

Cyclophilin–CD147 interactions: a new target for anti-inflammatory therapeutics

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Introduction

Leucocyte trafficking and recruitment are critical components of inflammation-mediated pathology. The main regulators of leucocyte trafficking are chemokines, a family of chemoattracting cytokines that control cell migration and adhesion [1]. However, other factors, in particular extracellular cyclophilins, can also induce potent chemotactic responses in immune cells (reviewed in [2]). We [3–6] and others [7,8] have observed that secreted cyclophilin A (CypA) is a potent leucocyte chemoattractant *in vitro*. In addition, CypA has also been shown to elicit inflammatory responses, characterized by a rapid influx of leucocytes, when injected *in vivo* [7,8]. Based on the potent chemotactic properties of cyclophilins, we proposed several years ago [2] that extracellular cyclophilins might contribute directly to leucocyte recruitment during inflammatory responses and thereby complement chemokines as innate immunity factors. In studies aimed at establishing the mechanism whereby cyclophilins mediate their chemotactic activity, our

Summary

CD147 is a widely expressed plasma membrane protein that has been implicated in a variety of physiological and pathological activities. It is best known for its ability to function as extracellular matrix metalloproteinase inducer (hence the other name for this protein, EMMPRIN), but has also been shown to regulate lymphocyte responsiveness, monocarboxylate transporter expression and spermatogenesis. These functions reflect multiple interacting partners of CD147. Among these CD147-interacting proteins cyclophilins represent a particularly interesting class, both in terms of structural considerations and potential medical implications. CD147 has been shown to function as a signalling receptor for extracellular cyclophilins A and B and to mediate chemotactic activity of cyclophilins towards a variety of immune cells. Recent studies using *in vitro* and *in vivo* models have demonstrated a role for cyclophilin–CD147 interactions in the regulation of inflammatory responses in a number of diseases, including acute lung inflammation, rheumatoid arthritis and cardiovascular disease. Agents targeting either CD147 or cyclophilin activity showed significant anti-inflammatory effects in experimental models, suggesting CD147–cyclophilin interactions may be a good target for new anti-inflammatory therapeutics. Here, we review the recent literature on different aspects of cyclophilin–CD147 interactions and their role in inflammatory diseases.

Keywords: CD147, cyclophilin, inflammation, receptor, structure

group was the first to identify CD147 as the principal signalling receptor for extracellular cyclophilins [3]. Indeed, all human [3,6] and mouse [4,5] leucocytes examined to date require expression of CD147 for extracellular cyclophilin-dependent chemotaxis to occur. A recently published review covered CD147 function in health and disease [9], so in this review we will focus upon cyclophilin–CD147 interactions and will overview the role that these interactions might play in disease pathology.

Physiological functions of CD147 and cyclophilins

CD147 nomenclature

CD147 is a widely expressed integral plasma membrane glycoprotein. It has been characterized under a variety of names in different species: OX-47 antigen [10] and CE9 [11] in rats, gp42 [12] and basigin [13,14] in mice, HT7 [15], neurothelin [16,17] and 5A11 antigen [18] in chickens. In humans, this protein was first discovered by Biswas and

colleagues as a tumour cell-derived factor stimulating production of a collagenase (matrix metalloproteinase type 1, MMP-1) by fibroblasts [19,20] and was designated 'tumour cell-derived collagenase stimulatory factor' (TCSF) [21]. Later, it was found that TCSF is expressed not only on cancer cells, but also on normal cells [22,23]. The same human protein was described in other studies as hBasigin, M6 or Hab18G [24,25]. It has become better known under the name 'extracellular matrix metalloproteinase inducer' (EMMPRIN), because this property of the protein has been studied most extensively. For consistency, in this review we will refer to this protein by its recently adopted designation, CD147 [26].

CD147 is expressed at varying levels in many cell types, including haematopoietic, epithelial and endothelial cells [10,22,27]. It is up-regulated markedly on CD71-positive early erythroblasts, and in heart, placenta and thyroid tissues [28]. Human CD147 is a 269 amino acid-long protein that belongs to the type I integral membrane protein family with a predicted molecular mass of 27 kDa [23]. The N-terminal extracellular part of CD147 consists of two immunoglobulin (Ig)-like domains that are heavily glycosylated [12–14,29,30]. Endoglycosidase F treatment leads to a mobility shift from 58 kDa to 28 kDa approximately, suggesting that the majority of CD147 glycosylation is N-linked [24]. Recently, another form of CD147, containing an additional extracellular membrane-distal Ig-like domain, has been characterized [31]. This form was shown to be responsible for the majority of homophilic CD147 interactions.

Phylogenetically, the CD147-like molecules can be traced in invertebrate organisms as far back as *Drosophila* and *Schistosoma* [32,33]. When compared with other members of the immunoglobulin superfamily, CD147 is placed as a separate lineage neighbouring the CD2 and CD4a clusters [34].

CD147 functions

Much of our understanding of CD147 functions comes from studies of CD147 knock-out mice [35,36]. These animals are defective in lymphocyte responsiveness [35], spermatogenesis [37,38], retinal [39,40] and neurological [41] functions at the early stages of development. Female mice deficient in CD147 are infertile due to the failure of female reproductive processes including implantation and fertilization [36,37]. The implantation defect may indicate a misregulation of MMP production [42]. CD147-null animals also show a dramatic reduction in accumulation of the monocarboxylate transporter (MCT)-1 and -3 proteins in the retinal pigment epithelium, supporting a proposed role for CD147 in targeting these transporters to the plasma membrane [43,44]. The deletion of MCT-3 in the basolateral membrane of the retinal pigment epithelium results in severely diminished expression of CD147, confirming the functional importance of this interaction as a regulator of CD147 expression [45]. Interestingly, positioning of the retinal lactate transporters

appears to be regulated by the rare 3-Ig-like domain form of CD147, as cDNAs for this form have been identified only in human and mouse retina [31]. Additionally, CD147 knock-out mice are characterized by enhanced mitogenic response of T lymphocytes in mixed lymphocyte reactions [35], suggesting a potential negative regulatory function of CD147 in T cell activation.

In support of such a negative regulatory role for CD147, recent studies in which CD147 was over-expressed in Jurkat T cells demonstrated an inhibition of nuclear factor-activated T cell (NF-AT)-mediated T cell activation, with a converse increase in activation when CD147 was silenced, via the Vav1/Rac1 signalling pathway [46]. However, another study, in which CD147 expression was silenced in Jurkat T cells, showed a reduction, rather than an increase, in T cell activation [47]. The reasons for this discrepancy are unknown, although it should be noted that the first study focused upon changes in intracellular signalling pathways and the second measured changes in cell function. Interestingly, the authors of the signalling study reported that the inhibition of NF-AT activity by CD147 was mediated exclusively by its intracellular tail, with no participation from either the extracellular or transmembrane regions [46]. Thus, variable outcomes between studies could be due to different functional parameters, regulated by distinct regions of CD147, having been measured. Additional support for a negative regulatory role by CD147 during T cell activation is provided by *in vitro* studies in which anti-CD147 monoclonal antibodies (mAbs) were shown to inhibit activation mediated by anti-CD3 [48–51], or phorbol myristate acetate (PMA)/ionomycin [49], in human peripheral blood T cells and T cell lines. Because the observed effects were functional in nature, anti-CD147 clones with a signalling capacity must have been selected. Alternatively, the antibodies could have been mediating their effect by hindering sterically certain interactions between CD147 molecules and other ligands, including signalling partners within membrane lipid rafts [50], adhesion partners on the cell surface [52,53] and/or soluble partners in the extracellular microenvironment (see below).

Cyclophilins: intracellular and extracellular activities

The second player in the cyclophilin–CD147 chemotactic pathway is extracellular cyclophilin. Cyclophilins are best known as ubiquitously distributed intracellular proteins which were first recognized as the host cell receptors for the potent immunosuppressive drug, cyclosporin A (CsA) [54]. While most studies to date have focused upon the intracellular activities of cyclophilins, including their role in regulating protein folding, their function as molecular chaperones [55], and the activity of CypA as a modulator of CD4⁺ T cell signal transduction and T helper type 2 (Th2) cytokine production [56], accumulating evidence suggests a role for cyclophilins as mediators of intercellular communi-

cation via extracellular sources of the proteins [2]. Some members of the cyclophilin family, notably cyclophilin B (CypB), contain endoplasmic reticulum (ER)-directed signal sequences that promote their secretion [57]. Indeed, CypB is detected readily in both human milk [58] and plasma [59]. CypB can also be released from chondrocytes by activated MMPs [60]. Cyclophilin A (CypA) has been shown to be secreted by cells in response to inflammatory stimuli [7,8] and oxidative stress [61,62]. Activated platelets have also been demonstrated to secrete CypA [63]. Unlike CypB, CypA does not contain any of the prototypical signal peptides found on most proteins undergoing secretion through a classical pathway. Instead, the mechanism of CypA secretion was shown recently to proceed via a vesicular pathway [62]. In these studies, CypA was found to localize to the plasma membrane of vascular smooth muscle cells following reactive oxygen species (ROS) stimulation, with secreted CypA protein detectable within 30 min of stimulation. Apart from CypA and CypB, no other members of the cyclophilin family have been shown to be secreted actively, although the possibility remains that some intracellular cyclophilins become extracellular due to protein release by dead or dying cells.

The active site residues of cyclophilins have been demonstrated to be critical for both the signalling and chemotactic activities induced by these proteins. For example, peptidyl-prolyl *cis-trans* isomerase-defective CypA mutants fail to initiate signalling events [3]. This suggests an unusual rotamase-dependent mechanism of signalling through the CD147 receptor. Such a mode of signalling requires only a transient interaction between the ligand and the receptor, consistent with a low-affinity binding interaction between CD147 and CypA. Indeed, we demonstrated recently that CypA can catalyse the peptidyl-prolyl *cis-trans* isomerization of Pro211 in CD147 [64] (see below). Similarly, CypB has also been shown to be enzymatically active on CD147 [65], although in this case the catalysed residue was identified as Pro180.

It is important to note that both the signalling and chemotactic activities of CypA and CypB are also dependent upon the presence of heparan sulphate proteoglycans (HSPGs), which probably serve as primary binding sites for these cyclophilins on target cells. Removal of HSPGs from the cell surface of neutrophils eliminates signalling responses to cyclophilins and abolishes cyclophilin-dependent chemotaxis and adhesion of neutrophils and T cells [3,65]. Interestingly, activation of T cells was shown to remove the dependence of CypA-specific responses on heparans [6], suggesting that increased CD147 expression and/or dimerization in activated T cells may substitute for heparans by enhancing CypA binding to CD147. This result supports a model whereby cyclophilin binding to HSPGs is required to complement a low-affinity interaction between cyclophilins and CD147 expressed on non-activated cells. Importantly, the rotamase activity of cyclophilins is not influenced by HSPGs expressed on the cell surface [65].

CD147 and cyclophilins: structural and signalling aspects

CD147 is a multi-functional molecule. In addition to its activities described above as a cyclophilin receptor and an inducer of MMPs, CD147 can also affect the activation and development of T cells [48,50,66], regulate transport of monocarboxylate transporters (MCT) to the plasma membrane [67] and contribute to the blood–brain barrier function of cerebral endothelial cells [68]. Interestingly, these different activities appear to involve different domains of CD147. CD147 consists of a 206 amino acid extracellular region containing two Ig-like domains, a 24 aa residue transmembrane domain and a 39 aa cytoplasmic domain (Fig. 1a). The extracellular region contains three N-linked glycosylation sites. The extracellular portion of CD147 is quite diverse, while the 24 residue-long transmembrane domain, represented by a hydrophobic stretch of amino acids interrupted by a charged residue (glutamic acid), is almost identical among different species [3,69]. This structural feature of the transmembrane domain suggests a potential for additional functional roles besides anchoring CD147 in the membrane. Charged residues are not usually found in proteins spanning the membrane only once (as is the case for CD147), because a charged residue in the middle of the lipid bilayer is highly energetically unfavourable. Thus, CD147 has a propensity to form complexes with other membrane proteins thereby shielding the charge in an energetically stable state. Indeed, the transmembrane domain is responsible for many of the interactions between CD147 and other transmembrane proteins [70], including β 1 integrins [52,71], CD43 [72] and syndecan [73] (Fig. 1a). Such interactions may contribute to the activity of CD147 in leucocyte adhesion [72,73]. They may also be involved in CD147-mediated signalling responses. Indeed, our recent study [74] demonstrated that the cytoplasmic domain of CD147 is not required for extracellular-regulated kinase (ERK) activation, a key signalling event initiated by cyclophilin-CD147 interaction [3,75–77], providing support for the involvement of transmembrane CD147-associated proteins in CD147-mediated signal transduction.

CD147 has been shown to interact with several other proteins (Table 1). For example, interaction of CD147 with MCTs, the proton-coupled transporters of monocarboxylates [31,44,67], occurs within the cellular membrane and depends critically upon the described above centrally positioned glutamic acid residue 218 in the CD147 transmembrane domain. When association of CD147 with monocarboxylate transporter MCT1 was disrupted by mutating this glutamic acid, neither CD147 nor MCT1 reached the plasma membrane [78], suggesting that CD147 might be a part of the heteromeric membrane complex involving MCTs. In support of this notion, a recent study [79] showed the association of MCT4, CD147 and β ₁-integrin at the basolateral membrane, and suggested that this complex

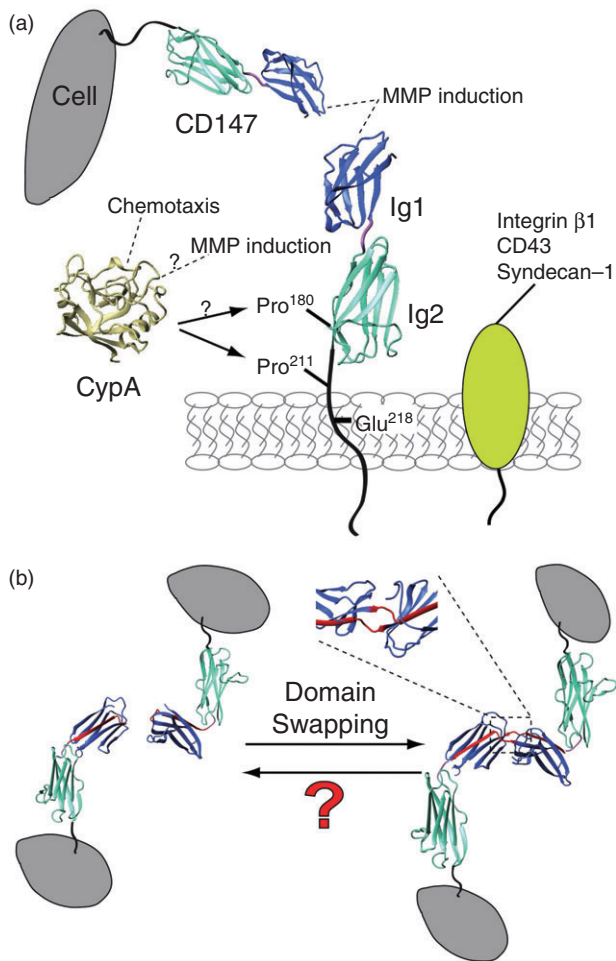


Fig. 1. Schematic representation of CD147 and its interactions. (a) Matrix metalloproteinase (MMP) induction is mediated by a homotypic interaction between CD147 molecules on different cells; chemotactic responses are initiated by interaction between cyclophilin and CD147. Immunoglobulin 1 (Ig1) domain is involved in MMP induction, whereas proline 211 and possibly proline 180 are required for interaction with cyclophilins and for cyclophilin-induced signalling. Glutamic acid in position 218 is potentially involved in interactions with other transmembrane proteins, such as CD43, β 1 integrin and syndecan. The relevance of these interactions to disease pathogenesis is described in the text. (b) Potential model of CD147 homophilic interactions. A recently solved structure of CD147 Ig1 domain alone has revealed that the C-terminal beta-strand of one subunit is swapped with that of the other subunit [99]. It is still unclear how this process is regulated. See text for details.

may regulate cell migration through modulation of focal adhesions. CD147 also interacts with caveolin-1 on cell surfaces and this interaction seems to regulate CD147 clustering and activity negatively, thus exerting tumour-suppressing activity [80]. Conversely, several reports suggested carcinogenic activity of caveolin-1 via up-regulation of CD147 glycosylation, which is linked to MMP induction and tumour invasion [81,82]. Association with caveolin-1 depends upon the second Ig domain in the extracellular portion of CD147.

Finally, leucine 252 (along with the adjacent amino acids 243–246 in the cytoplasmic domain of CD147) was identified as a signal targeting CD147 to the basolateral membrane in extraocular epithelia. Deletion of these amino acids results in mistargeting of CD147 to the apical membranes [83]. This signal seems to function only in some cell types (e.g. it was not recognized in human retinal pigment epithelium cells [83]), suggesting that it mediates interaction with limited cell-specific regulators of protein trafficking. Future studies will hopefully integrate these findings into a unifying model of CD147 trafficking. Such a model will suggest not only new targets for therapeutic interventions in diseases where CD147 is recognized as a pathogenic factor [e.g. cancer or rheumatoid arthritis (RA)], but will also explain the role of CD147 in other biological processes, such as development of the eye or spermatogenesis [84,85].

Addition of CypA or CypB to CD147-expressing cells initiates a signalling response characterized by Ca^{2+} flux and activation of ERK1/2 kinases [3,75–77]. Genetic analysis demonstrated that amino acids Pro²⁸⁰Gly²⁸¹ are critical for this signalling [3]. In addition, Pro²¹¹ is involved in interaction with another cyclophilin, Cyp60, which regulates cell surface expression of CD147 [86]. Pro²¹¹ is located either near the end of the transmembrane domain facing the outside of the cell or may be partially exposed and accessible to extracellular cyclophilins. Indeed, nuclear magnetic resonance (NMR) studies of the recombinant proteins revealed that CypA-mediated isomerization of CD147 stabilizes the rare *cis*-conformer of the Trp²¹⁰-Pro²¹¹ peptidyl-prolyl bond, potentially representing a ‘proline switch’ [64]. Thus, cyclophilin/CD147 interactions may represent the first discovered ligand/receptor interaction in which proline isomerization on the outside of the cell results in intracellular signalling on the inside of the cell. Although no direct interaction of CypA was found with Pro180 of CD147, there may be other mediators involved in sequestering cyclophilins to this site by way of ternary interactions. CypA forms ternary complexes with calcineurin and calcineurin inhibitors such as cyclosporin [87], suggesting that a complex array of interactions may underlie cyclophilin/CD147 signalling. Therefore, interaction of cyclophilin with Pro¹⁸⁰ may be necessary for binding, whereas subsequent interaction with Pro²¹¹ induces signal transduction. As with signalling induced by homotypic interaction between CD147 molecules, the mechanisms of cyclophilin-induced signalling remain unknown. Again, additional molecules that are associated directly and indirectly with CD147 appear to be involved in signalling, as the cytoplasmic tail of CD147 is not necessary for CypA-induced ERK activation [74]. Adding to the complexity of the issue, it remains to be determined whether ERK activation is in fact required for chemotactic responses mediated by cyclophilin–CD147 interaction, or whether some other signalling pathway is involved.

While different CD147 domains are involved in MMP induction and chemotactic responses, these domains may be

Table 1. CD147-interacting proteins.

Protein	CD147 domain involved	Interaction experiments	Result of interaction	Disease relevance	References
CD147	Extracellular, Ig-like domain 1	Cell adhesion assay; biotin label transfer/MS; peptide screening	MMP induction	Promotes tumour cell invasion	[96,98,160]
Monocarboxylate transporters MCT1, 3, 4	Transmembrane	Cross-linking/co-IP; FRET; co-localization analysis	Facilitates MCT surface expression	Tumour cell glycolysis	[67,78,79,155,161]
CD98, β 1-integrin	Extracellular	Co-IP; cross-linking/MS	Induces homotypic cell aggregation; affects cytoskeletal architecture	Aberrant cell migration in proliferative vitreoretinopathy and metastatic cancer	[52,79,162–164]
MMP-1, MT1-MMP	Extracellular	Phage display; affinity chromatography; immunocytochemistry; co-localization	Induces the production of secreted MMPs	Mediates CD147 shedding; modifies the tumour cell pericellular matrix to promote invasion	[92,93]
Caveolin-1	Extracellular, Ig domain 2	Co-IP	Inhibits CD147 dimerization and activity; upregulates CD147 glycosylation	Tumour-suppressing effect but also promotes MMP induction and tumour invasion	[80–82]
CypA	Extracellular, P180; P211	Cross-linking/co-IP; cell binding; solution binding; functional assays (signalling, chemotaxis), NMR	Induces intracellular signalling events and chemotaxis; up-regulates MMP-9	Immune cell chemotaxis in inflammatory diseases; cartilage destruction in RA	[3,64,77,165]
CypB	Extracellular, P180	Functional assays (signalling, chemotaxis, CD147 isomerization)	Induces intracellular signalling events and adhesion to matrix	Immune cell adhesion in inflammatory diseases	[53,65,75,166]
Cyp60	Transmembrane, P211	Co-localization; co-IP	Stimulates CD147 surface expression	Unknown	[86]

FRET, fluorescence resonance energy transfer; Ig1, immunoglobulin 1; IP, immunoprecipitation; MCT, monocarboxylate transporter; MMP, matrix metalloproteinase; MS, multiple sclerosis; NMR, nuclear magnetic resonance; RA, rheumatoid arthritis.

close to each other due to intermolecular interactions with other mediators. Bending of the CD147 molecule due to interaction between the Ig domains would explain how a single monoclonal antibody to CD147 (clone UM-8D6) can inhibit both MMP induction and chemotactic responses (unpublished observation).

Structural aspects of cyclophilin-independent activities of CD147

Stimulation of MMP production by CD147 occurs both via heterotypic cell interactions, such as those between tumour cells and fibroblasts, and by homotypic cell interactions, potentially representing a cyclophilin-independent means of signalling. In fact, multiple extracellular CD147 forms have been identified that include full-length CD147 associated

with large microvesicles where CD147 continues to stimulate the secretion of MMPs and proinflammatory cytokines [88–91]. Interestingly, the entire CD147 ectodomain as well as the individual Ig-like domains are cleaved from the cell surface by many of exactly the same MMPs that are secreted due to CD147 stimulation [92–95]. The stimulatory activity of these extracellular CD147-derived peptides has been demonstrated recently. Here, the recombinant CD147 ectodomain that comprises both Ig-like domains (residues 22–205) was shown to stimulate secretion of MMPs [96] and proinflammatory cytokines [64]. The first Ig-like domain (Ig1 in Fig. 1a) and N-linked glycosylation are responsible for MMP-stimulating activity [23,97,98]; however, how this occurs remains unknown. For example, CD147 Ig-like domains appear not to associate directly with each other at even millimolar concentrations [64], suggesting that other

protein interactions may mediate the proposed CD147 Ig1 homophilic association. Adding to this complexity, the CD147 Ig1 domain has been found to form a highly stable 'swapped dimer', where one C-terminal beta-strand (residues 94–103) folds structurally into the other monomer [99] (Fig. 1b). Although this appears to be mediated by two proline *cis/trans* isomerizations (Pro91 and Pro93), there is currently no evidence that CypA (or any other cyclophilin) mediates such an interaction or that this isomerization can occur spontaneously in solution [64]. Thus, how swapping occurs, whether CypA is involved and whether domain-swapping underlies CD147 homophilic interactions remains to be seen. CD147 Ig1 domain-swapping may, in turn, result in a conformational change to other interacting proteins, similar to that of the cadherin family [100]. However, unlike the cadherins, there is no evidence of a monomer/dimer equilibrium for CD147 and all extracellular forms have been found to be monomeric. Thus, CD147 Ig1 domain-swapping represents either a misfolded form that rarely occurs for recombinant Ig-like domains [101] or there may be mediators of CD147 activity that induce domain-swapping and subsequent signalling. With regard to intracellular signalling associated with this cyclophilin-independent activity, experiments where purified CD147 was added to fibroblasts to stimulate MMP-1 transcription demonstrated a critical role of p38 mitogen-activated protein kinase (MAPK) in this activation [102]. Whether p38 activation is mediated by signalling originating from the cytoplasmic tail of CD147, or from a CD147-associated protein, remains unknown. In contrast, MMP-2 production by fibroblasts was shown to be dependent upon the phospholipase A₂/5-lipoxygenase pathway, but not on MAPK p38 activation [88]. It appears that different signalling pathways leading to MMP induction can be initiated by CD147, suggesting a complex regulation probably involving two kinds of signalling molecules: those that associate directly with the CD147 cytoplasmic tail and those that associate with CD147 indirectly, via a bridging protein.

Role of CD147 in disease pathogenesis

Given the multiple partners and activities of CD147 it is not surprising that this protein has been implicated in the pathogenesis of a number of diseases. For example, CD147 might also represent a universal co-receptor for viral entry into host cells, as it was shown to enhance infection by human immunodeficiency virus (HIV-1) and severe acute respiratory syndrome (SARS) coronavirus [74,103,104]. In addition, recent reports identified CD147 as a crucial part of the multi-protein γ -secretase complex [105,106]. This complex cleaves the β -amyloid precursor protein to produce amyloid β -peptides associated with the formation of amyloid plaques in Alzheimer's disease patients [106]. What is surprising is that most of pathogenic effects of CD147 are related either to MMP induction or CD147 capacity to mediate chemotactic activity

by extracellular cyclophilins. It could be that other activities of CD147 are not sufficiently obvious to contribute significantly to disease pathogenesis, but most probably we simply do not know enough to make such connections.

CD147 in cancer

The best-studied activity of CD147 is its role in cancer. This activity is linked tightly to CD147-mediated induction of MMPs, which promote tissue destruction and facilitate tumour metastasis [28]. The role of CD147 in cancer has been the topic of many studies and reviews [9,28,107,108]. CD147 stimulates MMP production by stromal fibroblasts and endothelial cells around the tumour, as well as by tumour cells themselves, through a mechanism involving homophilic interactions between CD147 molecules on opposing cells [88,93,102,109]. Elevated levels of CD147 are detected in numerous malignant tumours and have been shown to correlate with tumour progression in experimental and clinical conditions [88,110–113]. Recently, CD147 was proposed as a novel marker of poor outcome in serous ovarian [114], hepatocellular carcinoma [115,116], advanced bladder [117] and cervical cancer [118], lung adenocarcinoma [119] and gallbladder carcinoma [120]. The MMP-inducing function of CD147 is also known to contribute significantly to tissue repair and remodelling during cancer development as well as several pathological conditions (reviewed recently in [121]). Notably, CD147 has been shown to promote tissue remodelling by inducing the expression of α -smooth muscle actin in models of cardiovascular disease [122] and corneal wound healing [123]. It has been suggested that this function of CD147 may be tissue-specific, as well as MMP-specific [124]. Interestingly, there is some evidence linking cancer-promoting activity of CD147 to interaction with extracellular cyclophilin. The extracellular CypA was shown to stimulate proliferation of lung cancer cell line by inducing ERK1/2 signals [125], activity shown previously to be mediated by CD147 [3]. A similar proliferation-promoting activity of CypA was shown for human pancreatic cancer cells, where CypA activated the ERK1/2 and p38 pathways [126]. The exact mechanisms of this proliferative activity and its role in pathogenesis of cancer remain unclear and await further confirmation.

Role of CD147–cyclophilin interactions in inflammatory diseases

CD147 and cyclophilins are up-regulated in human inflammatory diseases

Although a requirement for up-regulated levels of CD147 to mediate MMP induction has not been demonstrated formally, many pathological conditions involving an inflammatory component are associated with increased expression of CD147 in tissues and cells. These include lung inflammatory

diseases [127,128], RA [77,129–132], systemic lupus erythematosus (SLE) [133], chronic liver disease induced by hepatitis C virus (HCV) [134], atherosclerosis [135–138] and ischaemia [76,139]. High levels of extracellular cyclophilins have also been detected in several different human inflammatory diseases, such as severe sepsis [140,141], vascular smooth muscle cell disease [61], atherosclerosis [63], lupus [142], Lyme disease [143] and RA [144,145]. Of note, the list of diseases with increased cyclophilin levels overlaps with diseases where CD147 is up-regulated, suggesting that cyclophilins, via their interactions with CD147, may contribute to the recruitment of immune cells to sites of inflammation via chemokine-like activity [146]. For example, the level of CypA in synovial fluid isolated from RA patients was reported to correlate with the numbers of neutrophils present within synovial spaces, as well as disease severity [145]. In another study, cartilage chondrocytes were shown to secrete cyclophilins in response to matrix metalloproteinases or other stimuli, providing an additional source of extracellular cyclophilins released during ongoing RA [147,148].

Interestingly, studies looking at proinflammatory leucocytes have reported increased expression of cell surface CD147 on these cells, relative to non-inflammatory cells [149]. For example, an up-regulated expression of CD147 was observed in the synovial membrane [132], as well as on circulating and synovial monocytes/macrophages [149], in RA patients. Increased levels of CD147 were also reported recently on a murine synovial fibroblast cell line used for studies of cartilage invasion and destruction [150]. One might postulate that an increase in CD147 expression would enhance the interaction between leucocytes and extracellular cyclophilins, thereby promoting their recruitment. In support of this, we reported recently that activated CD4⁺ T cells showed enhanced cyclophilin-mediated chemotaxis that correlated with an up-regulated expression of CD147 [5,6].

Animal models of inflammatory diseases

Recent studies in several animal models of human disease have underscored the important role of cyclophilin–CD147 interaction in disease pathogenesis. Our study using a mouse model of lipopolysaccharide (LPS)-induced acute lung inflammation demonstrated that treatment with either anti-CD147 mAb, or a non-immunosuppressive CsA analogue, NIM811, reduced the inflammatory response significantly [4]. Both treatments led to a 40–50% inhibition of neutrophilia within lung tissues and airways. Importantly, treating mice with a combination of anti-CD147 mAb and CsA led to an inhibition of neutrophil infiltration only slightly greater than that induced by the individual treatments, indicating that anti-CD147 and CsA are probably acting on the same cyclophilin–CD147 interaction. We also demonstrated in a mouse model of acute asthmatic inflammation that *in vivo* treatment with anti-CD147 mAb reduced significantly (by up to 50%) the accumulation of eosinophils and effector/

memory CD4⁺ T lymphocytes, as well as antigen-specific Th2 cytokine secretion, in pulmonary airways and tissues of allergen challenged mice [5]. This treatment also reduced significantly airway epithelial mucin production and bronchial hyperreactivity to methacholine challenge.

In the collagen-induced arthritis mouse model of human RA, *in vivo* treatment with anti-CD147 mAb inhibited the development of joint inflammation by more than 75% [129]. Factors associated with the presence of proinflammatory leucocytes, including tumour necrosis factor (TNF)- α and myeloperoxidase, were also reduced significantly, suggesting that anti-CD147 treatment was impacting leucocyte recruitment into joints. These findings are consistent with a recent report demonstrating that anti-CD147 alone or in combination with anti-TNF- α inhibited cartilage erosion and synovitis in the severe combined immunodeficiency (SCID) mouse model of RA [151].

Cyclophilin–CD147 interaction can promote MMP production

As described above, MMPs play important role in pathogenesis of many diseases, including inflammatory conditions, and there is evidence that extracellular cyclophilins, probably via interaction with CD147, may contribute to MMP production. A report by Seizer and co-authors [152], studying atherosclerosis in an apolipoprotein E (apoE)-deficient mouse model, demonstrated that silencing of CD147 expression by siRNA during the cell differentiation process hindered up-regulation of MMPs (MT1-MMP, MMP-9). The presence of a cyclophilin inhibitor, NIM811, also reduced MMP-9 secretion significantly during the differentiation process. Conversely, the presence of CypA enhanced MMP-9 secretion by mature foam cells. CypA and CD147 were found consistently in atherosclerotic plaques of apoE-deficient mice. These results suggest that the CypA/CD147 pathway may play a relevant role in promoting the vulnerability of atherosclerotic plaques and thus contribute to the pathogenesis of atherosclerosis. A similar effect was reported by Yang *et al.* [77] in human RA. They demonstrated that CypA increased the *in vitro* production and activation of MMP-9 in monocytes/macrophages derived from RA synovial fluid, whereas anti-CD147 antibody decreased the observed MMP-9 expression dramatically. Therefore, MMP up-regulation may be another mechanism by which cyclophilin–CD147 interaction might contribute to RA pathogenesis by promoting cartilage destruction.

Therapeutic targeting of CD147–cyclophilin interactions

Given the role that cyclophilin–CD147 interactions play in pathogenesis of inflammatory diseases, they present an attractive target for therapeutic interventions. The agents that can potentially disrupt these interactions can be

grouped into agents targeting CD147 and drugs targeting cyclophilins. These agents may also be useful for treatment of other diseases involving cyclophilins and/or CD147, such as cancer or HIV infection [74,103,153].

Inhibition of CD147 using anti-CD147 monoclonal antibody provided a more than 50% reduction of inflammation in mouse models of acute lung inflammation, asthma and RA [4,5,129,151]. Therapeutically useful antagonistic antibodies would prevent cyclophilin-induced signalling and MMP-inducing activity of CD147. Interestingly, the sites responsible for these two functions appear to be adjacent in a secondary structure of CD147 [64], so it may be possible to inhibit both functions with a single monoclonal antibody (S. C. and M. B., unpublished observation). For future clinical applications, it would be necessary to ensure that the antibody does not exert any agonistic activity, which may compromise the therapeutic effect.

An attractive approach to inhibit CD147 activity is via antagonistic peptides derived from extracellular domains of CD147. Such 12-amino acid peptides were shown to inhibit CD147-dependent MMP production and invasiveness of synoviocytes from RA patients [130], MMP-2 and MMP-9 production and invasive potential of PMA-differentiated THP-1 cells (human monocytic leukaemia cell line) [154], and infection of host cells by SARS coronavirus [104]. No report yet has shown *in vivo* activity of CD147-targeting peptides in an animal model of human disease.

Yet another possible way to target CD147 is to down-regulate its expression using the RNAi approach. This technique works usefully *in vitro* to suppress CD147-dependent cell proliferation, invasiveness and metastatic activity of cancer cells [47,155,156] and induce their apoptosis [157], but its usefulness for clinical applications awaits further studies.

Another arm of the CD147-cyclophilin axis are cyclophilins, and cyclophilin-targeting drugs CsA and FK-506 have been used for many years as immunosuppressors. Obviously, immunosuppressive activity would be an unwanted complication in clinical use of these drugs as anti-inflammatory or anti-cancer agents. Furthermore, as chemotaxis of inflammatory cells depends upon the activity of extracellular cyclophilins, there is no need to inhibit calcineurin function to suppress cyclophilin-dependent chemotaxis. Our studies demonstrated that non-immunosuppressive CsA derivative, NIM811, exerted a potent anti-inflammatory activity, comparable to that of unmodified CsA, in a mouse model of acute lung inflammation [4]. Even more exciting, a recent report described a modification that, when introduced into the CsA molecule, makes it unable to penetrate cell membrane but still retain cyclophilin-binding activity [158]. When such non-permeable CsA derivative was used in a mouse model of acute lung inflammation, it showed an extremely potent anti-inflammatory activity, significantly exceeding that of NIM811 [158]. Non-permeable CsA is likely to have very

few adverse effects and appears to be an ideal candidate for development as an anti-inflammatory drug to treat such diseases as RA, asthma and atherosclerosis.

Taken together, these results show an important contribution of cyclophilin-CD147 interactions to the initiation and/or progression of inflammatory responses via recruitment of leucocytes into inflamed tissues and stimulation of MMP production, and show great potential of therapeutic targeting of these interactions for treatment of inflammatory diseases.

Conclusions

Based upon the various studies reviewed above, it is clear that both CD147 and cyclophilins have multi-functional properties, both independently and as an interacting complex. A number of mechanistic details of interactions between cyclophilins and CD147 is still unknown and awaits further studies. In particular, it would be extremely important to refine our understanding of cyclophilin-induced signalling through CD147. How does isomerization of Pro211 on CD147 initiate intracellular signals? What other sites on CD147, besides Pro211, are involved in signalling response to cyclophilin? Does this signalling involve any other proteins? What signalling pathways are initiated by cyclophilin and what are signal transduction mechanisms for these pathways? Answers to these questions would be essential for future translational efforts aimed at targeting cyclophilin/CD147 pathway. Indeed, demonstration that these molecules and their interactions play a direct role in different types of inflammatory conditions provides an attractive new target for intervention. Although reagents that block either CD147 or cyclophilin function were shown to be effective in reducing inflammatory responses in experimental models of disease, the specificity of these reagents is still quite broad, in that multiple functions of CD147 and cyclophilins were probably inhibited. The current challenge is to design therapeutic agents with the capacity to block specific functions of these molecules, while leaving other functions unaffected. In this context, a recent study reported the development of a small-molecule compound with the capacity to specifically inhibit the function of CypA, without any effect on CypB activity [159]. Similar approaches are under investigation to develop reagents that impact selective functions of CD147, for example by targeting different domains of the molecule. Progress in these endeavours will provide new treatment opportunities for many inflammatory diseases, including RA and asthma, and may also contribute to treatment of such diseases as atherosclerosis and cancer.

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Disclosure

None.

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