Review Article

Now in 3D! Novel insights into CD36 structure and function

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Abstract: The class B scavenger receptor CD36 is a driving force in pathological events, such as malarial infection, platelet-induced thrombus formation, and macrophage lipid loading during atherogenesis, as well as physiological events involving fatty acid transport. The mechanisms underlying these and other functions of CD36 have not been fully defined at the structural level, largely because previous studies were limited by the lack of a high-resolution CD36 structure. Recently, a high-resolution, three-dimensional structure of the CD36 extracellular domain was determined by X-ray crystallography. This new structural information necessitates a review of past literature to determine how reported structural features fit into the newly solved structure. In this review, we provide the first comprehensive summary of known structural features of CD36 within the context of its newly solved three-dimensional structure. Importantly, the CD36 structure confirms the presence of one or more hydrophobic channels within the extracellular domain that likely function to transport fatty acids and, potentially, cholesterol. While the extracellular CD36 structure greatly enhances our mechanistic understanding of ligand binding and transport, a full-length structure that includes the transmembrane and intracellular domains will be critical to understand the positioning of CD36 on the plasma membrane and how it may interact with other proteins. Nonetheless, the current solved structure builds on our previous understanding of CD36 ligand binding sites and post-translational modifications and paves the way for future mechanistic studies to better understand CD36 function. In this review, we emphasize structural features relevant to platelet biology, highlighting new insights and suggesting additional areas of study into CD36 structure-function relationships.

Keywords: CD36; platelet; oxLDL; thrombospondin; structure

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Introduction

CD36 is a cell surface receptor with wide cellular distribution. Its affinity for diverse ligands and distinctive structural features enable it to perform an impressive array of biological functions. Among the many cell types expressing CD36 are adipocytes (1), myocytes (2), monocytes/macrophages (3), microvascular endothelial cells (4), and platelets (5). In adipocytes and myocytes, CD36 (also known as fatty acid translocase) contributes to approximately 50% of total long chain fatty acid uptake (1). Additionally, CD36-mediated fatty acid uptake can be harnessed by tumor cells as a means to accelerate their own growth (6). CD36 present on sensory epithelial cells of the tongue mediates preference for lipid-rich foods (7), while CD36 in the small intestinal epithelium assists in fat-induced satiety (8). In macrophages, CD36 binds oxidized low density lipoprotein (oxLDL), and the excess uptake of oxLDL-associated cholesterol leads to the formation of lipid-laden macrophage foam cells that eventually progress to atherosclerotic lesions (9). Macrophage CD36 also assists

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in the recognition, phagocytosis, and clearance of apoptotic cells upon oxidized phosphatidylserine exposure (10), a process that is critical for resolving inflammation (11). Endothelial cell CD36 binds the matricellular glycoprotein thrombospondin-1, which regulates angiogenesis (12), and also tethers *Plasmodium falciparum (P. falciparum)*-infected erythrocytes to the vascular wall, thus preventing their splenic clearance and prolonging malarial infection (13-15). In platelets, binding of CD36 to oxLDL and other danger-associated molecular pattern structures promotes platelet activation and a pro-thrombotic state associated with chronic inflammatory disorders (16-18). For an excellent review of this subject, see Yang *et al.* (19). Additionally, CD36 (also known as platelet glycoprotein IV) binds the adhesive glycoprotein thrombospondin-1, which promotes platelet adhesion and thrombus stabilization (20).

The exceptional diversity of CD36-mediated biological functions is made possible, in part, by various structural features and post-translational modifications. Over the last three decades, researchers have employed various biochemical strategies that have led to the identification of several important structural features of CD36. However, due to the lack of a CD36 structure, many of these studies relied upon structural feature prediction software and homology modeling. Recently, a high-resolution extracellular crystal structure of CD36 was determined (21), offering additional insights into CD36 structure-function relationships. In this narrative literature review, structural features relevant to platelet biology will be emphasized. To obtain relevant literature, our search results were limited to publications within the PubMed database using the keywords "*CD36*" in combination with other words that include "*structure*", "*platelet*", "*mutant*", and "*oligomerization*".

General CD36 structural features

CD36 is a 472-amino-acid transmembrane glycoprotein and member of the class B scavenger receptor family, which includes the related proteins lysosomal integral membrane protein-2 (LIMP-2) and scavenger receptor class B type I (SR-BI). Like all class B scavenger receptors, the overall structure of CD36 consists of a large extracellular domain that is anchored to the cell membrane by two transmembrane domains adjacent to short N- and C-terminal cytosolic tails (15,22). The amino acid sequence of human CD36 can be subcategorized into five regions: N-terminal cytosolic domain (residues 1–7), N-terminal transmembrane domain that also functions as a noncleaved signal peptide (residues 8–29), extracellular domain (residues 30–439), C-terminal transmembrane domain (residues 440–461), and C-terminal cytosolic domain (residues 462–472) (*Figure 1*). While each subdomain plays a unique role in maintaining CD36 function, the extracellular domain is perhaps most critical, as it binds to the various ligands and facilitates fatty acid uptake.

High-resolution structure of CD36

Until recently, structure-function studies of CD36 were hindered by the lack of a high-resolution CD36 structure, and researchers relied on various biochemical techniques (e.g., mutagenesis) to predict biologically-relevant structural features of CD36. However, interpretation of mutagenesis studies can be limited in cases where a mutation unexpectedly reduces protein stability or expression. With the recent structural determination of the extracellular domain of human CD36 (residues 35–439) by X-ray crystallography (21), we now have a detailed blueprint to better understand the mechanisms underlying CD36 function. As predicted by homology modeling (27), the CD36 extracellular domain adopts an oval-shaped structure with an antiparallel β-barrel core (21). The β-barrel core forms a hydrophobic cavity that traverses the length of the extracellular domain (21). During structure determination, the core cavity was identified as having two possible entrances (termed "entrance 1" and "entrance 2"; *Figure 1*), both of which were crystallized in the presence of long chain fatty acids (i.e., palmitic acid and stearic acid) (21). Interactions between the long chain fatty acids and the central cavity are primarily mediated by hydrophobic effects between the fatty acid tail and hydrophobic residues lining the cavity, as well as hydrogen bonding between the carboxylic acid head group of fatty acids and Thr195 within the hydrophobic cavity of CD36 (21). This is in agreement with a previous study that utilized homology modeling to predict a fatty acid binding pocket on CD36, which contained Thr195 (28). As CD36 was crystallized in the presence of a CD36 binding domain of *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), Hsieh and colleagues were able to determine that binding of PfEMP1 to CD36 is largely facilitated by Phe153, a CD36 membrane-distal residue located near entrance 1 of the hydrophobic cavity (21). Further, binding of PfEMP1 competes with oxLDL binding, suggesting that oxLDL binds to the same or overlapping sites on CD36 (21).

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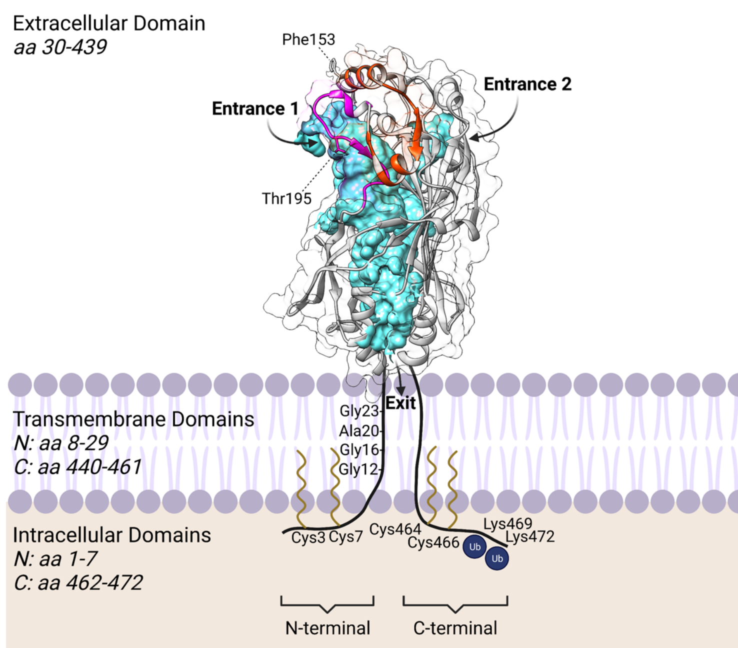

Figure 1 Human CD36 contains an extracellular hydrophobic cavity, transmembrane dimerization motif, and intracellular post-translational modifications. The human CD36 extracellular domain structure (residues 35–439) was downloaded from the Protein Data Bank (PDB ID: 5LGD), and images were generated using UCSF Chimera (23). High-resolution structures of the transmembrane and intracellular domains have not yet been solved and are represented as simple schematics. The hydrophobic cavity (cyan) with two separate entrances was located by the Computed Atlas of Surface Topography of proteins (CASTp) server (24). The epitope recognized by several CD36 monoclonal antibodies (amino acids 155–183) (25,26) is highlighted in orange. A predominantly hydrophobic stretch of amino acids (amino acids 186–204) is highlighted in pink. Thr195 (a residue that binds fatty acids) and Phe153 (a critical residue for ligand binding) are indicated. Four N-terminal transmembrane domain residues (Gly12, Gly16, Ala20, Gly23) comprise a glycine dimerization motif. CD36 is palmitoylated at four intracellular cysteine residues (wavy lines extending from Cys3, Cys7, Cys464, Cys466). CD36 may be mono- or poly-ubiquitinated at C-terminal lysine residues Lys469 and Lys472, as indicated by a blue Ub symbol. Amino acids (aa) shown are Ala (alanine), Cys (cysteine), Phe (phenylalanine), Gly (glycine), Lys (lysine), and Thr (threonine). Figure was created with BioRender.com.

The CD36 crystal structure also helps to clarify some structure-function-based studies pre-dating CD36 homology modeling and structural determination. A hydrophobic stretch of amino acids in the CD36 extracellular domain (amino acids 186–204) was previously thought to embed into the outer leaflet of the plasma membrane near the transmembrane domains (29). The CD36 crystal structure appears to contradict this hypothesis, as amino acids 186–204 are membrane distal and some residues in this region face the inner hydrophobic cavity (e.g., Thr195) (*Figure 1*). Another discrepancy between the CD36 crystal structure and previous studies is the lack of phosphorylation at Thr92 and the relationship between Thr92 phosphorylation status and PfEMP1 binding (as described below). The absence of Thr92 phosphorylation on the CD36 crystal structure holds important implications in platelets, which are thought to be constitutively phosphorylated at Thr92 and thus inhibited from binding thrombospondin-1 in a resting (non-activated) state (22).

CD36 ligands and binding sites

As a member of the scavenger receptor superfamily, CD36 (also known as scavenger receptor class B member 3) binds a remarkable assortment of ligands. These include unmodified and modified lipoproteins (30-32), anionic phospholipids (33), long chain (1) and very long chain (34) fatty acids, *P. falciparum*-infected erythrocytes (15), thrombospondin-1 (35), pro-inflammatory S100A family proteins (including the myeloid-related protein-8/14 (MRP-8/14) heterodimer) (36), advanced glycation end-products (18,37), growth hormone-releasing peptide hexarelin (38),

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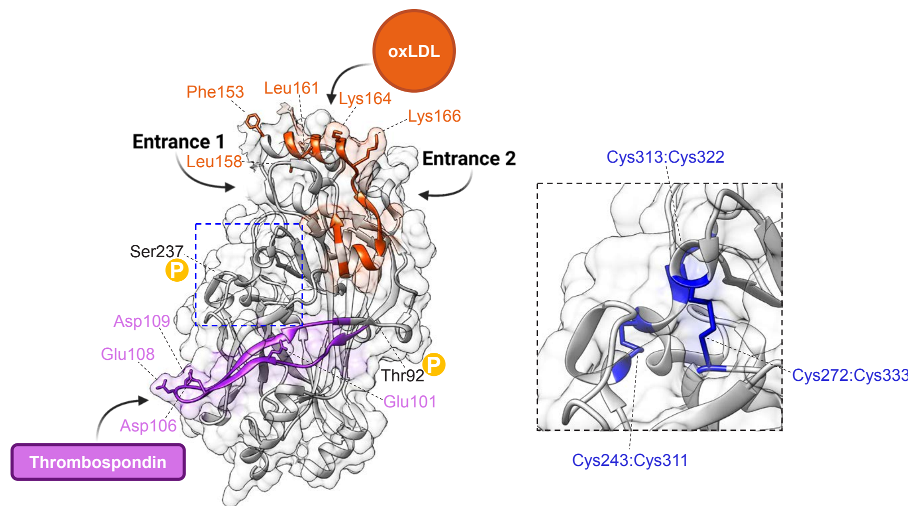

Figure 2 Ligand binding regions and post-translational modifications in the extracellular domain of human CD36. The oxLDL binding region (amino acids 155–183), which overlaps with the binding sites of PfEMP1 and anionic phospholipids, is highlighted in orange, and the thrombospondin binding region is highlighted in purple. Critical residues for ligand binding are indicated in their respective regions. Possible phosphorylation sites are designated by the yellow P symbol at residues Thr92 and Ser237. The area within the dashed box is enlarged to show the three disulfide bond linkages (in blue). CD36 extracellular domain structure was downloaded from the Protein Data Bank (PDB ID: 5LGD) and annotated using Chimera software. Amino acids shown are Cys (cysteine), Asp (aspartic acid), Glu (glutamic acid), Phe (phenylalanine), Lys (lysine), Leu (leucine), Ser (serine) and Thr (threonine). Figure was created with BioRender.com.

amyloid-β (39), apoptotic cells (40), endothelial cell-derived microvesicles (41), and, to some extent, collagen (42). Different ligands have been shown to bind to CD36 on the same site, overlapping sites, or distant sites. In this review, we will focus on the binding sites of CD36 ligands that are most relevant to platelet biology, namely, oxLDL, thrombospondin-1, and anionic phospholipids.

The binding site for oxLDL was determined by monoclonal antibody inhibition to be a region spanning amino acids 155–183 on human CD36 (25,26,43) (*Figure 2*). Within this region, which is located near the apex of the extracellular domain (21,27), the positive charges on Lys164 and Lys166 were identified through mutagenesis studies as critical for oxLDL binding (27,44). Also in the apex region, mutation of Leu158 or Leu161 to negatively-charged glutamate disrupted oxLDL binding (27). Directly adjacent to the proposed oxLDL binding site, mutation of Phe153 to alanine also blocked oxLDL binding to CD36 (21). Altogether, these mutational studies suggest that oxLDL binding to CD36 may be mediated by both hydrophobic and ionic interactions. Other ligands thought to share a binding site with oxLDL and/or compete with oxLDL for binding to CD36 are unmodified and oxidatively-modified lipoproteins (30), long chain fatty acids (45), oxidized phosphatidylcholine (44), *P. falciparum*-infected erythrocytes/PfEMP1 (21,46), apoptotic neutrophils (47), and hexarelin (48).

The binding site of thrombospondin-1 is distinct from that of oxLDL (21) and was defined through binding studies of recombinant CD36 peptides (fused to glutathione S-transferase) as a region spanning amino acids 93–120, known as a CD36, LIMP-2, Emp sequence homology (CLESH) domain, which is sufficient for binding thrombospondin-1 type 1 repeats (49,50) (see *Figure 2*). The binding interface, as revealed by mutagenesis, molecular modeling, and NMR studies, is comprised of several acidic residues on CD36 (Glu101, Asp106, Glu108, and Asp109) that interact with positively-charged residues on thrombospondin (12). As discussed, the binding of thrombospondin-1 to platelet CD36 may be activated by de-phosphorylation of Thr92, which simultaneously reduces collagen binding (22).

Anionic phospholipids (e.g., phosphatidylserine exposed on apoptotic cells, cell-derived microvesicles, or activated platelets) do not share a binding site with thrombospondin or collagen (51). However, phosphatidylserine-containing liposomes were determined in competition assays using different monoclonal antibodies to bind CD36 at a similar

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but non-identical site to oxLDL, spanning amino acids 162–183 (52).

The large number of CD36 ligands and oftentimes overlapping nature of their binding sites could have important implications for cellular homeostasis. For example, small molecules that inhibit amyloid-β-CD36 interactions were predicted to bind near the exit point (see *Figure 1*) of the large hydrophobic cavity that shuttles fatty acids into cells (53). Additionally, PfEMP1 was demonstrated to compete with oxLDL for binding to CD36 (21). In these cases, binding of disease-associated ligands (e.g., amyloid-β or PfEMP1) may prevent necessary physiological functions of CD36 (e.g., fatty acid transport).

Post-translational modifications of CD36

To date, several types of post-translational modifications have been identified on CD36, including glycosylation, phosphorylation, ubiquitination, acetylation, and palmitoylation. Many of these modifications play dynamic regulatory roles in CD36 function. While this subject was reviewed in depth by Luiken *et al.* (54), some of the known CD36 post-translational modifications are briefly summarized below and in *Figure 2*.

CD36 is heavily glycosylated, which may account for its remarkable resistance to protease digestion, as well as its migration at approximately 88 kDa on SDS-polyacrylamide gel electrophoresis instead of the predicted 53 kDa. The extracellular domain of human CD36 contains 10 putative asparagine (N)-linked glycosylation sites, nine of which are confirmed to be glycosylated (55). Glycosylation of three sites on the carboxy terminal side of CD36 (Asn247, Asn321, and Asn417) is required for trafficking of CD36 to the plasma membrane (55). In macrophages, CD36 was identified as a novel protein partner of sialidase 1 (NEU1), which cleaves terminal sialic acid moieties from glycoproteins (56). CD36 sialylation levels and oxLDL uptake were demonstrated to be regulated by NEU1 activity (56).

Two potential phosphorylation sites have been identified on CD36 at Thr92 and Ser237, which are located within consensus sites for phosphorylation by protein kinase C and protein kinase A, respectively (22,57). However, it is important to note that there is a lack of evidence of CD36 phosphorylation *in vivo* (58) and in the CD36 crystal structure (21). The exact mechanisms of CD36 phosphorylation are unknown, but there is some evidence that phosphorylation is mediated by ectoprotein kinases (57-59). Phosphorylation status of Thr92 and Ser237 could contribute to the regulation of multiple functions of CD36. Due to its proximity to the CLESH domain, Thr92 phosphorylation inhibits thrombospondin-1 binding to platelets, while it enhances collagen binding (22,58). Interestingly, Thr92 is constitutively phosphorylated on resting platelets, which may explain the lack of thrombospondin-1 binding to resting platelets (22). Others report that Thr92 phosphorylation may also increase the affinity of CD36 for *P. falciparum*-infected erythrocytes (60). Contradicting these previous studies, the crystal structure of CD36 lacks Thr92 phosphorylation and shows that Thr92 is distal from the binding site of *P. falciparum*-infected erythrocytes (21) (*Figure 2*). Thus, it is unlikely that Thr92 phosphorylation blocks PfEMP1 binding. This is not entirely unexpected, as *P. falciparum*-infected erythrocytes and thrombospondin-1 are thought to bind non-overlapping sites on CD36. Nonetheless, more work is needed to reconcile these conflicting results. Less is known about a potential role for Ser237 phosphorylation in regulating CD36 function, but there is a single report that it inhibits fatty acid uptake in platelets (59). There was no mention of phosphorylation at Ser237 in the recent CD36 crystal structure (21).

CD36 is potentially ubiquitinated at Lys469 and Lys472, which regulates protein stability (61). In C2C12 myotubes and CD36/insulin receptor-overexpressing CHO cells, it was demonstrated that CD36 poly-ubiquitination and subsequent degradation increase with fatty acid treatment and decrease with insulin treatment (61). Mutation of both Lys469 and Lys472 to alanine almost completely blocked CD36 ubiquitination (61). The relative individual contributions of Lys469 and Lys472 to CD36 poly-ubiquitination were not investigated. Various de-ubiquitinases have recently been implicated in removing ubiquitin from CD36, including ubiquitin-specific peptidases 10 and 14 (USP10 and USP14) and ubiquitin C-terminal hydrolase L1 (UCHL1), and inhibition of each of these enzymes led to CD36 degradation and reduced foam cell formation (62-64). While UCHL1 expression is localized primarily to brain tissues, USP10 and USP14 are ubiquitously expressed (65). Therefore, USP10- and USP14-mediated increases in CD36 stability may be particularly relevant to other cell types besides macrophages. In contrast to poly-ubiquitination, CD36 mono-ubiquitination by the E3 ubiquitin ligase Parkin is thought to enhance CD36 stability and cell surface expression levels (66,67). Mono-ubiquitin likely occurs on Lys469 and/or Lys472, but this is pending more detailed

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investigation.

Acetylation has been detected on the extracellular domain of CD36 at the ε-amino position of four lysine residues: Lys52, Lys166, Lys231, and Lys403 (45,68); however, our current understanding of the functional roles of CD36 lysine acetylation remains limited. In general, lysine acetylation neutralizes the positive charge and increases the hydrophobicity of lysine residue sidechains. As Lys166 is required for oxLDL and oxidized phospholipid binding to CD36 (27,44), it is possible that Lys166 acetylation/deacetylation could alter the affinity of ligands for CD36. Protein lysine acetylation may also influence protein synthesis, stability, localization, and cell signaling. The significance of CD36 lysine acetylation is just beginning to be understood. For example, CD36 acetylation/deacetylation events were recently reported to play a role in INS 832/13 beta cell lipid accumulation and apoptosis signaling (69).

CD36 is known to be palmitoylated at cysteine residues within its N-terminal cytosolic domain (Cys3 and Cys7) and C-terminal cytosolic domain (Cys464 and Cys466) (70). CD36 mutants lacking palmitoylation at one or all of these residues retain their ability to express at the cell surface, but they exhibit shorter half-lives, impaired lipid raft localization, and failure to translocate to the plasma membrane in response to insulin or AMP-kinase stimulation (71,72). It was recently demonstrated that treatment of adipocytes with fatty acids induced CD36 de-palmitoylation and internalization (73). The relative contributions of different cysteine palmitoylation sites to CD36 internalization have not been investigated thus far. It was reported that the N-terminal cytosolic domain, unlike the C-terminal cytosolic domain (74), is dispensable for oxLDL uptake (75). Therefore, it may be suggested that Cys464 and/or Cys466 play a more significant role in regulating CD36 stability.

Cysteine disulfide bonds

The extracellular domain of CD36 contains six cysteine residues that were all reported to reside in disulfide bonds (Cys243–Cys311, Cys272–Cys333, and Cys313–Cys322) (76), which has now been confirmed by the CD36 extracellular domain crystal structure (21) (*Figure 2*). It has been reported that these disulfide bonds play a role in CD36 processing and ER-to-Golgi transport (77) and in CD36 homo-dimerization (78). Studies using chemical reducing agents showed that CD36 extracellular disulfide bonds were required for adherence of *P. falciparum*-infected erythrocytes but were not required for oxLDL binding (79,80). Recently, the Cys333-Cys272 disulfide bond pair was reported to act as a molecular switch in response to hydrogen sulfide-mediated disulfide bond cleavage (81). Loss of the Cys333-Cys272 disulfide bond may open another entrance to the central hydrophobic cavity that is inaccessible when the disulfide bond is present, resulting in increased uptake of long chain fatty acids and activation of cell signaling pathways promoting gastric cancer cell metastasis (81). More research is needed to determine the possible implications of a Cys333-Cys272 molecular switch in other biological functions of CD36 (e.g., in atherosclerosis development and platelet activation).

CD36 dimerization

CD36 has been previously reported to form homo-dimers and oligomers, which may influence the ability of CD36 to bind ligands or initiate cell signaling events. Few studies thus far have investigated the structural features necessary for dimerization of CD36. A related class B scavenger receptor, SR-BI, has been reported to dimerize via an N-terminal transmembrane glycine motif, as well as a C-terminal transmembrane leucine zipper motif (82-84). CD36 has a corresponding glycine dimerization motif in its N-terminal transmembrane domain, consisting of residues Gly12, Gly16, Ala20, and Gly23 (85). Analysis of both CD36 transmembrane domain segments by fluorescence resonance energy transfer and TOXCAT transmembrane dimer assays indicated that only the N-terminal transmembrane domain dimerizes and that mutation of any of the four glycine motif residues impaired dimerization (85). A single report showed that intermolecular disulfide bonds covalently link CD36 homo-dimers and multimers in the kidney COS-7 cell line and platelets (78). It was inferred that the extracellular cysteine residues mediate dimerization, as mutating all intracellular cysteines did not disrupt dimerization (78). However, this has not been directly tested, and the CD36 structure confirms that all six extracellular cysteine residues are present in intramolecular disulfide bonds (21).

Many questions remain as to the functional role(s) of CD36 dimerization. While SR-BI was reported to form large multimeric complexes on the cell surface that are required for its membrane retention (84), such a phenomenon has not been reported for CD36. Furthermore, loss of SR-BI dimerization correlated with decreased

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ability of SR-BI to bind high density lipoprotein (HDL) and mediate HDL-cholesterol delivery into cells (82). So far, there have been no reports that CD36 dimerization is required for ligand binding. In fact, purified monomeric CD36 was shown to be capable of binding oxLDL and acetylated LDL with high affinity (86), and recombinant and synthetic CD36 peptides have been shown to bind to oxLDL and thrombospondin-1 (12,44,49). Conversely, ligand binding may activate CD36 dimerization. For instance, thrombospondin-1 triggered CD36 dimerization in transfected HeLa cells, and dimerization required the C-terminal transmembrane domain and/or C-terminal intracellular domain (87). The possibility of ligand-induced conformational changes that facilitate CD36 dimerization or oligomerization requires future investigation. It remains unknown if thrombospondin-1 triggers CD36 homo-dimerization in platelets or if dimerization is required for CD36 function.

CD36-interacting proteins and downstream signaling events

CD36 can form signaling complexes with other transmembrane proteins, including Toll-like receptors (TLRs) (88,89), sodium-potassium-ATPase (NKA) (90), and tetraspanins and integrins (91-94), that engage with downstream signaling molecules. In macrophages, oxLDL and amyloid-β promote CD36-dependent TLR4-TLR6 activation and downstream NF-κB pro-inflammatory signaling (89). OxLDL binding to CD36 also stimulates the formation of a protein complex with NKA and the Src family kinase Lyn, that promotes oxLDL uptake and foam cell formation in macrophages (90). Complexes consisting of β1 and/or β2 integrins, tetraspanins (CD9 and CD81), and Fc receptor γ-chain (FcRγ) adapter protein lead to activation of Src and Syk kinases and CD36 internalization (95). The structural features of CD36 that mediate interactions with other transmembrane proteins have not been characterized, nor is it well established which protein partners interact directly or indirectly with CD36.

The short C-terminal intracellular region of CD36, consisting of approximately 11 amino acids (residues 462–472), directly interacts with protein tyrosine kinase 2 (also known as focal adhesion kinase), the focal adhesion adaptor protein paxillin, and the Src family kinase Lyn (89). In platelets, CD36 has been shown to interact with Src family kinases, including Fyn, Lyn, and Yes (96). CD36 stimulation generates reactive oxygen species (namely hydrogen peroxide), leading to cysteine sulfenylation and activation of Src family kinases (97). Downstream of Src family kinases, caspases and extracellular signal-regulated kinase 5 (ERK5), mediate phosphatidylserine exposure and subsequent thrombosis in response to oxLDL binding to CD36 (16). The interaction of CD36 with Lyn is mediated by Tyr463 of CD36 and is critical for oxLDL-induced TLR4-TLR6 heterodimerization and NF-κB activation (89). Likewise, mutation of Tyr463 or Cys464 on CD36 blocked lipoteichoic acid (a bacterial cell wall component) internalization and subsequent NF-κB activation, indicating a role for these C-terminal residues in other signaling events, including phagocytic pathways (98). Syk kinase also appears to play a role in platelet signaling responses to oxLDL and thrombospondin-1 (99). However, the exact residues or regions of CD36 that interact with Syk kinase have not been established.

Conclusions

Despite the integral role of CD36 in various physiological and pathological states and its possible implications for human health, until recently, we lacked a comprehensive understanding of the structural features contributing to its multitude of functions. In this review, we have summarized our current knowledge of CD36 structural features and highlighted several areas in which more in-depth studies are needed. For example, additional studies must be performed to address the purpose of CD36 acetylation and to clarify if CD36 phosphorylation occurs *in vivo*. The structural features mediating CD36 dimerization are understudied, as is the function of CD36 dimerization or multimerization (e.g., increased membrane retention). Most importantly, high-resolution structures of the transmembrane and cytosolic domains will provide new insight into the structural mechanisms that facilitate interactions between CD36 and other protein partners and how these interactions may drive downstream signaling events. Potential therapeutic strategies targeting CD36 are being investigated in clinical trials for cancer, but investigations are still in early stages for other conditions, including Alzheimer's disease, diabetes, atherosclerosis, and thrombosis. One inherent challenge to developing CD36-based therapeutics lies in its ability to perform many cellular functions, including some that are physiologically necessary. With the emergence of new structural information for CD36, perhaps researchers will now be able to target different functions of CD36 with greater specificity.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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