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CD36: Implications in Cardiovascular Disease

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Abstract

CD36 is a broadly expressed membrane glycoprotein that acts as a facilitator of fatty acid uptake, a signaling molecule, and a receptor for a wide range of ligands, including apoptotic cells, modified forms of low density lipoprotein, thrombospondins, fibrillar beta-amyloid, components of gram positive bacterial walls and malaria infected erythrocytes. CD36 expression on macrophages, dendritic and endothelial cells, and in tissues including muscle, heart, and fat, suggest diverse roles, and indeed, this is truly a multifunctional receptor involved in both homeostatic and pathologic conditions. Despite an impressive increase in our knowledge of CD36 functions, in depth understanding of the mechanistic aspects of this protein remains elusive. This review focuses on CD36 in cardiovascular disease—what we know, and what we have yet to learn.

Introduction

In the last 30 years, study of CD36 has led to a deep appreciation of its multi-functionality. First described on platelets and named glycoprotein IV (GPIV) (Tandon, Lipsky, Burgess & Jamieson, 1989), it was subsequently discovered as a macrophage receptor for oxidized LDL (CD36) (Endemann, Stanton, Madden, Bryant, White, & Protter, 1993) and as an adipocyte fatty acid transporter (FAT) (Abumrad, el-Maghrabi, Amri, Lopez, & Grimaldi, 1993). We now know that the broad expression pattern of CD36 is mirrored by its equally broad list of functions. In the last 5 years, CD36 has figured prominently in the fields of cardiovascular function and disease (Ma, et al. 2004, Kuang, Febbraio, Wagg, Lopaschuk, & Dyck, 2004), parasitology (Franke-Fayard, et al., 2005), cancer biology (Huang, et al., 2004), Alzheimer's disease (Moore, et al., 2004), stroke (Cho, et al., 2005) angiogenesis (Simantov, Febbraio, & Silverstein, 2005), diabetes (Corpeleijn, et al., 2006, Lepretre, et al., 2004), platelet biology (Englyst, Taube, Aitman, Baglin, & Byrne, (2003), muscle function and metabolism (Koonen, Glatz, Bonen and Luiken, 2005), and even food choice (Laugerette, et al., 2005). The creation of the CD36 knock out (KO) mouse and subsequent crossing to other murine mutants has enabled many of these studies (Febbraio, et al., 1999). Apart from a recent publication (Moore, et al., 2005) suggesting that CD36 expression is beneficial in the pathogenesis of atherosclerosis (which we will address specifically), the consensus of the literature is that macrophage CD36 plays a major role in the uptake of pro-atherogenic lipoproteins, and in the absence of up-regulation of efflux mechanisms, this results in foam cell formation, the initiating lesion in atherosclerosis. This review will focus on CD36 as it relates to the cardiovascular system, and thus is not meant to be exhaustive and will omit ligands and functions that may not be pertinent to this focus. It will also look to what is yet to be learned about CD36 as it relates to cardiovascular function and disease.

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CD36 Structure and Expression

The scope of functions attributed to CD36 is remarkable in the context of its structure. CD36 is an 88 Kd ditopic heavily N-linked glycosylated membrane protein (Gruarin, Thorne, Dorahy, Burns, Sitia, and Alessio, 2000). The human CD36 gene is currently reported to extend about 28 kb on chromosome 7q (XenneX, Inc., GeneCards, Fernandez-Ruiz, Armesilla, Sanchez-Madrid, & Vega, 1993, Wyler, Daviet, Borkiewicz, Bordet, & McGregor, 1993) and encodes a predicted protein of 471 amino acids with a predicted molecular weight of 52,922 Da (XenneX, Inc., GeneCards). Other putative promoter and exons have been identified, thus the gene size may change. Human CD36 has a large extracellular domain characterized by 10 N-linked glycosylation sites, and as a result the actual molecular weight varies from ~80–90 kDa (Oquendo, Hundt, Lawler, & Seed, 1989). Variant transcripts have been identified, as have a multitude of (predominantly) non-coding single nucleotide polymorphisms (NCBI single nucleotide polymorphism (SNP) database, Wyler, Daviet, Borkiewicz, Bordet, & McGregor, 1993, Taylor, Tang, Sobieski, & Lipsky, 1993, Gelhaus, Scheduling, Browne, Burchard, & Horstmann, 2001). Mutations which result in absence of CD36 expression in platelets (Type I CD36 deficiency) or in all cells (Type II CD36 deficiency) have been characterized, and are found in Asian and African populations predominantly (Yamamoto, Akamatsu, Sakuraba, Yamazaki, & Tanoue, 1994, Lee, et al., 1999). There is some suggestion of selective pressure from the malaria parasite, *Plasmodium falciparum* for these mutations, but whether absence of CD36 is protective against the lethality of the parasite remains controversial (Aitman, et al., 2000, Serghides, Smith, Patel, & Kain, 2003). Extracellular CD36 is characterized by a hydrophobic domain that may extend into the plasma membrane. Binding sites for fatty acids (Baillie, Coburn, & Abumrad, 1996), thrombospondin-1 (Pearce, Wu, & Silverstein, 1995), modified low density lipoprotein (LDL) (Pearce, Roy, Nicholson, Hajjar, Febbraio, & Silverstein, 1998) and the growth hormone releasing peptide, (GHRP) hexarelin (Demers, et al., 2004) have been mapped. An immuno dominant domain (amino acids 155–183, Daviet, Buckland, Puente Navazo, M.D. & McGregor, 1995) has also been implicated in binding apoptotic cells (Navazo, Daviet, Savill, Ren, Leung, & McGregor, 1996) and modified LDL (Puente Navazo, Daviet, Ninio, & McGregor, 1996), but because antibody binding to this domain disrupts all CD36 functions, it may relate more to conformational change of the receptor than actual binding site for these ligands. An interesting property of CD36 is the ectophosphorylation of threonine 92 which has been shown to impact binding of certain ligands (Asch, et al., 1993, Hatmi, Gavaret, Elalamy, Vargaftig, & Jacquemin, 1996, Ho, et al., 2005). The intracellular domains of CD36 are located on very short cytoplasmic tails: the N-terminal tail is probably the result of an uncleaved signal peptide. Both tails are characterized by a pair of cysteine residues that are palmitoylated (Jochen, & Hays, 1993, Tao, Wagner, & Lublin, 1996) and these are important in positioning CD36 in caveolae and lipid rafts. Both the N-terminal and the C-terminal cytoplasmic domains have been shown to be important for efficient plasma membrane CD36 expression (Gruarin, Thorne, Dorahy, Burns, Sitia, & Alessio, 2000, Eyre, Cleland, Tandon, & Mayrhofer, 2006). In some cell types, expression of caveolin-1 has been shown to be necessary for plasma membrane targeting of CD36, and disruption of caveolae may effect some CD36 dependent functions (Ring, Le Lay, Pohl, Verkade, & Stremmel 2006, Vistisen, Roepstorff, Roepstorff, Bonen, van Deurs, & Kiens, 2004, Frank, Lee, Park, Tandon, Scherer, & Lisanti, 2004, Pohl, Ring, Korkmaz, Ehehalt, & Stremmel, 2005, Kincer, et al., 2002, Dorahy, Lincz, Meldrum, & Burns, 1996). The partitioning of CD36 to specific plasma membrane domains may facilitate interaction with signaling partners that are essential to CD36 dependent responses. What is notably absent from CD36 structure are clear cut domains that are associated with kinases, adaptor proteins, or motifs that may specify interaction with other proteins.

CD36 is expressed on an extensive range of cells and tissues, including microvascular endothelial cells (Swerlick, Lee, Wick, & Lawley, 1992), monocytes and macrophages

(Endemann, Stanton, Madden, Bryant, White, and Protter, 1993, Huh, Pearce, Yesner, Schindler, & Silverstein, 1996), dendritic cells (Rouabhia, Jobin, Doucet, Jr., Bergeron, & Auger, 1994, Albert, et al., 1998), adipocytes (Abumrad, el-Maghrabi, Amri, Lopez, & Grimaldi, 1993), keratinocytes (Allen, Barker, & MacDonald, 1991), cardiac and skeletal muscle (Van Nieuwenhoven, et al., 1995), retinal pigment epithelium (Ryeom, Sparrow, & Silverstein, 1996), microglia (Husemann, Loike, Anankov, Febbraio, & Silverstein, 2002), reticulocytes (Sugihara, Sugihara, Mohandas, & Hebbel, 1992), breast, (Cleardin, Frappart, Clerget, Pechoux, & Delmas, 1993), gut (Chen, Yang, Braunstein, Georgeson, & Harmon, 2001), and renal epithelium (Susztak, Ciccone, McCue, Sharma, & Bottinger, 2005), and platelets (Bolin, Medina, & Cheney 1981). More recently, expression has been reported on hepatocytes under certain circumstances (Vosper, et al., 2001, Yu, et al., 2001, Zhou, et al., 2006) and smooth muscle cells (Lim, et al., 2006, de Oliveira Silva, Delbosc, Arais, Monnier, Cristol, & Pares-Herbute, 2006, Kwok, Juan, and Ho, 2006). CD36 plays a role in uptake of apoptotic cells (Savill, Hogg, Ren, and Haslett, 1992), shed photoreceptor outer segments (Ryeom, Sparrow, & Silverstein, 1996), and modified lipoproteins (Endemann, Stanton, Madden, Bryant, White, & Protter, 1993, Podrez, et al., 2000), and in recognition of ligands that trigger an innate immune response, including components of gram positive bacteria cell walls (Hoebe, et al., 2005, Stuart, et al., 2005) (as a co-receptor with Toll Like Receptor (TLR) 2), fibrillar amyloid β (Bamberger, Harris, McDonald, Husemann, & Landreth, 2003, El Khoury, et al., 2003), which is a constituent of Alzheimer plaque, and resembles fibrillar amyloid protein (Medeiros, et al., 2004), that may occur in atherosclerotic plaque. In addition to facilitating fatty acid transport into adipocytes and cardiac and skeletal muscle (and perhaps other cells), CD36 was recently shown to be a sensor for fatty acids in taste buds, eliciting a secretory response in the gut (Laugerette, et al., 2005). CD36 interacts with ligands which contain a thrombospondin 1 (TSP-1) type 1 repeat element (TSR) to inhibit a pro-angiogenic signal, resulting in endothelial cell apoptosis (Dawson, Pearce, Zhong, Silverstein, Frazier, & Bouck, 1997, Dawson, et al., 1999, Jimenez, Volpert, Crawford, Febbraio, Silverstein, & Bouck, 2000, Miao, Seng, Duquette, Lawler, Laus, & Lawler, 2001, Simantov, Febbraio & Silverstein, 2005).

CD36 is presumed to be an endocytic receptor for most ligands with the exception of long chain fatty acids, where it may facilitate their transfer across the lipid membrane, but this remains a poorly defined process. It is possible that CD36 directly interacts with fatty acids (a binding site has been broadly mapped) and/or this is coupled with cytoplasmic fatty acid binding proteins for efficient translocation (Glatz, Bonen, & Luiken, 2002, Spitsberg, Matitashvili, & Gorewit, 1995), or that CD36 is a member of a specific plasma membrane domain that has increased permeability to fatty acids, and CD36 may "corral" fatty acids to this domain for efficient translocation (this could also be coupled to cytoplasmic fatty acid binding proteins). It is also possible that CD36 oligomerizes to form a pore. Whatever the mechanism, absence of CD36 affects fatty acid uptake by various tissues, including adipocytes and muscle, and this leads to measurable phenotype (Febbraio, et al., 1999). CD36 KO mice have a fasting hypoglycemia and different energy substrate use in heart (Kuang, Febbraio, Wagg, Lopaschuk, & Dyck, 2004). Uptake of fatty acid analogs was specifically reduced in muscle and adipocytes of mice, and has been shown to be reduced in heart of CD36-deficient humans (Coburn, Knapp, Febbraio, Beets, Silverstein, & Abumrad, 2000, Watanabe, et al., 1998, Hwang, et al., 1998, Tanaka, et al. 2001).

CD36 Ligands and Functions

CD36 was originally identified as a receptor for TSP-1, a large trimeric multi-domain extracellular matrix protein that has a diverse range of functions, some of which are CD36 dependent (Kieffer, Nurden, Hasitz, Titeux, & Breton-Gorius, 1988, Adams & Lawler, 2004). One function of this receptor-ligand pair with relevance to cardiovascular biology and

pathology is inhibition of angiogenesis (Dawson, Pearce, Zhong, Silverstein, Frazier, & Bouck, 1997). Angiogenesis is the body's response to ischemia and vascular injury, and work has demonstrated that oxidatively modified LDL (oxLDL) which may be found in hyperlipidemic states, including atherosclerosis, diabetes and the metabolic syndrome, can inhibit endothelial cell proliferation and angiogenesis (Chen, et al., 1997, Imanishi, Hano, Matsuo, & Nishio, 2003, Mwaikambo, Sennlaub, Ong, Chemtob, & Hardy, 2006). Hyperlipidemia has also been shown to delay arteriogenesis in hypercholesterolemic mice (Henry, 1993, Tirziu, et al., 2005, van Weel, et al., 2006). Interestingly, oxLDL up regulates CD36 expression via peroxisome proliferator activated receptor (PPAR) γ , and this may contribute to inhibition of angiogenesis by initiating a feed forward loop of CD36 expression that amplifies the anti-angiogenic effect observed in these states (Tontonoz, Nagy, Alvarez, Thomazy, & Evans, 1998). Thus, in a hyperlipidemic setting, expression of CD36 may play a role in ischemia, and may contribute to ischemia in the aftermath of myocardial infarction and stroke. Inhibition of angiogenesis by exploiting this pathway has led to the development of TSP-1 peptides and mimetics that are currently in clinical trials for application in cancer and diabetic retinopathy (Dawson, et al., 1999, Rusk, et al., 2006, Gietema, et al., 2006). The idea of up regulation of CD36 to inhibit angiogenesis by TSP-1 has been explored to increase the efficacy of the anti-angiogenic effect in a tumor model (Huang, et al., 2004). CD36-TSP-1 interaction is also important in maintenance of an anti-inflammatory milieu in the uptake of apoptotic cells as a homeostatic process, and during wound resolution (see later).

CD36 is classified as a class B scavenger receptor (Platt, & Gordon, 1998, Krieger, 1997), and is part of a gene family that includes lysosomal integral membrane protein II (LIMP-II), which plays a role in nerve myelination (Gamp, et al., 2003), CD36 and LIMP-II analogous-I protein (CLA-1) (known as scavenger receptor BI (SR-BI) in mice), which mediates the selective uptake of cholesterol esters from high density lipoprotein (HDL) (Acton, Rigotti, Landschulz, Xu, Hobbs, & Krieger, 1996), and Croquemorte, a drosophila protein, that phagocytoses apoptotic cells and senescent erythrocytes (Franc, Dimarcq, Lagueux, Hoffmann, & Ezekowitz, 1996, Franc, Heitzler, Ezekowitz, & White, 1999). Scavenger receptors are found in both primitive and immunologically advanced organisms and their continued evolutionary conservation suggest their important role at the forefront of the initial organism response to pathogens and in normal homeostasis (Krieger, 1997, Gordon, 2002). For example, BLAST analysis reveals CD36 homologues in fly, worm and sponge, and based on the functions of these relatives, we can speculate that uptake of apoptotic cells is the most ancient function of CD36. CD36 recognizes and binds apparent pattern motifs which are often non-protein repetitive molecules, such as found on the outer membranes or walls of bacteria. Hoebe, *et al.* (2005) characterized a recessive mutation in N-ethyl-N-nitrosurea (enu) mutated mice which did not respond to some TLR 2/6 ligands, and showed it to be within the CD36 gene, resulting in absent expression (*oblivious* mice). Interestingly, they found that CD36 was a necessary co-receptor for TLR 2 ligands containing diacylglycerides but not triacylglycerides. Recently, there has been some controversy about the exact nature of the ligand on gram positive bacteria. Hoebe *et al.* reported it to be lipoteichoic acid, but one group argues that the actual ligand is a lipoprotein that co-isolates with lipoteichoic acid, and that when bacteria are mutated such that the lipoprotein cannot be biosynthesized, the resulting lipoteichoic acid has only 1/100 of the activating properties as lipoprotein (Hashimoto, et al., 2006). Whether lipoprotein or lipoteichoic acid, macrophages from CD36 KO mice were less efficient at phagocytosis of gram positive *Staphylococcus aureus*, less able to clear infection, and more susceptible to abscess and death (Stuart, et al., 2005).

Scavenger receptors also recognize modified lipoproteins, which may arise as byproducts during an inflammatory response or by other mechanisms. In terms of modified LDL, the exact nature of the CD36 ligand has been recently defined as a truncated phosphatidylcholine species, with a specific sn-2 esterified γ -hydroxy (or oxo) – α,β -unsaturated carbonyl containing fatty

acid (Podrez, et al., 2002a, Podrez, et al., 2002b). These modifications can occur as a result of the action of reactive oxygen or nitrogen species. CD36 has also been reported to bind HDL and very low density lipoprotein (VLDL), but the nature of the ligand on these lipoproteins has not been characterized (Calvo, Gomez-Coronado, Suarez, Lasuncion, & Vega, 1998). Binding and uptake of modified LDL may have arisen as a homeostatic response of macrophages, and would have protected the organism from pathology associated with these aberrant lipoproteins. In our Western civilization, this function apparently is inadequate to keep pace with the heavy lipid load from our diet and thus atherosclerosis results.

In addition to protection against pathogens and clearance of aberrant lipoproteins, scavenger receptors also protect the host against inflammation in the setting of the normal turnover of cells by apoptosis and during wound resolution. Apoptotic cell membranes lose asymmetry, such that the outer membrane becomes enriched in anionic phosphatidylserine (Pittoni, & Valesini, 2002). Indeed, previous work identified phosphatidylserine species as the ligand for CD36, but those earlier studies were done without attention paid to the potential for oxidative changes (Fadok, Bratton, Frasch, Warner, & Henson, 1998, Ryeom, Silverstein, Scotto, & Sparrow, 1996). Greenberg, *et al.* (2006) demonstrated that the same oxidative changes that occur in phosphatidylcholine species of lipoproteins, which generate specific structures that are recognized by CD36, can analogously occur in phosphatidylserine species of apoptotic cells. These are specifically recognized by CD36, and not competed by non-oxidized phosphatidylserine. Similarly, but unrelated to vascular biology, the docosahexaenoic acid of 2-lyso-phosphatidylcholine, which is enriched in rod outer segments in the retina, are photo oxidized to generate analogous sn-2 esterified γ -hydroxy (or oxo) – α,β -unsaturated carbonyl containing fatty acids, and this creates a recognition signal for CD36 expressed on retinal pigment epithelium for phagocytosis (Sun, et al., 2006). These studies established that the truncated fatty acid needs to be in the context of a phospholipid in order to be recognized and signal phagocytosis. Understanding the structural properties of ligands for CD36 represents one of the major advances in CD36 biology over the last 5 years, and will be essential to assessing the physiologic role of CD36, as well as provide insight into design of therapeutics.

CD36 also interacts with advanced glycation end products (AGE) (Ohgami, et al., 2001), which are generated in diabetes and chronic inflammatory settings such as atherosclerosis (Forbes, Soldatos, & Thomas, 2005, Brownlee, 2005, Basta, Schmidt, & De Caterina, 2004). Advanced glycation end products are protein adducts which are thought to accumulate, and thus may form a repetitive motif recognized by CD36 and other scavenger receptors.

Another ligand for CD36 is the GHRP, hexarelin, and a derivative with no growth hormone releasing properties, EP 80317 (Bodart, et al., 2002). Previous work had shown that hexarelin pretreatment of growth hormone deficient rats protected against cardiac damage in ischemia/reperfusion models. Because this effect could be separated from growth hormone effects, it was hypothesized that it was due to a cardiac specific receptor. Using a photoactivatable derivative of hexarelin to cross-link it to the putative receptor in heart, CD36 was identified (Demers, et al., 2004). Cross-linking experiments using hearts from CD36 KO mice showed no binding partner. In an isolated perfused heart system, hexarelin induced a dose dependent vasoconstriction that again was not observed in hearts from CD36 KO mice and spontaneous hypertensive rats (SHR), which have also been shown to lack CD36 (Bodart, et al., 2002). Detailed mapping by enzymatic and chemical degradation showed that the binding site for hexarelin overlapped with the oxLDL site and the apparent point of contact was methionine 169 (Demers, et al., 2004). This observation led to the hypothesis that hexarelin or EP 80317 could interfere with oxLDL binding and perhaps have a protective effect in atherosclerosis (see later).

Modulation of the binding of platelets to collagen and thrombospondin-1, and the binding of *Plasmodium falciparum* infected erythrocytes to microvascular endothelium has been shown to be regulated by phosphorylation/dephosphorylation of the ectodomain of CD36, specifically, threonine 92 (Asch, et al. 1993, Ho, et al., 2005). Asch *et al.* found that resting platelets constitutively express phosphorylated CD36, and have greater affinity for collagen compared to TSP-1. Initial low affinity interaction between CD36 and TSP-1 results in platelet degranulation and the release of phosphatases that can dephosphorylate CD36, resulting in higher affinity binding of TSP-1. Similarly, Ho *et al.* showed that microvascular endothelial CD36 is constitutively expressed in the phosphorylated form. Interaction with *falciparum* infected erythrocytes resulted in *src* family kinase activation, and subsequent activation of an endothelial cell surface phosphatase which led to higher affinity for infected erythrocytes under flow conditions. This novel mechanism of modulation of ligand binding has important implications in vascular biology, including thrombosis mediated by platelet aggregation and angiogenesis, but has largely been unexplored.

CD36 Signaling

Despite its short cytoplasmic domains, it has become apparent that CD36 is a signaling molecule. As mentioned above, interaction of CD36 with TSP-1 has potent anti-angiogenic effect. Structure-function analyses have mapped the domain on TSP-1 responsible for this effect to the type I repeat (Iruela-Arispe, Lombardo, Krutzsch, Lawler, & Roberts, 1999) and other proteins such as TSP-2, which contain this domain, are also anti-angiogenic in a CD36 dependent manner (Simantov, Febbraio, & Silverstein, 2005). On CD36, the TSP-interacting domain has been mapped to the CLESH-1 domain (CD36, LIMPII, emp, SR-BI homology) which is also present in other proteins (Crombie, & Silverstein, 1998). Work from our lab in collaboration with Noel Bouck demonstrated that in endothelial cells, when CD36 binds to TSP-1 there is association with and phosphorylation of the *src* kinase *fyn*, and this leads to downstream phosphorylation of caspases and the mitogen activated protein (MAP) kinase p38, and ultimately cellular apoptosis which prevents angiogenesis (Figure 1a) (Jimenez, Volpert, Crawford, Febbraio, Silverstein, & Bouck, 2000). Primo *et al.*, (2005) using site directed mutagenesis to create C-terminal tail mutants of CD36 expressed in human umbilical vein endothelial cells by a retroviral vector, showed that specific amino acids, cysteine 464, arginine 467 and lysine 469, were essential to the TSP-1 inhibitory activity. They further showed that CD36-TSP-1 interaction led to down regulation of vascular endothelial growth factor (VEGF) receptor 2 and the p38 mediated phosphorylation induced by VEGF-A₁₆₅, and this was dependent upon cysteine 464.

Apoptotic cell phagocytosis can be functionally separated from signaling events that are anti-inflammatory, and there appear to be multiple redundant pathways (Lucas, et al. 2006). One pathway, however, involves CD36-TSP-1 interaction, and reminiscent of what occurs in endothelial cells, this interaction can interrupt another signal—in this case a lipopolysaccharide (LPS) induced pro-inflammatory cascade (Voll, Herrmann, Roth, Stach, Kalden, & Girkontaite, 1997). The details of these events are yet to be elucidated, but the result is secretion of IL-10, an anti-inflammatory cytokine, and inhibition of secretion of the pro-inflammatory cytokines TNF- α , IL-12 and IL-1 β .

In contrast, binding of β -amyloid by microglia expressing CD36 (in conjunction with $\alpha_6\beta_1$ integrin and CD47) leads to assembly of a signaling complex which includes F-actin, *fyn*, *lyn*, *pax*, *pyk2* and *cas* (Figure 1b) (Moore, et al., 2002). This leads to the downstream phosphorylation of p44/42 MAP kinases, and subsequent expression of TNF- α , MCP-1, MIP-1, MIP-2, IL-1 β and reactive oxygen species (ROS). The *vav* guanine nucleotide exchange factor has recently been shown to link this signaling complex to the respiratory burst and phagocytosis in both monocytes and microglia (Figure 1b) (Wilkinson, Koenigsnecht-Talboo, Grommes,

Lee, & Landreth, 2006). Similarly, fibrillar amyloid found in atheroma also elicits a CD36-dependent signaling cascade involving *lyn* and p44/42 MAP kinases, and ultimately CD36-dependent secretion of ROS and TNF- α (Stewart, et al., 2005). Recently, the association between CD36 and *lyn* has been shown to be lipid-mediated (Thorne, et al, 2006).

In macrophages/dendritic cells, CD36 has been found to be essential to some TLR2/6 responses evoked by extracts of gram positive bacteria (as mentioned above, the exact ligand is currently quite controversial). This leads to the classic TLR signaling cascade resulting in NF κ B activation and secretion of TNF- α , IL-6 and IL-12. Triantafilou et al. (2006) showed that heterodimers of TLR2/6 exist preformed in the plasma membrane prior to ligand engagement, but that in contrast, association with CD36 is ligand dependent. The newly formed receptor complex is then recruited to lipid rafts where activation/signaling occurs. Using CD36 mutants, Stuart, et al. (2005) went on to show that phagocytosis of gram positive bacteria was mediated by specific amino acids (tyrosine 463 and cysteine 464) in the C-terminal cytoplasmic tail of CD36, which apparently are necessary for TLR2/6 signaling. In contrast, for binding and capture of oxLDL, the terminal 6 amino acids (467–472) have been implicated (Malaud, Hourton, Giroux, Ninio, Buckland, & McGregor, 2002). The C-terminal cytoplasmic domain has also been implicated in fatty acid uptake (Eyre, Cleland, Tandon, & Mayrhofer, 2006).

We recently demonstrated that macrophage CD36 is necessary for activation of *lyn* kinase, MEKK2 and ultimately *jnk* (specifically *jnk2* in mice) and this results in phagocytosis of pro-atherogenic LDL (Figure 1c) (Rahaman, Lennon, Febbraio, Podrez, Hazen, & Silverstein, 2006). This pathway is essential for foam cell formation, which is the cellular component of fatty streaks, the initial gross lesion in the pathogenesis of atherosclerosis. Indeed, pharmacological inhibition of *jnk* or macrophage specific deletion of *jnk* reduced atherosclerosis in murine models, and atherosclerosis is also reduced in *lyn* KO mice. Activation of *jnk* also controls scavenger receptor A I/II (SRA) macrophage phagocytic activity (Ricci, et al., 2004). This report showed that inactivation of *jnk* trapped SRA on the cell surface and reduced binding and uptake of modified LDL. Whether *jnk* activation links activity of these 2 scavenger receptors is an intriguing hypothesis which may have important therapeutic implications.

In platelets, CD36 was found to co-precipitate with *fyn*, *lyn* and *yes*, and although CD36 was initially isolated and characterized from platelets, its role remains largely a mystery (Huang, Bolen, Barnwell, Shattil, & Brugge, 1991). However, work in mice and humans underscore the important role for platelets in cardiovascular disease, and thus this remains an unexplored area of CD36 biology.

One can conclude that signaling cascades link CD36 to cellular responses related to innate immunity, scavenger receptor activity, NF κ B activation, cytokine and ROS secretion, the initiation of anti-inflammatory and pro-apoptotic pathways, and this has ramifications for the development of atherosclerosis, diabetes, inflammation and the metabolic syndrome, among other pathological states. An important observation from these data is that the consequence of CD36 binding and signaling is apparently both ligand dependent and cell type dependent. Additionally, the proximal event to CD36 binding appears to be, in many cases, activation of a *src* kinase that leads to MAP kinase activation. Whether CD36 is pro- or anti-inflammatory may also relate to expression of co-receptors. It is then apparent that the outcome of inhibition or activation of CD36 signaling/receptor function is difficult to predict in complex environments.

CD36 Regulation

In monocytes/macrophages, CD36 expression is up regulated by adhesion (Prieto, Eklund, & Patarroyo, 1994, Huh, Lo, Yesner, & Silverstein, 1995), differentiation (Huh, Pearce, Yesner,

Schindler, & Silverstein, 1996), certain nuclear hormone receptors and cytokines. For example, CD36 is up regulated in response to the cytokine IL-4 and oxLDL by a common signaling pathway involving protein kinase C and PPAR- γ (Feng, et al., 2000). Transforming growth factor (TGF) β 1/2 can modulate this affect, by activating mitogen-activated protein (MAP) kinase to phosphorylate and inactivate PPAR- γ (Han, Hajjar, Tauras, Feng, Gotto, & Nicholson, 2000). Agonists of PPAR- γ , such as rosiglitazone also increase CD36 expression (Tontonoz, & Nagy, 1999). Zhao *et al.* (2002) reported that the p38 MAP kinase pathway may also affect PPAR- γ activation and induction of CD36 gene expression. The role of interferon- γ in CD36 regulation remains controversial, although in our hands, we observed no effect (Nakagawa, et al., 1998, Zuckerman, Panousis, Mizrahi, & Evans, 2000, Yesner, Huh, Pearce, & Silverstein, 1996). As mentioned previously, CD36 interaction with apoptotic cells can lead to IL-10 secretion, and Rubic and Lorenz (2006) have reported that IL-10 decreases CD36 expression. This may have anti-atherosclerotic effect as well.

Most statins apparently down regulate CD36 expression, and this may contribute to their efficacy (Pietsch, Erl, & Lorenz, 1996, Fuhrman, Koren, Volkova, Keidar, Hayek, Aviram, 2002, Han, Zhou, Yokoyama, Hajjar, Gotto, & Nicholson, 2004, Puccetti, Sawamura, Pasqui, Pastorelli, Auteri, & Bruni, 2005, Bruni, et al., 2005, Ruiz-Velasco, Dominguez, & Vega, 2004). HIV protease inhibitors up regulate CD36 in male mice and increase atherosclerosis (Dressman, et al., 2003), but have an opposite effect in female mice (Allred, Smart, & Wilson, 2006). In human macrophages, CD36 expression has also been reported up and down regulated by HIV protease inhibitors (Serghides, Nathoo, Walmsley, & Kain, 2002, Munteanu, Zingg, Ricciarelli, & Azzi, 2005) but the reason for the discrepancy has not yet been sorted out. Both up and down regulation of CD36 can have pathological sequelae, as these reports indicate. Thiazolidinediones, a major new class of drugs to treat diabetes, up regulate CD36 in monocytes/macrophages, adipose and muscle (Wilmsen, Ciaraldi, Carter, Reehman, Mudaliar, & Henry, 2003, Kolak, et al., 2006, Hirakata, Tozawa, Imura, & Sugiyama, 2004, Llaverias, et al., 2006), and may therefore contribute to the insulin-sensitizing effects of these drugs as a result of plasma fatty acid clearance, but also potentially to atherosclerosis and obesity in these patients. Interestingly, glucose/insulin appears to increase CD36 expression (Sampson, Davies, Braschi, Ivory, & Hughes, 2003, Griffin, et al., 2001, Chabowski, et al., 2004, Chen, Yang, Loux, Georgeson, & Harmon, 2006), and because CD36 is expressed on tissues important in fatty acid metabolism (heart, skeletal muscle, fat, and in pathological states, liver) this may imply an important role for CD36 in insulin resistance (see later). Regulation of CD36 expression can be mediated both pre- and post- transcription.

Another level of CD36 regulation is via regulation of movement of CD36 from intracellular stores to the plasma membrane. Significant intracellular pools of CD36 have been documented in monocyte/macrophages and muscle (Huh, Pearce, Yesner, Schindler, & Silverstein, 1996, Luiken, et al., 2002). In muscle, increased plasma membrane CD36 expression has been shown to occur after muscle contraction and insulin stimulation (Luiken, et al., 2002, Koonen, et al., 2004, Koonen, Glatz, Bonen, & Luiken, 2005), and analogous to glucose transporter redistribution, may effect energy substrate choice and utilization. In obesity and insulin resistance, there is impairment of this normal recycling, and instead CD36 expression appears locked on the membrane in skeletal muscle (Bonen, et al., 2004, Coort, et al., 2004). The effect of these conditions on localization of CD36 in other tissues/cells has been less well studied, but one may speculate that changes in CD36 localization (and thus function) in cells which are so intimately involved in glucose and fatty acid metabolism may contribute to insulin resistance states and obesity.

Less is known about CD36 regulation in other tissues, although PPAR species are apparently important to regulation in adipocytes, smooth muscle cells and liver (Wilmsen, Ciaraldi, Carter, Reehman, Mudaliar, & Henry, 2003, Motojima, Passilly, Peters, Gonzalez, & Latruffe,

1998, Lim, et al., 2006). In adipose tissue, CD36 expression coincides with differentiation from pre-adipocyte to adipocyte, and capacity to take up fatty acids (Sfeir, Ibrahim, Amri, Grimaldi, & Abumrad, 1997). In muscle cells, the transcription factor FoxO1, which orchestrates a gene program involved in insulin regulation, impacts CD36 expression, and thus has an important effect on fatty acid uptake by these cells (Bastie, et al., 2005). A recent report has shown that CD36 is a downstream target of the pregnane X receptor in liver, and may be involved in lipid accumulation as a result of activation of this pathway (Zhou, et al., 2006).

CD36 and Insulin Resistance

CD36 KO mice do not show insulin resistance when administered an intraperitoneal bolus of glucose (Febbraio, et al., 1999). In fact, using the euglycemic clamp technique, CD36 KO mice showed slightly higher whole body glucose uptake, oxidation and lower glucose storage at basal conditions when compared with background matched wild type control mice (Goudriaan, et al., 2003). Under hyperinsulinemic conditions, again, CD36 KO mice showed increased whole body glucose uptake and oxidation (Goudriaan, et al., 2003). Interestingly, hepatic glucose production was not inhibited, as one would expect under these conditions (Goudriaan, et al., 2003). Analysis of tissue uptake of labeled glucose showed a significant increase in uptake in cardiac muscle in CD36 KO mice, consistent with our hypothesis that absence of fatty acid uptake by CD36 in heart leads to altered substrate utilization for energy and the fasting hypoglycemia. This hypothesis was more fully tested in an isolated perfused heart system (see later). Thus while absence of CD36 does not lead to diabetes in mice, the mice do have hepatic insulin resistance. In rats, which, unlike mice and humans, express CD36 (males) in liver, a mutation in CD36 was shown to underlie some of the phenotypes of a strain of spontaneously hypertensive rats (SHR) (Aitman, et al., 1999). This is complicated by the fact that several strains of this rat exist and not all have the CD36 mutation (Gotoda, et al., 1999). These rats are hypertensive, insulin resistant and have impaired fatty acid uptake (Pravenec, et al., 1999). The CD36 mutation correlates best with the impaired fatty acid uptake phenotype, which then may affect insulin resistance in this model (especially given the expression of CD36 in liver) (Pravenec, et al., 1999, Collison, et al., 2000, Pravenec, et al., 2001, Hajri, et al., 2001, Zhang, et al., 2003). Indeed, work using CD36 KO mice showed secondary effects to decreased peripheral fatty acid uptake. Goudriaan *et al.* (2005) showed that the increased plasma fatty acids in CD36 KO mice led to inhibition of lipoprotein lipase activity and delayed metabolism of VLDL, resulting in higher plasma triacylglyceride levels.

In humans, the data with regard to insulin resistance and CD36 has been more difficult to sort out. It is estimated that about 1% of the Japanese population has Type I CD36 deficiency (total), but there have been conflicting reports on insulin resistance in this population (Miyaoaka, Kuwasako, Hirano, Nozaki, Yamashita, & Matsuzawa, 2001, Yanai, Chiba, Morimoto, Jamieson, & Matsuno, 2000, Furuhashi, Ura, Nakata, & Shimamoto, 2003, Furuhashi, Ura, Nakata, Tanaka, & Shimamoto, 2004, Kuwasako, et al., 2003, Kajihara, et al., 2001). Polymorphisms in CD36 that are associated with insulin resistance have been identified, but the mechanism by which CD36 impacts insulin resistance remains undefined, and whether these polymorphisms interact with other genetic determinants is not known (Lepretre, et al., 2004a, Lepretre, et al., 2004b, Corpeleijn, et al., 2006). Clearly, fatty acid uptake does differ in muscle in Type I CD36 deficiency (Hwang, et al., 1998, Tanaka, et al., 2001), and this may have differential impact on insulin resistance depending on diet, life style and other genetic factors. The type of genetic mutation (promoter versus coding) may also affect the outcome, as the mutation may affect CD36 expression differentially in different tissues. This aspect of CD36 biology remains one of the most interesting and complicated because of the number of polymorphisms and haplotypes that exist.

The Role of CD36 in Atherogenesis

Endemann et al. (1993) first recognized that CD36 was a receptor for oxLDL, and subsequent work showed that CD36 and scavenger receptor A (SRA), were the principal macrophage receptors responsible for the uptake of modified forms of LDL (Kunjathoor, et al., 2002). Prior to the ability to create murine models of atherosclerosis and scavenger receptor knockouts in the background of these models, one could only speculate as to their role in atherogenesis. Our lab has made significant contributions to the relevance of CD36 to the pathogenesis of atherosclerosis using the apoE KO model. CD36/apoE double KO mice of both genders had significantly less lesion area in the aortic tree after 12 weeks of Western diet feeding (0.15% cholesterol, no cholate) (Febbraio, et al., 2000). This was despite a pro-atherogenic increase in plasma LDL/LDL cholesterol in female mice. Male but not female mice also had significantly reduced lesion area at the level of the aortic sinus on a normal chow diet (Febbraio, et al., 2000). Using a bone marrow transplant approach, we showed that absence of CD36 in hematopoietic cells accounted for the protection observed in the apoE KO model (Febbraio, Guy, & Silverstein, 2004). This study was again using a 12 week Western diet regimen. Mice of both genders lacking CD36 in macrophages alone were profoundly protected against lesion development throughout the aortic tree, and when CD36 was re-introduced into double knock outs, lesion area increased by ~2-fold. In long term Western diet feeding studies, we found that CD36 continued to play a role in lesion development as a consequence of continued recruitment of macrophages and development of foam cells even in late stage lesions (Guy, Kuchibhotla, Silverstein, & Febbraio, 2006). This was particularly dramatic at 35 weeks of feeding, when aortae from apoE KO mice showed near occlusion with lesion and demonstrated calcification associated with sclerosis. The result of this study was difficult to predict beforehand, given the work of Folkman, *et al.*, who proposed the provocative hypothesis that angiogenesis contributes to the pathogenesis of atherosclerosis and showed that pharmacologic inhibition of angiogenesis led to decreased lesion area, presumably because plaque had inadequate nutrition to grow (Moulton, et al., 2003). Thus, one potential outcome would be that in the absence of the CD36-TSP anti-angiogenic pathway, lesions would actually catch up or grow larger in the CD36/apoE double KO mice. Although our data did not substantiate this hypothesis, it is possible that extensive vessel remodeling, such that vasa vasorum are not the only source of nutrition, played a role.

CD36 is a target gene of PPAR- γ , and activation of PPAR- γ by oxLDL was shown to lead to a feed-forward loop of CD36 expression, uptake of oxLDL and foam cell formation (Tontonoz, & Nagy, L., 1999, Tontonoz, Nagy, Alvarez, Thomazy, & Evans, 1998). Counterbalancing this is an LXR mediated pathway of genes necessary for efflux of cholesterol from macrophages, which can be triggered by oxysterols and the PPAR- γ agonist, rosiglitazone (Chawla, et al., 2001, Chinetti, et al., 2001). There may be situations, therefore, when scavenger receptors are important for inhibition or regression of atherosclerosis, and thus we concur with a recent review by van Berkel *et al.* that makes the point that the net effect of SRA or CD36 expression *in vivo* can depend on other factors (2005). For example, treatment with rosiglitazone up regulated CD36 gene and protein expression in male LDLR KO mice, but this was in the context of up regulation of efflux proteins, which apparently enhanced lipoprotein clearance, decreased foam cell formation and reduced atherosclerotic lesion area (Li, Brown, Silvestre, Willson, Palinski, & Glass, 2000). This effect was not observed in female mice for reasons that remain unclear.

In another study, treatment of apoE KO mice with the CD36 ligand and hexarelin derivative, EP 80317, which has no growth hormone releasing properties, decreased atherosclerosis (Marleau, et al., 2005). Examination of the effect of EP 80317 on isolated macrophages showed reduction of uptake of modified LDL, and up-regulation of genes involved in cholesterol/phospholipid efflux, including LXR α , PPAR- γ , ABCA1 and ABCG1 (Marleau, et al., 2005).

This was accompanied by decreased total plasma cholesterol suggesting effects both on macrophages and the liver (Marleau, et al., 2005). These effects were not observed in CD36/apoE double KO mice, suggesting a role for CD36.

The view that scavenger receptors (specifically CD36 and SRA) contribute to foam cell formation, particularly in a pro-inflammatory setting, which promotes lipoprotein modifications that enhance their specific recognition by such receptors, was questioned recently in a report by Moore *et al.* (2005). In that study, CD36/apoE double KO mice were fed a Western diet for 8 weeks and lesions evaluated at both the aortic sinus and throughout the aortic tree. In the case of CD36, in male mice, they reported no significant difference in lesion area at the aortic sinus, and reduced lesion area in the aortic tree, but the difference did not reach statistical significance. They reported disparate results in female mice. While they showed significantly reduced lesion burden throughout the aortic tree, they saw increased lesion area in the aortic sinus. From these data they concluded that absence of scavenger receptors was actually pro-atherogenic, by creating a more pro-inflammatory milieu as a result of lack of uptake of the modified lipid.

Important to this discussion is a recent commentary by Curtiss (2006) in response to a series of papers showing different effects of absence of macrophage ABCG1 in the LDLR KO (Mauldin, et al., 2006, Out, et al., 2006). This commentary suggested that lesion growth at the level of the aortic sinus in high fat/high cholesterol fed mice may not, in fact, be linear, and does not necessarily correlate with lesion burden in the aortic tree. We concur, and actually go further. Whereas in that commentary, size of lesion was compared to time on diet, we would suggest that size of lesion at that location may be a non-linear function of lesion progression. We speculate that perhaps there is a point when lesions not only stop growing linearly or even altogether, as shown in that commentary, but may actually get smaller. How? Like wounds, as lipid and cellular debris are replaced by collagen and other cell types, particularly smooth muscle cells, plaque area may contract, and this may underlie the ability of mice to escape occlusion even after prolonged periods on high fat and cholesterol diets. Because of recognition of the extensive remodeling at the aortic sinus, we have felt that it is more appropriate to measure aortic tree lesion area to assess atherosclerosis extent in Western diet fed mice in our studies. Re-examination of the data of Moore *et al.* (2005) then shows similar results to what we reported in the aortic tree; the difference in males may manifest more strongly at 12 weeks rather than 8 weeks.

In addition to directly studying the effect of CD36 using CD36 KO mice, a role for CD36 in atherogenesis has been indirectly implied by many other reports. For example, in a study by Hayek *et al.*, (2005) streptozotocin induced diabetic apoE KO mice were assessed for lesion formation. Not surprisingly, there was greater lesion area in diabetic apoE KO compared with non-diabetic controls, and this was statistically significant after 3 months of diabetes. Macrophages isolated from diabetic mice showed increased superoxide content and increased lipid peroxide content. In *in vitro* studies, macrophages isolated from diabetic apoE KO mice showed increased uptake and degradation of oxLDL and increased accumulation of cholesterol. Using the mouse macrophage cell line, J774, these authors went on to show that increasing glucose content, like oxLDL up regulated CD36 mRNA expression. This suggests a role for CD36 in the pathogenesis of atherosclerosis in type I and type II diabetes that needs further investigation.

Another aspect of CD36 biology that has not been explored and may also be involved in atherogenesis is that of CD36 on platelets. Although our bone marrow study ruled out CD36 expression in many tissues, it did not rule out a potential role for platelets in atherosclerosis and as mentioned previously, despite being the first cell type from which CD36 was characterized, the role of platelet CD36 remains largely undefined.

Other functions of CD36 that may impact cardiovascular disease

Using an isolated perfused heart system in collaboration with the lab of Jason Dyck, we showed that CD36 plays an important role in fuel substrate choice in the heart (Kuang, Febbraio, Wagg, Lopaschuk, & Dyck, 2004). In the absence of CD36, the heart, which normally derives most of its energy from fatty acids, instead relies more heavily on glucose. This confirmed our studies with the radio labeled tracers ^{125}I -BMIPP (a non-metabolizable fatty acid analog), ^{125}I -IPPA (a metabolizable fatty acid analog) and 8-fluorodeoxyglucose (a glucose analog), which were initiated because of the observation that CD36 KO mice have fasting hypoglycemia (Coburn, Knapp, Febbraio, Beets, Silverstein, & Abumrad, 2000). Under normal and high fat conditions, we found that the CD36 KO mouse heart is entirely compensated in terms of ATP and acyl-CoA fatty acids by utilization of glucose (Kuang, Febbraio, Wagg, Lopaschuk, & Dyck, 2004). Even at high work loads, CD36 KO mouse hearts performed as well, if not better than wild type hearts because of full compensation for energy by glucose. Our study results differ from that of Irie *et al.* (2003) most probably because of the initial condition of the hearts, wild type and CD36 KO, at the time of study. The hearts in our study were shown to be removed in a healthy state from the mice; in the study of Irie *et al.*, wild type hearts failed even in the initial pre-conditioning segment, indicating some technical difficulty. We also found that during ischemia, defined as 18 minutes of Doppler no-flow, CD36 KO mouse hearts were protected and performed better presumably as a result of their reliance on glucose. These results support a large body of literature demonstrating that at the time of myocardial infarction/ischemia, heart muscle converts to glucose metabolism as an energy source. In a recent report, Heather, et al. (2006) found decreased expression of plasma membrane and cytoplasmic fatty acid binding proteins, including CD36 following coronary artery ligation in rats. This correlated with reduced fatty acid oxidation and lipid incorporation.

Work by Cho *et al.*, (2005) using a murine model of middle carotid artery occlusion, showed that ischemic injury led to decreased infarct volume and better neurological outcome in CD36 KO mice. This correlated with decreased expression of damaging ROS, but the complete mechanism remains under investigation, and may also involve differences in platelet and endothelial responses, and angiogenesis. Secretion of ROS and reactive nitrogen species by responding leukocytes and injured cells may contribute to a feed forward loop in terms of generating ligands for CD36 by altering cell membrane and lipoprotein structure, thus providing recognition ligands for macrophages to signal phagocytosis. These ligands may also affect neighboring cell function. Smooth muscle cells, for example, migrate and proliferate in response to oxLDL and ROS (Zhao, Seng, Zhang, & She, 2005, Lyle, & Griendling, 2006). Thus decreased production of ROS and oxidized ligands as a result of absence of CD36 may impact on processes such as neointimal hyperplasia following endothelial injury as a result of less cell injury and apoptosis and reduced smooth muscle cell migration and proliferation. Similarly, there may also be differences in cell death following myocardial infarction/cardiac ischemia.

The relationship of CD36 to macrophage (and global) immune status, either pro- or anti-inflammatory, has been a complex issue. CD36 uptake of apoptotic cells was shown to be one pathway in the suppression of pro-inflammatory cytokines (Voll, Herrmann, Roth, Stach, Kalden, & Girkontaite, 1997), and CD36 is up-regulated in response to IL-4 (Yesner, Huh, Pearce, & Silverstein, 1996), a TH2 cytokine, and down regulated by LPS (Yesner, 1996, Memon, Feingold, Moser, Fuller, & Grunfeld, 1998). Foam cell formation, however, has hallmarks of both a pro-inflammatory (TH1) and innate, scavenger receptor (TH2) phenotype. Whether scavenger receptor uptake of oxLDL promotes or suppresses a pro-inflammatory milieu is an open question, which may impact cardiovascular disease on several levels.

In skeletal muscle, CD36 is important for fatty acid uptake, and its expression is regulated by both the environmental and cellular milieu (Chabowski, Gorski, Calles-Escandon, Tandon, & Bonen, 2006; Chabowski, et al., 2006; Chabowski, et al., 2004; Chabowski, et al., 2005; Benton, Han, Febbraio, Graham, & Bonen, 2006; Cameron-Smith, et al., 2003). Studies in isolated cardiac muscle cells, using a specific CD36 inhibitor, sulfo-N-succinimidyl oleate, also showed that CD36 is likely the major membrane protein involved in fatty acid uptake (Koonen, et al., 2005). The uptake of fatty acids in the periphery affects lipoprotein and glucose metabolism, and thus this indirectly affects cardiovascular health and pathology. Similarly, uptake of fatty acids by adipocyte CD36 also impacts lipoprotein and glucose metabolism. A role for CD36 in cardiovascular health and disease as it relates specifically to these tissues remains to be investigated. A difficulty in studying CD36 is that it is expressed not only in multiple tissues, but multiple cell types within a single tissue. The next generation of study will necessarily rely on transgenic knock in and tissue specific knock out approaches.

Future Prospects

As this review only partially demonstrates, CD36 earns its title as a multifunctional protein. Significant progress has been made in elucidating structure-function properties, ligand interactions, signaling pathways and roles in multiple homeostatic and pathological processes. Still, there is significant work to be done. We need better understanding of how CD36 distinguishes between different ligands, and how this discrimination translates in terms of the signaling pathways activated. Understanding tissue and cell specific roles of CD36, which may be dependent upon associated proteins or targeting to specific membrane domains, are also important to our overall knowledge of how this protein works. Given that several classes of widely used drugs impact CD36 expression, understanding the effect this has on normal and pathological processes becomes imperative.

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Figure 1a

Figure 1b

Figure 1c

Figure 1.

Binding of ligands to CD36 leads to cell specific activation of signaling pathways and responses. **(A)** Binding of TSR containing ligands of CD36, such as thrombospondin-1, leads to a specific signaling cascade involving the *src* kinase *fyn*, caspases and p38 MAP kinase in endothelial cells. The outcome of this pathway is apoptosis of the endothelial cell and inhibition of angiogenesis. **(B)** Binding of fibrillar β -amyloid to CD36 in a complex with other proteins (including SRA, CD47 and the integrin $\alpha_6\beta_1$) on microglial cells can lead to activation of several pathways. The outcome of these signaling cascades is an “activated” state as a result of reorganization of the actin cytoskeleton to confer phagocytic competency, secretion of ROS and cytokines. **(C)** On the macrophage, binding of modified LDL to CD36 leads to activation of the *src* kinase *lyn*, downstream activation of the MAP kinase kinase, MEKK2, and ultimately *jnk* phosphorylation, which is essential to modified LDL uptake and foam cell formation.

Figure 2.

CD36 wears multiple hats. As this review demonstrates functions of CD36 are homeostatic and contribute to normal cellular responses (CD36: The Good). However, in certain contexts, functions of CD36 contribute to pathological states (CD36: The Bad).

Uptake of apoptotic cells that occur as a part of normal homeostasis and in the context of inflammatory resolution

Uptake of pathogens; triggering the immune response

Uptake of modified proteins / lipids / lipoproteins that occur non-pathologically

Uptake of fatty acids

Inhibition of angiogenesis in the context of wound resolution

Down modulation of the immune response in the context of inflammatory resolution

Uptake of modified proteins / lipids / lipoproteins that occur in a pathological setting (e.g. hyperlipidemia, atherosclerosis, diabetes, alzheimer's disease)

Inhibition of angiogenesis in hyperlipidemic and diabetic settings

Triggering a pro-inflammatory response in the context of uptake of modified lipoprotein and protein ligands (e.g. fibrillar β -amyloid)

Dysregulation of insulin responsiveness as a result of fatty acid uptake in a diabetic setting