mediated immunity and inflammation [6].

The retinal specific CD147 contains three Ig-like domains and is also shown to be a potent stimulator of interleukin-6. Higher expression of CD147 is also reported in retinoblastoma [7]. CD147 activates specific class of MMPs (Matrix Metalloproteinase) leading to degradation of the basement membrane and stroma thereby promoting tumor invasion and metastasis in cancer cells [8]. Over expression of CD147 in SMMC-7721 cells (human hepatocellular carcinoma cells) is shown to drive tumor cell migration and metastasis. Moreover, when these cells were treated with U0126 (ERK inhibitor), it is found to result in the inhibition of CD147 mediated cell migration. This indicates the up-regulation of CD147 which in turn activates cell migration *via* ERK pathway [9].

CD147 also regulates VEGF production in tumor and stromal cells [10,11]. In breast cancer, it has been reported that activation of angiogenesis is initiated by over expression of CD147, which in turn results in the expression of VEGF *via* PI3K-Akt signalling pathway [10]. During metastatic process, cancer cells detach from the extracellular matrix and move to the lymphatic and circulatory system. Anoikis is a type of programmed cell death caused by detachment of the cell from its supportive matrix [12]. The up-regulation of CD147 is reported to

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activate PI3K/Akt pathway, which plays a vital role in the resistance to anoikis in Hepatocellular carcinoma [13,14]. CD147 also interacts with ABCG2 (ATP-binding sub-family G member 2) protein, which plays a crucial role in chemo-resistance by effluxing of drug compounds [15]. In breast cancer, it has been demonstrated that ABCG2 to co-localize with CD147 and also to form dimeric interactions, thereby favouring chemo-resistance [16].

In case of normal cells, CD147 is shown to regulate MMP biosynthesis, cell proliferation, and cell differentiation. CD147 knockdown studies in mice have revealed that the gelatinolytic activity in meibocytes is dependent on CD147. This study supports the role for CD147 in sustaining the normal development and function of the meibomian gland in eye [17]. In a recent study, CD147 expression (at protein level) was reported to be significantly increased in melanoma cells compared to normal melanocytes [18]. CD147 is not directly involved in tumorigenesis, however, it is highly expressed in cancerous conditions. CD147 null mice have shown nervous disorders, visual impairment and lesser sensitivity to irritating odours [19]. However, there is a paucity of understanding its proper role in normal cellular functions in humans [20]. Majority of the CD147 knockout studies were performed mostly in cancer cells. Targeting CD147 in cancer cell is advantageous as it is an exposed extracellular region [21] and also spans the major hallmarks of cancers which include cell proliferation, invasion, metastasis and apoptosis. The most ideal way of targeting CD147 would be to use antibody conjugates and also targeted delivery systems which will ensure higher selectivity to cancer cells.

All these reports collectively emphasize CD147 as a potential anticancer as well as anti-inflammatory target (Fig. 1). Molecular modelling and structural bioinformatics methodologies have proven to be highly efficient in terms of increasing the pace and cost effectiveness of the drug discovery process [22–24]. Better understanding of structural features and druggable hotspots on CD147 will lead to framing efficient structural bioinformatics and drug designing modalities for modulating cancerous conditions. Though there are classical reviews on CD147 [2,13,25–27], there is a paucity in literature on collective addressing of functionalities, pathogenesis, structural features, druggable hotspots, and intermolecular interactions. Thus, by this review we intend to collate all these details in relevance to cancer pathogenesis which shall form a platform for structure-based drug designing studies.

2. Cellular and structural organization of CD147

2.1. CD147 – cellular organization

CD147 is a Type 1 transmembrane glycoprotein and a member of the immunoglobulin superfamily (IgSF) [28]. It was first named as tumor cell-mediated collagen enzyme activation factor TCSF (tumor cell collagenase stimulatory factor) and then recoined as extracellular matrix metalloprotein inducer (EMMPRIN) based on its functional role [29]. CD147 is also alternatively named as Leukocyte activation antigen M6 [2], blood group antigen OX47 in rat [30], 5A11 [31], HT7 [32] and hepatoma-associated antigen (HAb18G) in human [33].

CD147 is also called as Basigin, as it is coded by *BSG* gene located on human chromosome 19 (p13.3) comprising of 10 exons spanning around 12 kb [34]. So far, four isoforms of CD147 (Basigin 1, 2, 3 and 4) has been identified. These isoforms occur due to differential splicing and variation in transcription initiation sites [35]. The overall tissue specific distribution of four isoforms is as follows, basigin-1 is retina specific isoform [7]. Basigin-2 is expressed ubiquitously and its mRNA expression is found to be higher in the heart, kidney, skeletal muscles and testis [35]. Basigin-3 is highly expressed in the bone marrow, fetal liver, lung, testis and thymus. The expression of basigin-4 was similar to that of basigin-3. The basigin-3 and 4 are generally expressed in various normal tissues. However, an increased transcript levels were observed in HCC tissues. Although, there is a clarity with respect to the functions of Basigin 1, 2 and 3; a clear function has not been attributed to basigin-4 [35]. However, it is over expressed in malignant conditions [3]. From the next section, Basigin will be used as a synonym for CD147 considering the convenience of the readers.

The Transmembrane domain of CD147 comprises of about 21 residues which play a crucial role in anchoring of CD147 to the membrane [6]. The hydrophobic region of TM domain also contains a conserved glutamic acid residue and leucine zipper like sequence [36]. These key residues interact with membrane components and provide

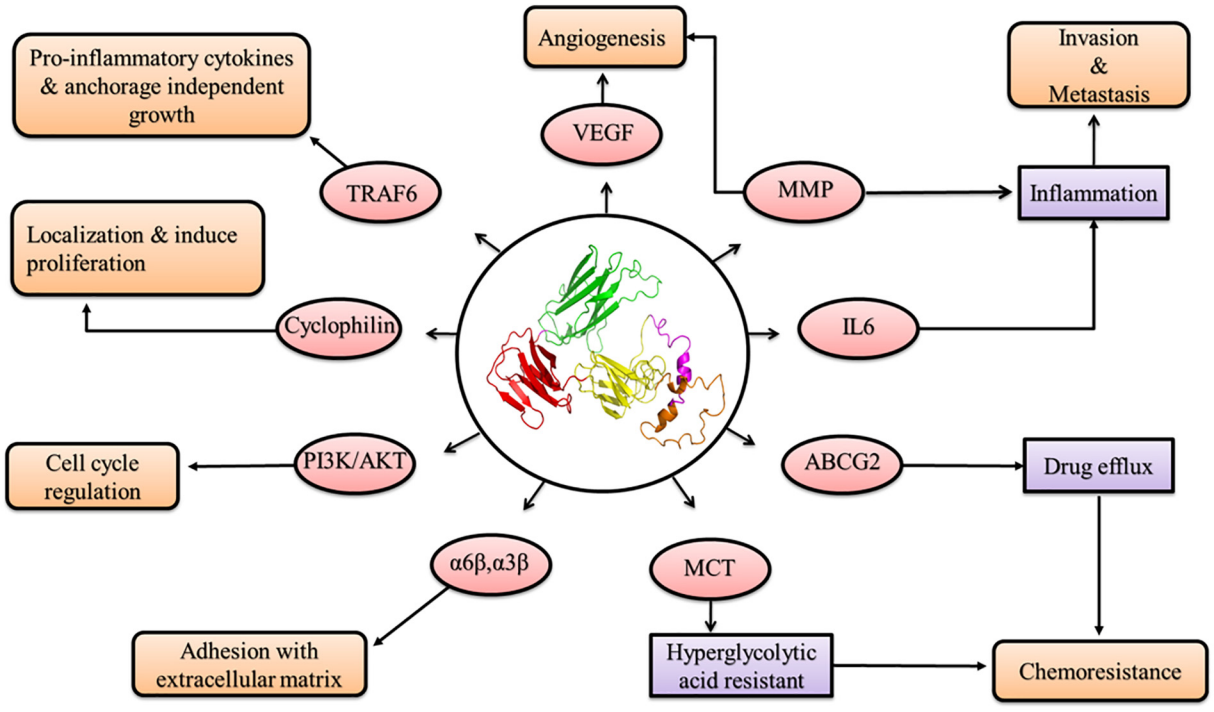

Fig. 1. Chart representing the multifunctional role of CD147 in pathogenesis of cancer.

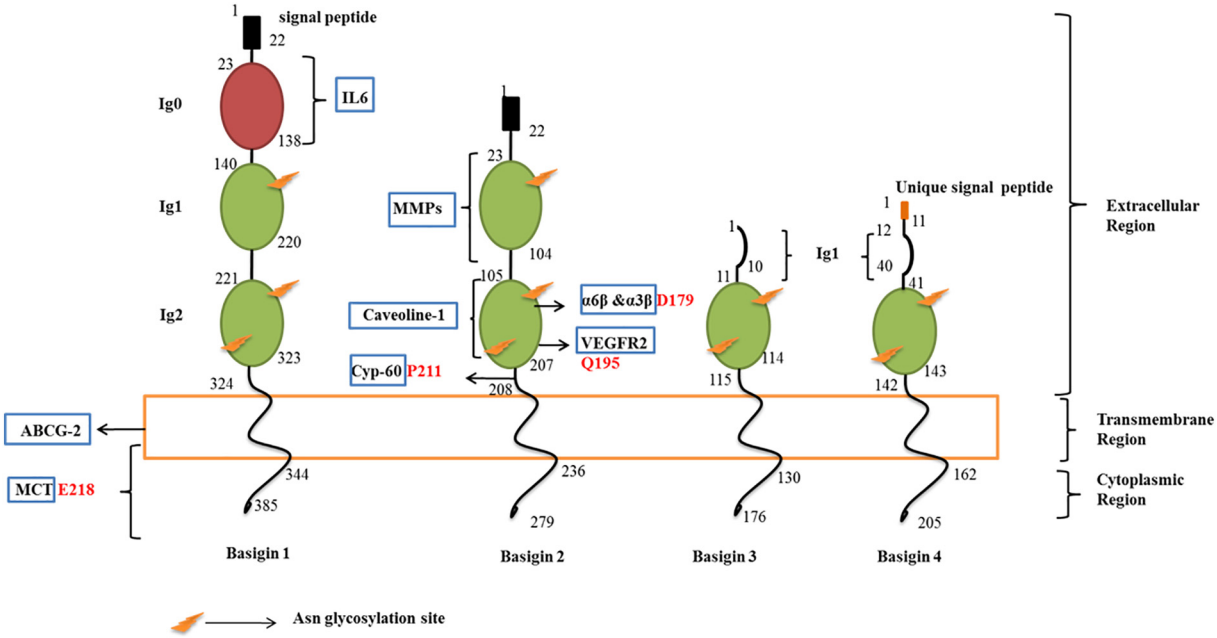

Fig. 2. Diagrammatic representation of CD147 in extra and intracellular space along with its protein interacting regions [2]. Hotspot residues are represented in red colour. Interacting proteins are represented as blue bordered box. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

support in anchoring of CD147 to cell membrane [30]. Fig. 2 shows the diagrammatic representation of CD147 (Basigin 1, 2, 3 & 4) in extra and intracellular space along with key hotspot residues. The retinal specific CD147 (Basigin-1) is of 385 amino acids in length (Uniprot ID: P35163). The signal peptide sequence spans from 1 to 21 amino acids and the other regions include:

i) Extracellular regions: Ig0 domain (22-138aa), Ig1 (140-220aa) and Ig2 (221-323aa).
ii) Transmembrane region: (324-344aa).
iii) Cytoplasmic region (345-385aa).

Extracellular vesicles (EVs) play an important role in cell-cell communications. The transfer of onco-proteins from the malignant to non-malignant cells is mediated by EVs in extracellular space. EVs stimulate the production of MMP9, IL6, TGF-β1 and induce the synthesis of CD147 [37]. In sarcoma cells, microvesicles encompassing CD147 is shown to trigger the production of MMP2. CD147 also exists in soluble form and it also gets localized to the membrane by vesicular transport and later gets secreted into the extracellular space. It shall also undergo proteolytic cleavage by MT1-MMP-14 (enzyme that cleaves off the N-terminal Ig-like domain) and get detached from cell surface [26,38].

2.2. Basigin 1: (Ig0-Ig1-Ig2)

Basigin-1 comprises of three domains namely, Ig0, Ig1and Ig2. Currently, the structural coordinates of Ig0 domain is available in protein data bank (PDB) (PDB ID: 3QR2 at 2.3 A° resolution). The Ig0 domain lacks N-glycosidic linkage and it comprises of 9 β-strands and 2 α-helices. The β-strands form two β-sheets: A, B, E and D strands form one β-sheet while the other is formed by A', G, F, C and C' strands. There are three Cysteine residues (C44, C108 and C67) in Ig0, wherein, C44-C108 is linked by intra disulfide bond and C67 is meant for intermolecular interactions (Fig. 3). In 3QR2 crystal structure, dimerization of Ig0 is formed between R130(A-Chain)-Q132(B-Chain) and E59(A-Chain)-K126 (B-Chain) [7]. This dimerization plays an important role in the molecular function of CD147 [39]. A total of four intermolecular hydrogen bonds is observed to be formed between R130

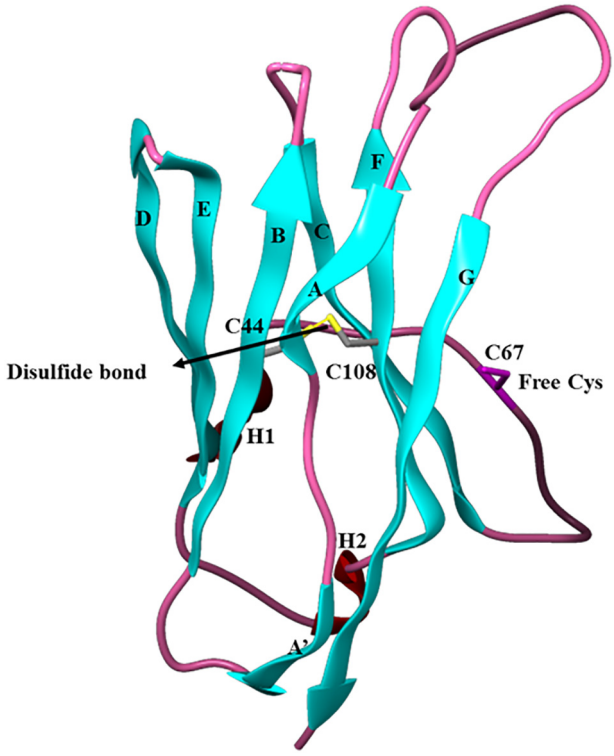

Fig. 3. Representing the monomeric Ig0 domain comprising of 9 β-strands and 2 β-sheets. Residues spanning each Strand: A (24–27), A' (32–35), B (40–47), E (89–95), D (79–84), G (128–137), F (104–111), C (53–60) in cyan and two short Helix region H1 (54–57) and H2 (100 – 103)in red. The disulfide-bonds are shown in grey colour and free Cys (C67) residue is shown in Magenta (stick representation). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and Q132, two per each residue at the CD147 Ig0 dimeric surface. Comparative studies on mutant forms inferred that Ig0 domain to be partially stabilized by the intermolecular interactions of E59-K126 and

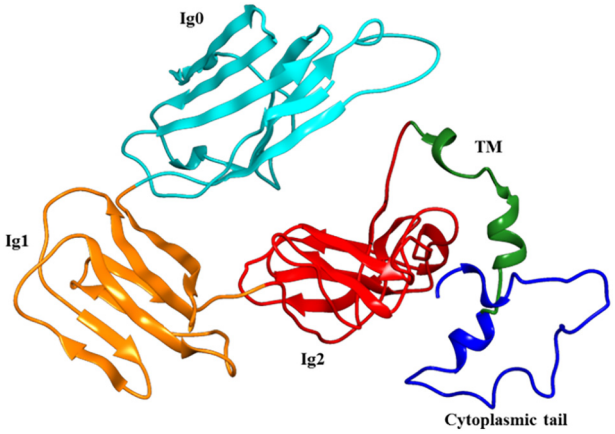

Fig. 4. Modelled structure of CD147 (Ig0-Ig1-Ig2) with retinal specific domain. Each domain is represented in different colours: Ig0 (cyan), Ig1 (orange), Ig2 (red) Transmembrane (TM) (green) and Cytoplasmic tail (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

highly stabilized by R130-Q132, as it forms four hydrogen bonds [7]. In this study, the complete structure comprising of Ig0-Ig1-Ig2 was also modelled using Modeller9.15 by multi-template (3B5H A chain and 3QR2 A chain as templates) based homology modelling in combination with I-Tasser based fold recognition (For TM and CT regions) to demonstrate the probable structural orientation (Fig. 4). Over expression of this retinal specific CD147 plays a vital role in up-regulation of MMPs secretion and is also responsible for the stimulation of IL-6 that may contribute to invasiveness in retinoblastoma [7].

The crystal coordinates of Basigin-2 (Ig1-Ig2) is available in PDB (PDB ID: 3B5H at 2.8 A° resolution). It consists of four monomers in an asymmetric unit (A, B, C, D). This structure comprises of two domains: IgC2 (constant 2-set arrangement) domain at N-terminal and IgI (membrane proximal intermediate set) domain at C-terminal [2]. Fig. 5 shows the diagrammatic representation of single monomer of CD147 (chain A), D1 Domain (residues 22–101) at the N-terminal and is a typical C2 set immunoglobulin domain consisting of a β-barrel formed by sheets EBA and GFCC' and has a disulfide bond between C41 and C87 residues of strands B and F strands, respectively. The D1 domain also contains one N-linked glycosylation site at N44, which spans at the end of strand B. The Domain D2 (residues 107–205) is the C-terminal IgI domain forming β-sheets DEBA and A'GFCC' which are packed against each other with disulfide bonds formed between C126 and C185, respectively. The D2 domain contains two N-linked glycosylation sites at N152 and N186, located in the middle of C'D loop and strand F. The biological function of D1 domain mainly depends on the centrally located glycosylation sites (two sites) around D2 domain which helps the D1 to get exposed to the cell surface for interactions with physiological ligands. These two immunoglobulin-like domains are interlinked by the five-residue linker [40]. There are four different combinations of CD147 (Ig1-Ig2) crystal structures, representing four dimer formation (dimers chain names: BC, AC, AD and DD') leading to the homo-oligomer formation in the crystal structure. Collectively, all these conformations highly suggest that the oligomerization-dependent biological functions of CD147 and might require both *cis* and *trans* homophilic interactions on the surface of plasma membrane [40].

2.3. Basigin 3 and 4

Basigin-3 and 4 are shorter isoforms with only one Ig domain, and both are glycosylated [34]. However, Basigin-3 lacks N-terminal IgC2 domain and the signal peptide. Basigin-4 contains a 11-mer of unique amino acid sequence in the N- terminal region (MKQSDASPQER) [34]. Basigin-2, 3, 4 are reported to be most abundant in Hepatocellular

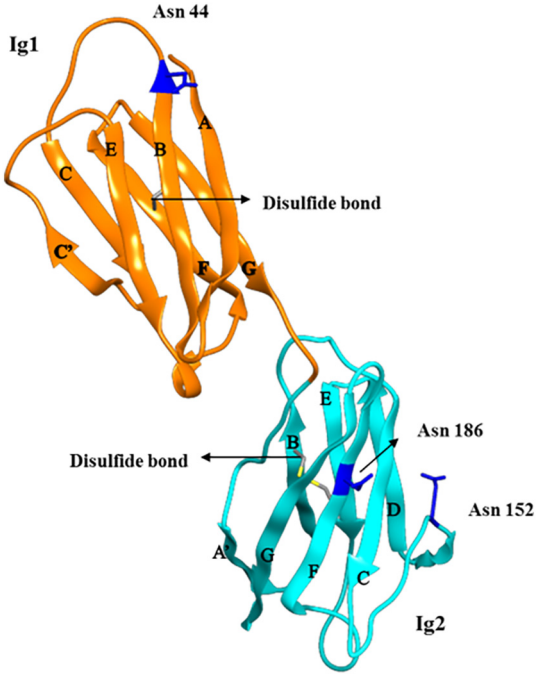

Fig. 5. Crystal structure of CD147 (Ig1-Ig2) (chain A) is represented as cartoon with Ig1 in orange and Ig2 in cyan colours. The disulfide-bonds in D1 domain is C41 and C87 and D2 is C126 and C185 in grey (stick representation) and the three potential N-glycosylation sites: N44, N152, N186 are shown in sticks (blue colour). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

carcinoma cells [34]. It has also been reported that basigin-3 to play an role as an endogenous inhibitor of basigin-2 [34]. The hetero-oligomerization of basigin-3 with basigin-2 through Ig-I set domain was shown to inhibit HCC cell proliferation, migration and invasion by decreasing the expression of MMPs. This shows that Basigin-3 could inhibit Basigin-2 function in HCC. Further, NMR studies for Basigin-2 + Basigin-3 complexes has revealed that amino acid residues: W82, G83, W118, M123, M151, G153, S154, E155, S156, R157, F158, F159, V160, S161, S162, E168, H170, E172, M176 at D2 of Basigin-2 to form the binding region of Basigin-3 [35]. The modelled surface representation of Basigin 3 and 4 is shown in Fig. 6a & b. Further, both the proteins were docked to understand the intermolecular interactions. For protein-protein docking of these isoforms, the robust ZDOCK algorithm was chosen [41]. To improve the success rate of initial ZDOCK ranking, the docked complexes were rescored using ZRANK score [42]. In Fig. 7a, ZDOCK based Basigin-2 + Basigin-3 complex is shown (ZRANK score is −71.1072). Further, the intermolecular interactions of this complex were visualized as 2D interaction map generated by PDBsum (Fig. 7b). The 2D interaction map of Basigin-2 + Basigin-3 complex infers that two hydrogen bonds are formed between N152-S20, and S163-E84, respectively. The residues N152, F159, V160, E172, H170, E168, S168, S162, E114, M123, R166, V110, S163, E164 and Y135 of Basigin-2 showed non-bonded contacts. This interaction map shall form a platform for the design of competitive peptide/chemical inhibitors targeting Basigin-2 + Basigin-3 complex formation.

2.4. Glycosylation of CD147

All the four isoforms of CD147 are known to be glycosylated [35]. However, Basigin-1 contains an extra Ig like domain Ig0 which is non-glycosylated [7], along with Ig1 and Ig2 domains showing glycosylation similar to basigin-2. The complete structural information is only available for basigin-2, hence the role of glycosylation in basigin-2 is discussed further. There are three potential glycosylation sites: N44

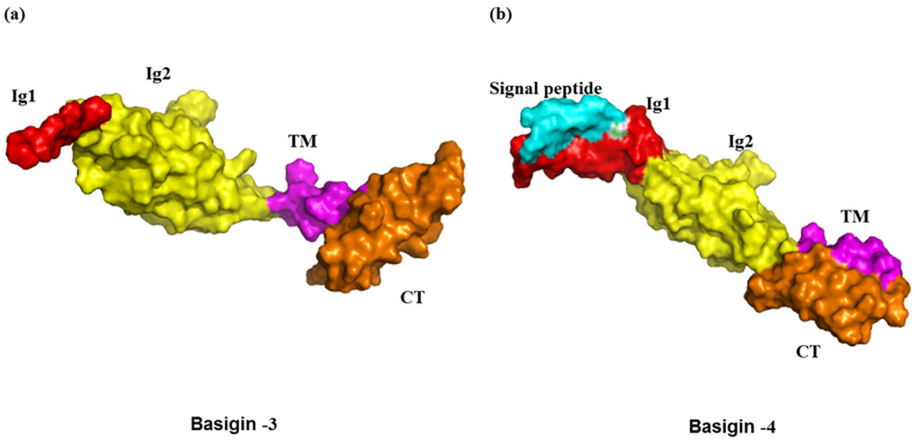

Fig. 6. Molecular Surface representation of I-TASSER modelled Basigin-3 and 4. (a) Basigin3 with first 10 amino acid sequences in Ig1 (red), Ig2 domain (yellow), transmembrane domain (magenta) and the cytoplasmic tail (orange). (b) Basigin4 cyans colour indicates the unique (1–11 residues) signal peptide. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Ig1) at the end of strand B, N152 (Ig2) at the middle of C'D loop and N186 (Ig2) at Strand F (Fig. 3). The malignant transformation of tumor is highly characteristic due to the glycans of glycoproteins and glycolipids [43]. Based on the degree of glycosylation, CD147 is also classified into two distinct categories: highly glycosylated CD147 (HG-CD147) molecular weight (~45–65 kDa) and low glycosylated CD147 (LG-CD147) (~32 kDa) [44]. In cancerous condition, HG-CD147 is present at elevated levels [45]. The HG-CD147 is responsible for induction of MMPs. The LG-CD147 is associated with Caveolin-1, which acts as a negative regulator for MMP inducing activity [44]. Glycosylation of CD147 plays a major role in the induction of MMP 1 and MMP 2. In MDA-435 cells, deglycosylated CD147 is shown to fail in inducing MMP2 [46]. The removal of glycans in SMMC-7721 and HepG2 cells is also shown to result in the lower level of MMP-9 and MMP-2 production. N-linked glycans on N152 plays a crucial role in the cell surface expression and function of CD147 [47]. In hepatocellular carcinoma, N-glycosylation at N152 in CD147 is shown to be essential for tumor invasion and migration [48]. It was also reported that mutation of N152 can result in misfolding or unfolding of CD147. The misfolded CD147 is prone to degradation by ER-associated degradation pathway. N152 is located in the middle of the Ig-V domain of CD147, which plays a pivotal role in protein folding at ER [48]. Thus, all these studies infer the importance of glycosylation in proper folding of CD147.

3. Molecular interactions of CD147

3.1. The homophilic interactions

Ig1 of CD147 (Basigin-2) features homophilic interactions [46]. Basigin-2 forms homo-oligomers in a *cis*-dependent manner at the intracellular plasma membrane (*cis*-recognition) [27,36]. CD147 also acts as a counter receptor for itself at the intercellular interface, thereby inducing MMPs. The N-terminal of Ig domain is responsible for the counter receptor binding of CD147 and the interaction occurs in a *trans* manner, thereby triggering the production of MMPs which leads to tumor invasion and metastasis [26,36]. The truncated protein expression studies in CD147 have demonstrated that amino acid residues spanning at 22–50 region of Ig1 domain to play a crucial role in MMP production. Moreover, lack of this region fails to induce cellular invasion to a maximal extent in COS cells [49]. Therefore, N-terminal region

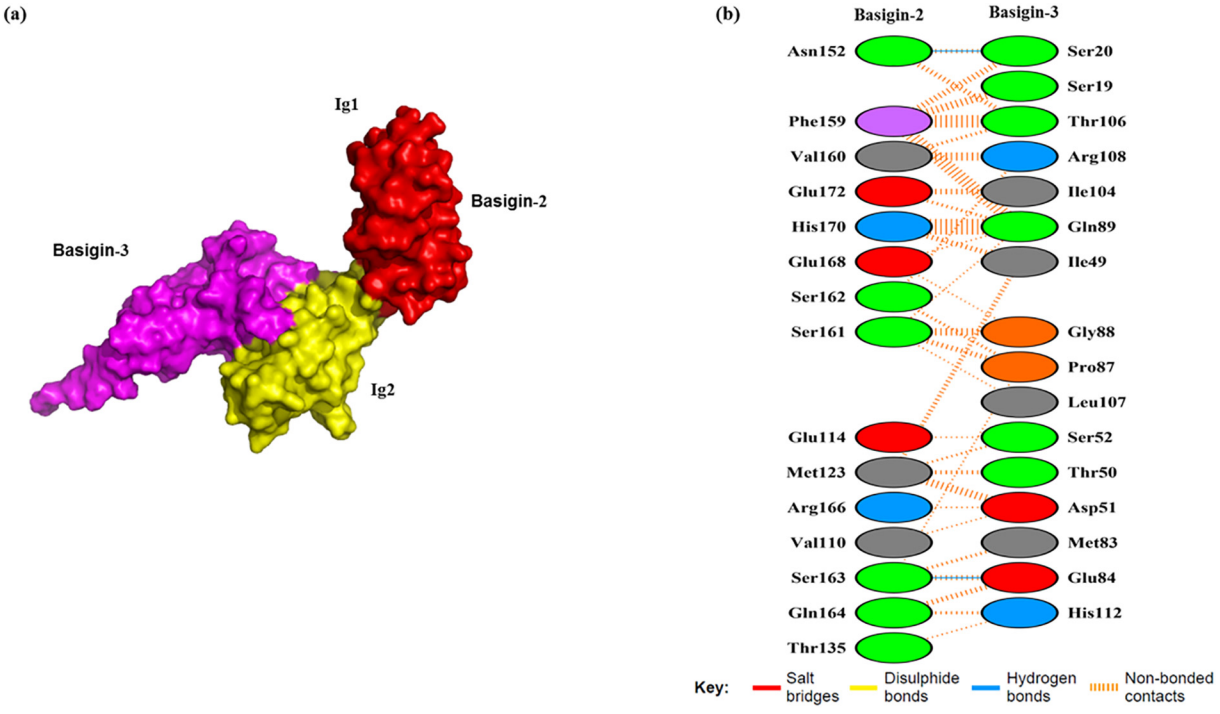

Fig. 7. (a) Basigin-2 + Basigin-3 docked complex. (b) Protein-protein interaction map of the docked complex generated from PDBsum.

interactions of CD147 (Basigin-2) plays an essential role in the expression of MMPs in cancerous conditions. Unlike Basigin 2; a study has shown that Basigin-3 lacks the Ig1 domain, hence it may not play a role in MMP synthesis [35]. However, it is hard to comment on the Basigin-4 due to lack of literature evidence.

3.2. The heterophilic interactions

CD147 is tightly associated with MCT-1 and 4, which transports lactate to the extracellular region of cancer cells. The transmembrane and the cytoplasmic regions of CD147 play a key role in establishing intermolecular interactions with MCT [4]. E218 at the transmembrane region of CD147 and R306 in the eighth TM domain of MCT are associated in these heterophilic interactions [50]. The conserved E218 (negatively charged) in TM of CD147 charge-pairs with R306 (positively charged) (TM8) of MCT1. This interaction aids in the transportation of lactate across the plasma membrane and could play an important role in pH homeostasis in the tumor microenvironment [50]. P211 in the transmembrane domain of CD147 is also proposed to interact with cyclophilin 60 (Cyp60). The interactions between the Cyp60 and CD147 aids in the trafficking of CD147 from Golgi to the plasma membrane [51]. CD147 also functions as a co-receptor of VEGFR-2 thereby promoting angiogenesis. The amino acids residues Q195/T199 of CD147 extracellular domain are proposed to interact with VEGFR-2 in *cis* manner. CD147-VEGFR-2 complex formation is regulated by VEGF levels [52]. CD147 also interacts with integrin α3β and α6β1, thereby, activating the downstream of FAK-PI3K-Ca2 + pathway, which helps in contributing to the tumor invasion and metastatic process. Moreover, D179 of CD147 also plays an important role in these interactions [5]. CD147 also interacts with ABCG2 and promotes the efflux of MTX drug (chemotherapeutic drug) *via* its transmembrane region. The dimerization of CD147 and ABCG2 is found to activate the chemoresistance process [15].

In HCC, CD147 is reported to co-localize and co-immunoprecipitate with ANXA2, which is responsible for cell migration and invasion [53]. In breast cancer, hyaluronan and CD44 interactions are shown to upregulate the expression of CD147 [54]. Invasiveness in breast epithelial cells is found to be linked with the signalling cascade between CD147, hyaluronan-CD44 interactions and EGFR-RAS-ERK pathway. This trio signalling complex is mainly associated with lipid raft-like domain on cell surface [54]. CD147, CD44, ANAX2, P-gp (P-glycoprotein), MMPs and UCH-L1 (ubiquitin carboxyl terminal hydrolase) proteins are also shown to be associated in the crosstalk between metastasis and chemoresistance processes [45]. In HCC, CD147 is also reported to localize at the basolateral membrane and is associated with cancer progression. CD147 is also reported to promote epithelial-mesenchymal transition and invasion of HCC [55]. TRAF6 is a protein (tumor necrosis factor Receptor-Associated Factor) that activates Akt or NF-κB pathway in response to pro-inflammatory cytokines, anchorage-independent growth and tumor formation. It has been demonstrated that CD147 is an interacting partner of TRAF6, which regulates CD147 membrane recruitment, CD147-dependent MMP9 expression and invasiveness in melanoma cells *via* K63-linked ubiquitination [56]. The three lysine (Lys233, Lys249 and Lys258) residues which are located at the cytoplasmic domain of CD147 are reported to be directly ubiquitinated. Moreover, knockdown of TRAF6 and deletion of these three lysine residues of CD147 is shown to reduce the MMP-9 expression and cancer invasiveness in melanoma [56,57]. Table 1 lists the overall potential druggable hotspots residues which shall aid in framing computational approaches for targeting CD147.

4. CD147 and cancer

4.1. Retinal specific CD147 and retinoblastoma

Retinoblastoma (RB) is a common intraocular malignancy of

Table 1
List of potential hotspots for targeting CD147 domains in cancer.

Pathogenic conditions	Interacting proteins/ modifications	Hotspot residues at different regions of CD147					References
		Ig0	Ig1	Ig2	TM region	Cyto-plasmic tail	
Inflammation	IL-6	FreeC67, dimeric interface R130-Q132 (PDB ID: 3QR2)[a]	–	–	–		Eisenmesser et al. [7]
pH homeostasis	MCT-1	–	–	–	E218, E221 and L252		Wilson et al. Deora et al. [50,58]
Chemotaxis	Cyp 60	–	–	–	P211		Pushkarshy et al. [51]
	CypA			P180 and G181	P211		Yurchenko et al. Hanoulle et al. [59,60]
	CypB	–		P180	–		Hanoulle et al. Schlegel et al. [59,61]
Angiogenesis	VEGFR-2	–	–	Q195/T199	–		Khayati et al. [52]
Invasion and metastasis	MMP-2	–	Dimeric interface E64 and E73 (PDB ID: 3B5H) (proven data)	–	–		Wang et al. [21]
	α3β and α6β1	–	–	D179	–		Li et al. [5]
	Glycosylation sites	–	N44	N186	–		Sun et al.
				N152			Huang et al. [46,48]
	TRAf6					K233, K249 and K258	Peng et al. Luo et al. [56,57]

[a] In the actual pdb file the residues are numbered as R129-Q131.

childhood. It is associated with the genetic abnormalities involving mutation in the *RB1* gene on chromosome 13 [62]. Retinoblastoma can be endophytic (spreading throughout eye) and exophytic (spreading through subretinal space) [63]. In general, the soluble form of CD147 (Basigin-1) has been detected in cellular and extracellular milieu of retinal pigment epithelium (RPE), retinal layers and also observed in the human tear fluid [64]. Tumor progression in RB is mainly contributed by MMPs, CD147 (Basigin-1) and TIMPS (tissue inhibitor of metalloproteinase) [65]. Among these, CD147 (Basigin-1) plays a key role by triggering the expression of MMP-2, thereby leading to the degradation of extracellular matrix, which favours tumor invasion and metastasis in RB [65]. In a recent study in RB patients, it was shown that CD147, MMP-1 and MMP-9 to be highly expressed in RB tissue [66]. In general, RB protein is a tumor suppressor in most of the cancers. Inactivation of RB gene is also shown to promote the pro-inflammatory signals by simulating the interleukin 6/STAT3 pathway [67]. The retinal specific CD147 (Basigin-1) contains an extra Ig-like domain which is reported to be a potent stimulator of IL6. CD147 is of dual characteristic, it can act as a receptor as well as a ligand in a context dependent manner. It acts as a receptor for various extracellular proteins like cyclophilin class of enzymes. The ligand activity is manifested in many of the disease conditions like rheumatoid arthritis and many cancers which includes retinoblastoma [7].

4.2. CD147 in tumor invasion and metastasis (CD147-MMP-VEGF cascade)

As discussed earlier, CD147 is one of the key protein that is involved in the activation of MMPs. In human, MMPs comprises of 23 families. These are zinc containing enzymes that degrade the components of extracellular matrix (ECM) [68]. MMPs act as endopeptidases and are involved in many of the physiological process such as wound healing, organogenesis and uterine involution processes. For many types of cancer, MMPs serve as diagnostic and prognostic biomarker [69]. The N-terminal region of CD147 is responsible for the activation of MMPs which would act as the counter receptor for itself (homo-oligomers). Fig. 8 describes the role of CD147 as the counter receptor, thereby, facilitating the extracellular matrix degradation, tumor cell invasion and metastasis [46]. CD147 creates a positive feedback loop for its own expression, which ends up in regulation of MMPs, cytokines and CD147 itself [7].

CD147 is responsible for the expression of several types of matrix metalloproteinase in tumorigenesis such as, MMP-1 and MMP-9 (over expressed in retinoblastoma tissues) [66]. Over expression of CD147 and MMP-9 in basal-like breast cancer (BLBC) has also been reported. The main function of MMP-9 is to degrade type IV collagen which is a major component of basement membrane and it is also involved invasion and metastasis [70]. In Hepatocellular carcinoma, CD147 is shown to promote MMP2 expression [71]. CD147 (Basigin-2) is also found to induce MMP-1 and MMP-2 in pancreatic neoplasm [72]. In melanoma cells, CD147 is shown to be highly expressed and found to interact with dermal fibroblasts to stimulate the production of MMP-1, MMP-2 and MMP-3 [73]. In colorectal cancer, CD147 and MMP-11 are demonstrated to be over expressed. MMP-11 is known to be involved in conferring resistance to apoptosis during cancer progression [74]. To date, CD147 has been shown to over express and mediate the activity of MMP-1, MMP-2, MMP-3, MMP-9 and MMP-11 in cancer invasiveness and metastasis [20,75].

As discussed earlier, the microvesicular release of CD147 from tumor cells leads to the upregulated expression of MMPs. These tumor-derived microvesicles also carry angiogenic factors that triggers angiogenesis by promoting endothelial cell migration and tubulogenesis. CD147 stimulates the expression of VEGF in tumor environment [76]. In an *in vitro* study, it was shown that, on treatment of epithelial ovarian cancer cell derived microvesicles on human umbilical vein endothelial cells (HUVECs) to induce angiogenesis and also to promote MMP gene expression [76]. MMP-9 may play a key role in the stimulation of VEGF expression through the Src tyrosine kinase signalling pathway. In case of human A498 renal carcinoma cells co-cultured with U937 monocytes, the soluble CD147 secreted by A498 was shown to induce the secretion of pro – angiogenic proteins such as MMP-9 and VEGF in U937 monocytes [77]. Co-localization of VEGF and CD147 in the plasma membrane is also reported in human lung carcinoma (A549) cells [78]. Hence, all these studies suggest a functional relationship of CD147-MMP-VEGF expression induces the tumor angiogenesis process [77,79].

Over expression of CD147 in cancer cells is also shown to activate the PI3K-Akt-signalling pathway and was found to be responsible for the regulation of VEGF production in renal cell carcinoma [80]. The malignant properties of tumor cells are also associated with the interactions of CD147 and VEGFR-2. CD147 acts as a co-receptor of VEGFR-2 and it is activated by VEGF, thereby contributing to angiogenesis. Amino acid residues Q195/T199 of CD147 which are proximal to the cell membrane are reported to be linked with CD147 and VEGFR-2 interactions [52]. In acute myeloid leukemia, immune-histochemical analysis has revealed that CD147 and VEGF to be co-expressed and shall prove to be a potential prognostic biomarker [81]. Thus, CD147 plays an important role in the induction of tumor angiogenesis, hence can be considered as an efficient target for therapeutic approaches in treating cancerous conditions.

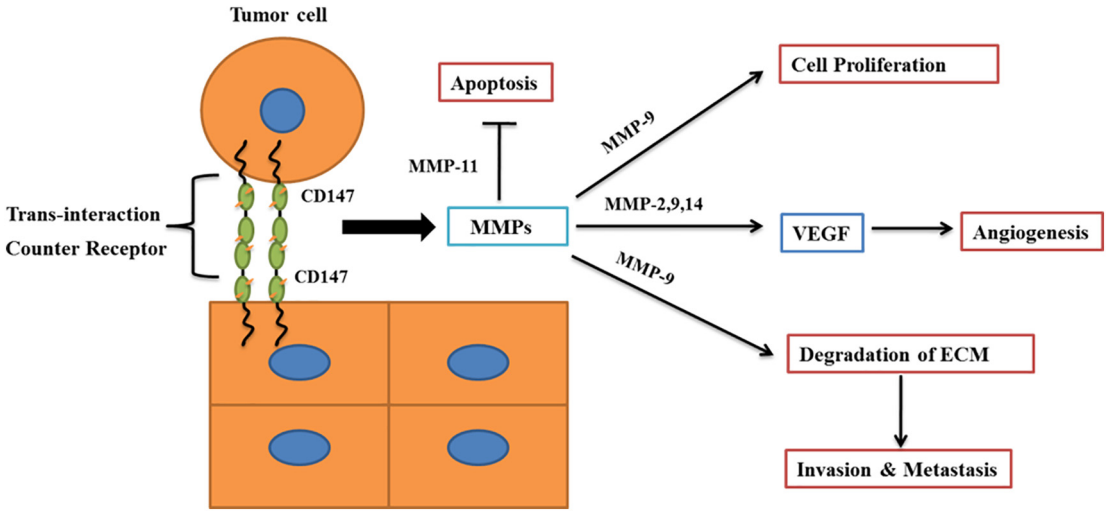

Fig. 8. The role of CD147 as a counter receptor.

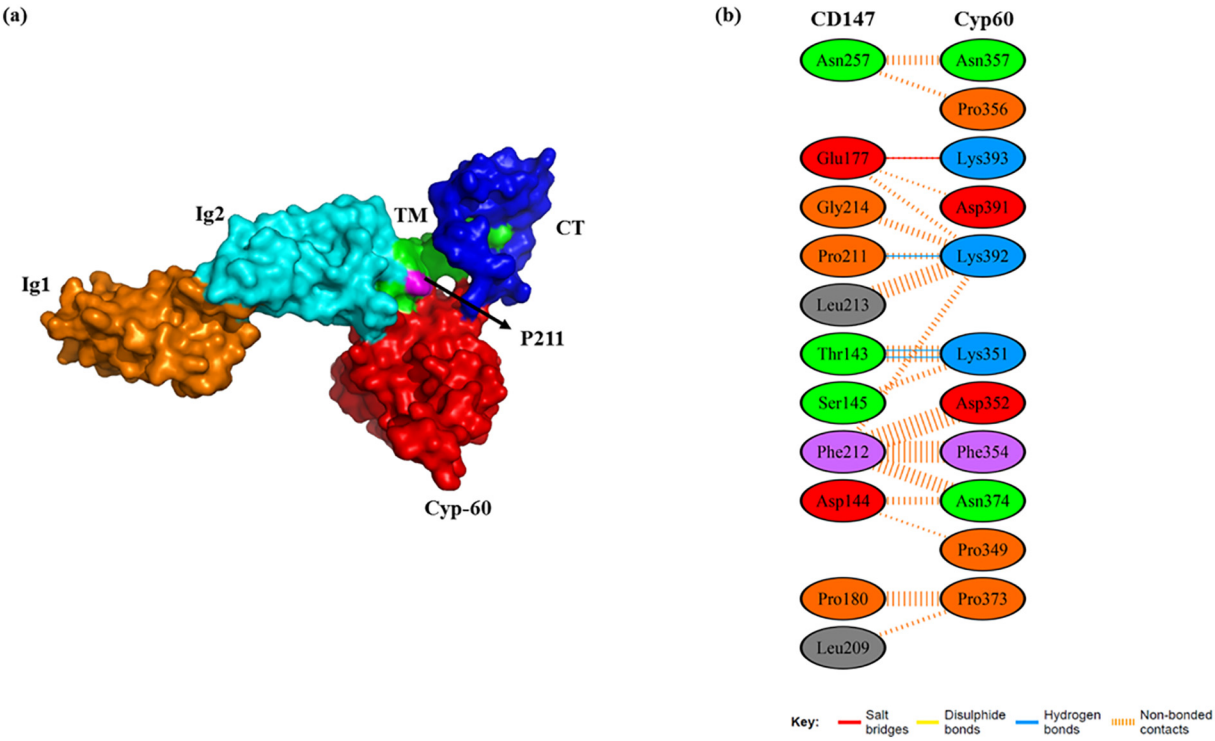

Fig. 9. (a) Molecular surface representation of CD147 (Basigin-2) + Cyp-60 docked complex: Ig1 (orange), Ig2 (cyan), TM region (green), CT (blue) and Cyp-60 in red, Proline211 of CD147 participating in interactions with Cyp-60 shaded in magenta. (b) Showing 2-D interaction map of CD147-Cyp60 docked complex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.3. CD147 and MCT (monocarboxylate transporter) interactions in cancer pathogenesis

As a result of Warburg effect, cancer cells undergo anaerobic glycolysis. This enhances acid-induced toxicity and aid in degradation of ECM, invasion and also promotes angiogenesis [82]. MCT is one of the key molecule in maintaining pH homeostasis in cancer cells. MCT belongs to SLC16 family of plasma-membrane proteins comprising of 12 trans-membrane domains. Lactate act as the primary substrate for MCT 1–4 [83]. MCT is reported to be tightly bound with CD147. In COS and HeLa cells, co-transfection of CD147 and MCT 1 or MCT4 is shown to result in the active expression of MCTs in the plasma membrane [4,25]. CD147 is also reported to serve as chaperones for MCTs [84]. In HCC, MCT-4 activates cell proliferation *via* AKT and ERK pathway and it also upregulates the integrin beta 4-SRC-FAK and MEK-ERK pathways and hence promoting tumor migration and invasion [85]. MCT not only transports lactate, but also the other monocarboxylate compounds like acetic acid, propionic acid, pyruvic acid and ketone bodies. MCT-1, 3, 4 are highly associated with CD147. The residues L252 and E221 of CD147 play a vital role in forming interactions with MCT-1 [58]. MCT1, MCT4 and CD147 were found to be over expressed in the plasma membrane of prostate cancer which helps to maintain acid efflux and maintenance of intracellular pH. MCT not only interacts with CD147, but also interacts with other proteins like VEGF, wherein, it aids in the metastasis and angiogenesis process. Thus, targeting MCT and CD147 interactions could serve as a potential strategy for combating tumor invasion and metastasis [86].

4.4. Chemotaxis (cyclophilins)

Human cyclophilins comprises of 16 family members, CypA is the most abundant form among these members. The key function of cyclophilins are protein folding, trafficking and T-cell activation [87]. CypA binds to CD147 and heparans on CHO cells, CypA typically binds to heparin sulphate and then to CD147. This signalling cascade leads to ERK activation. The extracellular domain of CD147 and the residues P180 and G181 plays an important role for signalling and chemotactic activity [60].

Co-localization of Cyp60 with CD147 is proposed to play a pivotal role in the secretory pathway. The cell surface expression of CD147 from Golgi to plasma membrane is regulated by cyclophilins. P211 in TM domain of CD147 (Basigin-2) is shown to interact with Cyp60. When CD147-cyclophilin interactions were blocked either by CsA (cyclosporin A) or by mutating the critical P211 residue, it was found to result in weakened transport of CD147 to the plasma membrane. This infers the regulatory role of cyclophilins in intracellular trafficking of CD147 [51]. The essential role of CD147 is also to act as a signalling receptor for extracellular cyclophilins. Earlier NMR studies have also demonstrated the structural interactions of CD147 with CypA. Here, P211 which spans exterior of the cell and adjacent to the transmembrane region of CD147 was shown interact with Cyp60, however not with P180 [61]. In an another other study, CypB was shown to interact with CD147 at P180, which thereby induces intracellular signalling events and adhesion to matrix [59,88].

The complete structure of CD147 (Basigin2) was homology modelled using modeller9.15 and the Cyp60 structure was retrieved from PDB (PDB ID: 1ZKC). Protein-protein blind docking of these proteins was performed using ZDOCK. ZRANK algorithm was used for structural refinement and rescoring of the docked complex. The modelled CD147-Cyp60 complex showed a significant ZRANK score of −37.8052. During the docking process, transmembrane region of CD147 was marked as active cavity. The 2D interaction map of CD147-Cyp60 complex shows that two hydrogen bonds are formed between P211-K392, and T143-K351, respectively. A salt bridge was also formed between E177 of CD147 and K393 of Cyp60. The residues N257, G214, L213, S145, F212, D144, P180 and L209 of CD147 were found to stabilize the complex by hydrophobic interactions (Fig. 9a & b). As the surface expression of CD147 is governed by Cyp60, it is necessary to know which active cavity of Cyp60 is involved in the interactions with CD147. Thus, the docked complex shall provide some valuable insights

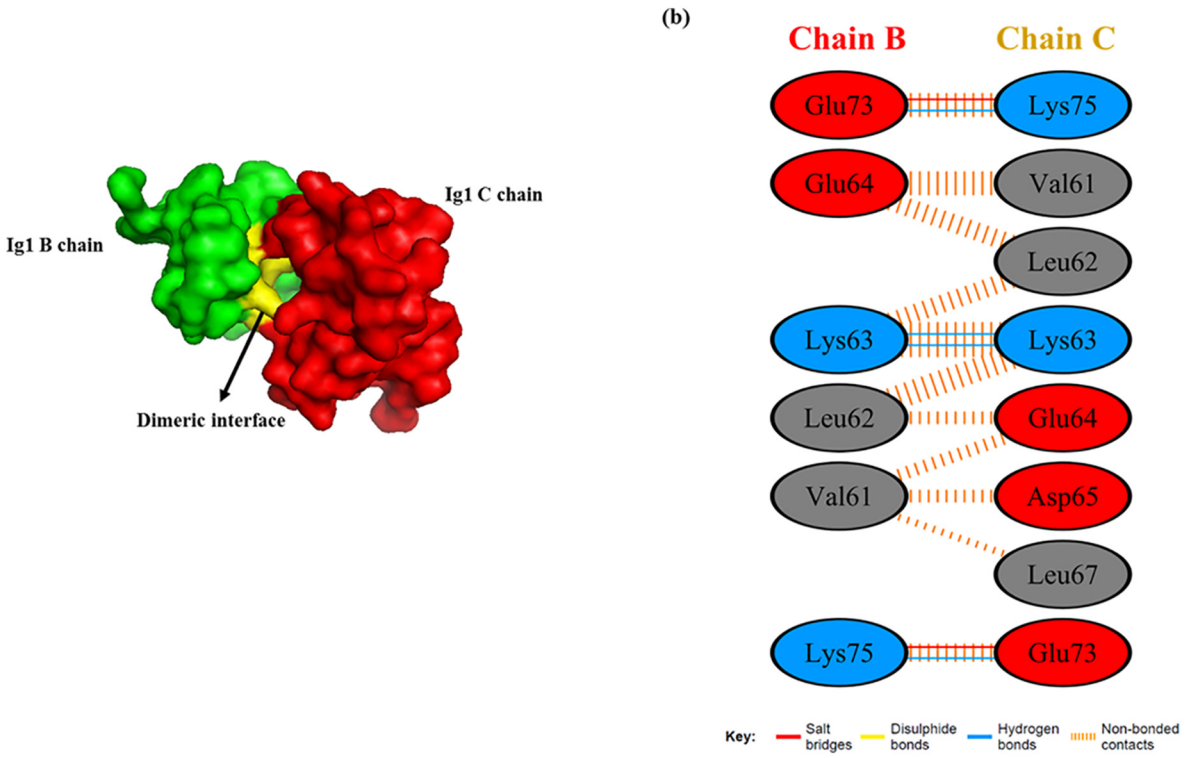

Fig. 10. (a) Surface representation of the crystal structure of BC dimer (PDB: 3B5H) Ig1 B chain (green) and Ig1C chain (red). The dimeric interface of B chain is shown in yellow. (b) 2D interaction map of Protein-Protein interactions of BC dimer, as generated by PDBsum. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

on probing druggable sites.

5. Need to inhibit this multifunctional protein in cancer pathogenesis

Cancer cell produces huge amount of lactate due to anaerobic glycolysis. CD147 is closely associated with MCT1 and MCT4 which aids in transport of lactate across the plasma membrane. This process helps in the modulation of extracellular pH and promotes in proliferation, invasiveness, metastasis and angiogenesis in tumor cell. In human malignant melanoma cells, silencing of CD147 leads to the abolition of MCT expression and also leading to the inhibition of VEGF production [18]. In CD147 null mice, decreased membrane aggregation of MCT1 and MCT3 in the RPE, and MCT1 and MCT4 in neural retina were observed [89]. Silencing of CD147 in HCC cells has shown to result in a severe reduction in VEGF-A expression and also found to boost the chemosensitivity to curcumin [90]. In HCC cells, P13K/AKT was also found to be partially activated by the over expression of CD147 which contributes to the gain of anoikis resistance and to aid the metastasis process in cancer cells. The knockdown of CD147 expression in SMMC-7721 (human HCC cell line) cells is shown to induce cell anoikis and also to inactivate Akt phosphorylation [14].

CD147 also plays a crucial role in drug resistance in cancer. It interacts with ABCG2 efflux protein *via* its transmembrane region. CD147 knockdown studies in Jurkat T cells is shown to decrease ABCG2 levels and to increase the MTX drug sensitivity [15]. Vacuolor H+ -ATPase (V-ATPase) plays a key role in the acidic microenvironment of the cancer cells. The expression level of both protein V-ATPase and CD147 were found to be high in case of chemotherapy resistant breast cancer [91]. It has also been reported that drug resistance in breast cancer is mediated by CD147 *via* regulating V-ATPase expression. The knockdown of CD147 in breast cancer cells was found to inhibit V-ATPase activity [91]. This reinforces that CD147 also to take part in chemoresistance in the cancer cells. CD147 is also shown to be associated with PMCA1 (plasma membrane calcium ATPase1) which is an important protein that is responsible for maintaining the intercellular calcium balance and extracellular calcium efflux [92]. Genetic ablation of CD147 is also shown to result in global changes to the metabolome and proteome thereby affecting the basic cellular process such as cell cycle arrest, calcium signalling, cellular metabolic reprogramming, epithelial to mesenchymal transition(EMT) in pancreatic ductal adenocarcinoma (PDAC) [92]. A recent study also demonstrated the influence of CD147 on malignancy-associated properties of MCF-7 cells to be functionally twined to both Wnt and JAK/STAT pathways [8]. All these studies strongly reinforce that targeting CD147 in cancer to be a beneficial therapeutic approach, as it serves as a hub protein many types cancers and also spans major hallmarks of cancer.

5.1. Potential inhibitors targeting CD147 dimeric interface

AC-73, a small molecule inhibitor is shown to disrupt CD147 (Ig1-Ig2) dimerization and also to modulate the CD147/ERK1/2/STAT3/MMP2 pathway in hepatocellular carcinoma cells. The molecular docking studies have shown that AC-73 (phenolic hydroxy group) forms hydrogen bonded interactions with CD147 at Glu64 and Glu73 of N-terminal Ig1 domain, thereby modulating MMP2 expression [21]. It is also shown to be efficacious in treating in Human AML (acute myeloid leukemia) cell lines, AC-73 found to inhibit the cell proliferation, induce autophagy and also boost chemosensitivity [93]. CD147 antagonist peptide-9 is a 12-mer oligopeptide (Tyr-Lys-Leu-Pro-Gly-His-His-His-His-Tyr-Arg-Pro) and is shown to specifically bind to CD147. AP-9 peptide shows the inhibitory rate upto 81.19% in HCC cells and also found to significantly reduce the MMPs activity [75,94,95].

In an earlier study, it has been reported that Ig1 to exist as four different homophilic dimeric forms (AC, AD, BC, DD') [40]. Among these, the binding free energy of BC dimer is reported to be lower (-20.84 ± 4.74 kcal/mol) than other dimeric complexes (AC dimer -16.18 ± 4.62 kcal/mol, AD dimer -29.69 ± 2.22 kcal/mol and

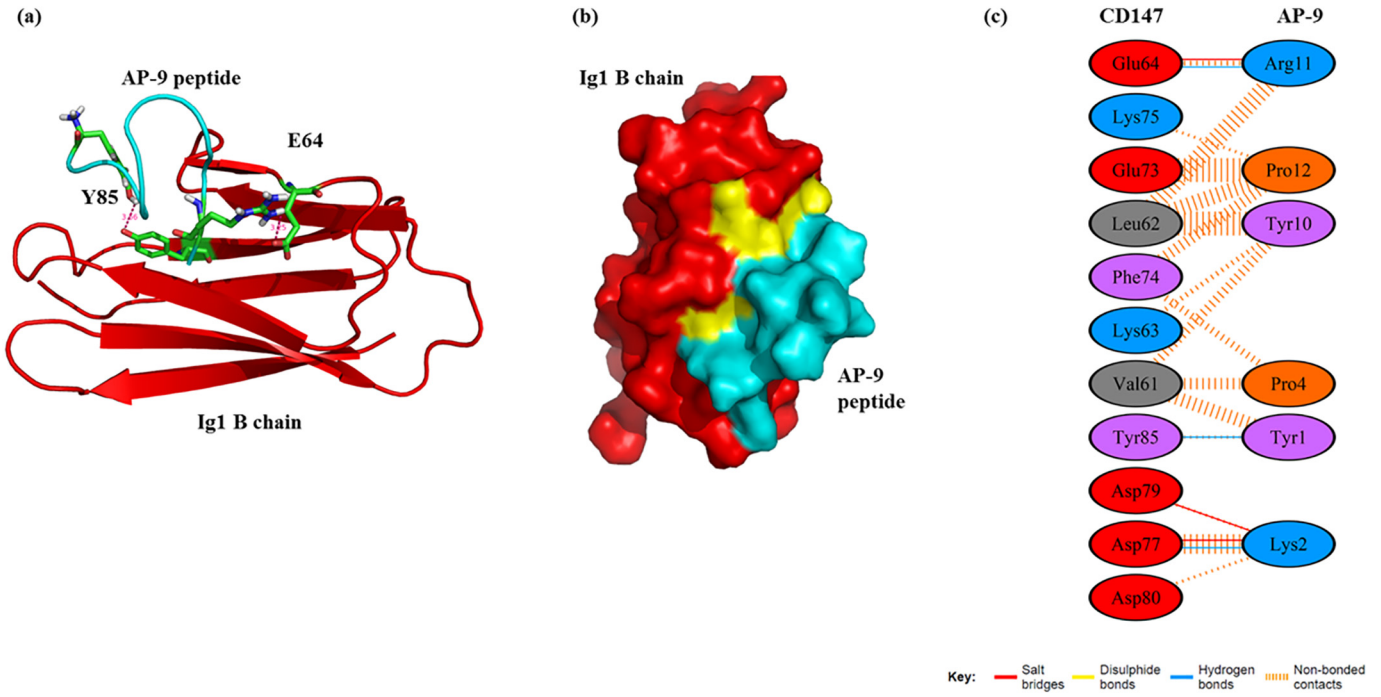

Fig. 11. (a) 3D interaction diagram of CD147 Ig1 domain with AP-9 peptide, (b) three dimensional representation of CD147 Ig1 B chain (red), AP-9 peptide (cyan) and interacting hotspot residues of BC dimer are shown in yellow. (c) 2D interaction map of protein-peptide interactions, as generated by PDBsum. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

DD' dimer −12.13 ± 3.79 kcal/mol) [40]. Surface representation of the crystal structure of BC dimer is shown in Fig. 10a. Moreover, the Anti-HCC (hepatocellular carcinoma) monoclonal antibody (mAb) targeting CD147 has been already reported. Earlier molecular docking and mutational studies reveal that the functional epitope of the antibody to target the BC interface [40]. Thus, disruption of BC dimer formation is considered to be a potential strategy for targeting CD147. In BC dimer, H-bonds are reported to be formed between K63/B-K63/C and two salt bridges between E73/B-K75/C and K75/B-E73/C in Fig. 10b [40].

Antagonist peptide-9 (AP9), an inhibitory peptide targeting CD147 has been already proposed to modulate MMP activity [95]. To provide more insights into its probable intermolecular interactions with CD147, this peptide was docked on to the BC dimer interface, as targeting this region modulates MMPs production. To start with, the 3D structure of AP9 was modelled in MODPEP sever. Further, the crystal structure of BC dimer (PDB: 3B5H) was chosen as receptor for docking AP-9 peptide using ZDOCK (Fig. 11a &b). The docked complex showed a significant ZRANK score (−69.8772). Hence, the complex was analyzed for intermolecular interactions. Fig. 11c depicts the 2D interaction map of CD147-AP-9 complex which shows that three hydrogen bonds to be formed between of E64-R11, Y85-Y1 and D77-K2, respectively. Salt bridges were also observed at E64-Arg11, D79-K2 and D77-K2 of CD147-AP-9 complex, respectively. V61, L62, E73, F74 and K75 of CD147 were found to stabilize the complex by conferring hydrophobic interactions. All these interactions shall strongly perturb the BC dimer formation. This interaction map shall aid in the computational design of peptides with enhanced activity.

6. Conclusion

CD147 is potential anticancer target, as it is highly expressed in many types of cancers like cancer of brain, breast cancer, cervical cancer, endometrial cancer, retinoblastoma and so on [13]. Targeting this protein shall prove to be highly beneficial in cancer as it spans the major hallmarks of carcinogenesis. CD147 is majorly targeted at the protein-protein interacting interfaces, it is ideal to target it by peptide or monoclonal antibodies over small molecules due its larger binding interface. In this review, we have provided the current structural insights on druggable hotspots in CD147 which shall guide in the development of novel lead compounds, thereby, providing way for efficient understanding and control of CD147 mediated targeting of cancerous conditions.

Conflict of interest

Authors declare no conflict of interest.

Author contribution to study

USV performed overall Planning of the study, co-collected the data, structured and wrote article together. DK Collected the Data, wrote the article as per the structured plan, SP Provided insights on cell biology aspects in the study. KKS Provided insights on Medical relevant information in this study.

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