Role of CD36 in membrane transport of long-chain fatty acids

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CD36 is a multispecific membrane glycoprotein that has been postulated to have a variety of functions. Evidence generated in isolated cells and in mice and rat models of altered CD36 expression has indicated an important role for CD36 in membrane transport of long-chain fatty acids. The cumulative data indicate that CD36 facilitates a major fraction of fatty acid uptake by muscle and fat, and that CD36 deficiency is associated with a large (60–80%) defect in fatty acid uptake by those tissues. In humans, polymorphisms in the CD36 gene may underlie defective fatty acid metabolism and some forms of heart disease. Herein we review our current understanding of the transport function and regulation of CD36. The realization that the transport step rate limits cellular fatty acid utilization suggests that abnormalities in CD36 expression or function may impact on susceptibility to certain metabolic diseases such as obesity and insulin resistance. Curr Opin Clin Nutr Metab Care 5:139–145.
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Abbreviations

BMIPP	15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid
FA	fatty acid
FAT	fatty acid transporter
PPAR	peroxisome proliferator-activated receptor
SHR	spontaneously hypertensive rat

Introduction

The mechanism of fatty acid (FA) transfer across plasma membranes has been shown to consist of two components: passive diffusion through the lipid bilayer [1] and protein-facilitated transfer [2–4,5•].

The search for the membrane proteins that are involved in facilitating FA uptake resulted in the identification of several candidates. Among these are the membrane-associated FA-binding protein, identified by oleate-agarose affinity chromatography [6]; and the FA transport protein, identified by functional expression cloning [7], and its family [8•]. CD36 was first implicated in membrane FA transport by the work of Harmon and Abumrad [9], who isolated an 88-kDa membrane protein (termed FAT, fatty acid transporter) by specific labeling with the reactive sulfo-N-succinimidyl derivative of oleic acid under conditions in which FA uptake was inhibited. The corresponding complementary DNA cloned from a rat adipose complementary DNA library [10] encoded a protein with 85% homology to human platelet CD36 [11]. Thus, FAT is the rat homolog of human CD36, and the two terms are often used interchangeably in studies that deal with FA uptake.

Evidence for CD36 function in fatty acid uptake

Tissue distribution and regulation of CD36 expression provided early, although indirect evidence for its role as a FA transporter.

Tissue distribution

Distribution of CD36 was found to be consistent with its role as a FA transporter, because it favored tissues with a high metabolic capacity for long-chain FAs [10]. Its concentration is high in the intestine [12–14], where it is differentially expressed along the longitudinal and horizontal axes of the tissue, and is most abundant in proximal segments and in villi enterocytes, where most lipid absorption occurs. Expression is high in adipose tissue [10], where FAs are stored as neutral lipids, and in the heart [10,15], which relies on energy from FA oxidation. In skeletal muscle, CD36 is highly expressed in muscles with a predominance of oxidative fibers, such as the soleus, whereas expression is low in muscles with a predominance of glycolytic fibres, such as the extensor digitorum longus [16].

CD36 is also expressed on macrophages [17], endothelial cells [18], platelets [19] and lung pneumocytes [20], where it has been linked to FA uptake [20–22], to lipid

accumulation [23] and to binding of oxidized low-density lipoproteins [24•].

Functional expression

Expression of CD36 in fibroblasts that lack it induced expression of a saturable, high affinity, phloretin-sensitive component of FA uptake [25]. The contribution of this component was high at low ratios of FA to albumin, and decreased as ratios were increased to 2.0. At the higher ratios, more FA permeated the membrane via the diffusion component that is constitutively present in the cell. These data suggested that CD36 mediated the high-affinity, saturable component of FA uptake, which had been characterized in early studies with isolated adipocytes [26,27]. In a complementary approach to the studies in fibroblasts, expression of the antisense CD36 complementary DNA in preadipocytes reduced FA uptake by those cells [28]. In addition, expression interfered with normal differentiation of those cells into adipocytes, illustrating the important role of FA uptake or of CD36-mediated transcriptional effects of FAs on the preadipocyte–adipocyte differentiation program [29].

Regulation of CD36 expression

CD36 appears to be under the control of a multitude of factors, which is in accord with its wide cellular distribution and the multiple roles that this multispecific protein may play. CD36 is regulated during differentiation and development. Its expression is a prominent marker of preadipocyte differentiation into adipocytes [10]. In the heart there is coregulation of the expression of CD36 and of muscle FA-binding protein, which is consistent with their complementary functions. Both proteins are upregulated during heart development when FA utilization increases [30].

CD36 expression is regulated by agonists of the nuclear peroxisome proliferator-activated receptors (PPARs), and different PPARs mediate the regulatory effects in a tissue-specific manner. In preadipocytes, CD36 expression is regulated by agonists of both PPAR-γ and PPAR-δ [31]. Two PPAR response elements located at -245 to -233 base pairs, and -120 to -108 base pairs from the transcription start site have been identified in the murine CD36 promoter [32••]. PPAR-γ agonists increase CD36 messenger RNA in adipose tissue [33], and the effect may involve recruitment of preadipocytes into adipocytes because CD36 levels in mature adipocytes are not altered by PPAR-γ agonists [34,35]. Both PPAR-γ [36,37] and PPAR-δ [23] mediate upregulation of CD36 in human macrophages. In the case of PPAR-δ this is associated with significant lipid deposition. PPAR-δ agonists have also been shown to be potent regulators of CD36 messenger RNA in keratinocytes [38]. In muscle, CD36 expression appears to be sensitive to

regulation by agonists of PPAR-γ [39] and probably of PPAR-α, because its expression is significantly decreased in the PPAR-α-null mouse [40]. By comparison, cardiac CD36 expression has only been reported to be responsive to PPAR-α, and not to PPAR-γ [41]. PPAR-γ [42] and PPAR-α also mediate regulation of CD36 expression in the liver [43].

Consistent with its role in FA transport, CD36 expression has been shown to be upregulated by long-chain FAs in isolated cells [34] and by dietary fat in tissues such as adipose tissue [44], intestine [12,45], mammary gland [46] and heart muscle [47]. We have observed a marked decrease in heart CD36 protein levels in mice fed diets supplemented with medium- and short-chain FAs (Ibrahimi A *et al*., unpublished data). A recent study [48] reported that infusion of FAs into rats decreased CD36 protein levels by more than 50%. However, Nisoli *et al.* [44] found that high fat increases CD36 messenger RNA in subcutaneous adipose tissue and Greenwalt *et al.* [47] reported an increase in heart CD36 protein levels in mice maintained on high fat diet. A more systematic approach is needed to determine the effects of dietary fat on CD36 levels in different tissues. It is possible that effects may depend on the type of fat used. In addition, messenger RNA and protein levels may not be regulated in the same way by dietary lipid. Post-transcriptional mechanisms may also be involved in fat regulation of CD36, as was shown recently in the case of glucose, which increases the translational efficiency of the CD36 messenger RNA [49••].

In summary, as is the case with many other nutritionally relevant genes, there is strong evidence for regulation of CD36 by dietary and metabolic factors, and these effects are likely to impact on the adaptive responses of different tissues to environmental challenges.

CD36 facilitates a major fraction of fatty acid uptake of muscle

Muscle, especially that rich in red oxidative fibers, has high dependence on energy from FA oxidation. As a result, it would be expected that CD36 expression in muscle would impact on FA utilization and the ability of muscle to perform work. Coburn *et al.* [50] demonstrated that mice null for CD36 have a greater than a 60% reduction in FA uptake by heart and red muscle. As a result, CD36-null mice have a decreased ability to perform strenuous exercise. In contrast, mice with CD36 over-expression perform better than wild-type mice (Abumrad NA *et al.*, unpublished data), which may reflect their enhanced ability for FA oxidation in response to contraction [51]. Bonen and coworkers [16,52] recently documented some of the molecular mechanisms that are involved in regulation of FA utilization by muscular activity. The acute regulation of

FA uptake by muscle activity involves the translocation of CD36 from intracellular stores to the sarcolemma, which is analogous to the regulation of glucose uptake by membrane recruitment of glucose transporter 4 [52]. More recent data by Steinberg et al. [53•] demonstrate that membrane recruitment of CD36 in muscle is influenced by leptin and could play a role in the peripheral effects of this hormone.

These data indicate that CD36 expression levels significantly impact on muscle function and performance. It would be informative to determine whether alterations in CD36 levels brought about by genetic or environmental factors determine muscular performance and athletic ability in humans.

CD36 expression in the heart and tolerance to ischemia

Studies of myocardial FA utilization in CD36 null animals [50], in spontaneously hypersensitive rats, SHR [54••], which have polymorphisms in the CD36 gene [55] and in CD36-deficient humans (see below) were done using the free fatty acid analogue 15-(p-iodophenyl)-3-(R,S)-methyl pentadecanoic acid (BMIPP).

Defect in fatty acid utilization and myocardial hypertrophy in animal models

CD36 null ($CD36^{-/-}$) mice exhibited between 60 and 80% reduction in BMIPP [50] uptake by heart tissue, which was similar in magnitude to that observed in CD36-deficient humans [56]. Lipid incorporation of BMIPP was severely altered in hearts of CD36-null mice, with a 20-fold increase in the ratio of diglyceride to triglyceride. This indicated a block in the conversion of diglyceride to triglyceride resulting from the defect in supply of FAs and FA-acyl coenzyme A for the enzyme diglyceride acyl-coenzyme A transferase. Hearts of SHRs exhibited similar but less pronounced defects in FA uptake and in conversion of diglycerides to triglycerides [54••].

$CD36^{-/-}$ mice have heart hypertrophy [57], as do SHRs [58]. Supplementation of the diet with short-chain FAs, which do not require CD36-facilitated transport, eliminated heart hypertrophy in SHRs [54••]. These data indicated that lack of metabolic energy resulting from deficient FA uptake is the primary defect that underlies myocardial heart hypertrophy in the SHR.

Under normal physiologic conditions optimal cardiac work is dependent on FA oxidation [59]; because the heart must often respond to changes in the workload, FA metabolism must be regulated in such a manner as to allow rapid adaptation. Energy from FA metabolism is also believed to play an important role in ischemic tolerance [60]. We recently examined whether alteration in expression of CD36 influences heart function during

normal perfusion conditions and in ischemia/reperfusion using the isolated working heart preparation (Ibrahimi A et al., unpublished data). Our studies showed an increase in end-diastolic pressure in CD36-null hearts under normal perfusion conditions, possibly suggesting a structural change in myocardial tissue. Tolerance to ischemia was significantly impaired as compared with wild-type mice, and rescuing CD36 expression reversed the impairment. In accord with this, CD36 over-expression in the heart appeared to be cardioprotective. A diet supplemented with short- and medium-chain FAs improved ischemic tolerance in CD36-null mice, but did not reverse the increase in end-diastolic pressure (Ibrahimi A et al., unpublished data). This supports the interpretation that energy from FA oxidation is important for ischemic tolerance and that FA provision may improve myocardial survival from ischemic episodes.

CD36 deficiency in humans

CD36 deficiency on platelets is present in 5–10% of the Asian, African and African-American populations, and in approximately 0.3% of the white population [61,62]. Recent analyses of genetic abnormalities identified mutations that cause CD36 deficiency type I in Japan [63,64]. This deficiency is linked to a single nucleotide insertion [63,64] and leads to a frameshift and appearance of a premature stop codon. In the case of type II CD36 deficiency, the mutation is a substitution, yielding an incompletely glycosylated protein that is not inserted in the membrane and is degraded in the cytoplasm [65,66].

The role of CD36 deficiency in the pathogenesis of cardiomyopathies in humans was investigated vigorously once evidence generated in vitro and later in laboratory animals documented the role of CD36 in FA utilization. Most of the studies were conducted in Japan, where BMIPP is available commercially and used for clinical evaluation of cardiac FA metabolism by noninvasive imaging techniques [67]. Patients with CD36 deficiency show reduced FA uptake in the heart [67,68], as visualized by scintigraphy using iodinated BMIPP. The deficiency may underlie some cases of cardiac hypertrophy [62,63,69••], and incidence of CD36 deficiency in patients with heart disease exceeds that in the general population [67]. Thus, studies conducted in humans document a strong association between CD36 deficiency, defective myocardial FA uptake, and some forms of heart hypertrophy. The increasing size of the population sample studied, together with the data generated in mice and rats, establish that the association is in fact a cause–effect relationship.

Role of CD36 in insulin resistance and diabetes

The first link between CD36 and diabetes was reported with the SHR model of human insulin-resistance

syndromes. Quantitative trait loci for SHR defects in glucose and FA metabolism map to a single locus on rat chromosome 4 [55]. The use of complementary DNA microarrays identified CD36 as a defective gene in SHR at the peak of linkage to these quantitative trait loci. The SHR-CD36 gene contained multiple sequence variants and the CD36 protein was undetectable in SHR adipocyte plasma membrane [55]. A congenic line, SHchr4, in which a piece of chromosome 4 with CD36 was integrated into the SHR genome [55], and later transgenic rescue of CD36 in SHR [70••] normalized blood lipids and insulin responsiveness, but hypertension was only marginally improved. These results suggested that CD36 deficiency underlies defective FA metabolism and hypertriglyceridemia in the SHR, and may be important in the pathogenesis of insulin-resistance in this animal model. In accord with this, feeding the SHR a diet supplemented with medium- and short-chain FAs reversed the hyperinsulinemia [54••] by providing tissues with energy from FA oxidation, because uptake of these FA is independent of CD36 [27].

Greenwalt *et al.* [47] documented several fold increases in myocardial CD36 in genetically diabetic KKA(y) and NOD mice. These changes may result to some extent from the hyperglycemia of diabetes. We found that muscle CD36 protein levels were significantly increased in streptozotocin diabetic rats, and that the magnitude of the increase correlated well with the severity of diabetes as assessed by the degree of hyperglycemia (Fig. 1; Ibrahimi A *et al.*, unpublished data). The effect appeared to reflect changes at the post-transcriptional level, because CD36 messenger RNA expression was not altered (not shown). As mentioned above, Griffin *et al.* [49••] established that high glucose upregulates CD36 by increasing translation efficiency of the messenger RNA.

Other evidence for a role of CD36 in insulin responsiveness comes from studies conducted in mice with muscle over-expression of CD36 [51] and in CD36-null mice (Hajri T *et al.*, unpublished data). These studies indicate that CD36 expression level strongly impacts on muscle glucose utilization and insulin sensitivity. For example, transgenic mice that over-express CD36 (6–8 months) show increases in plasma glucose and insulin levels. On the other hand, CD36-null mice are hypoglycemic [71], hypoinsulinemic, and more insulin sensitive than the wild-type mice, but they show reduced tolerance to fructose induced insulin resistance (Hajri T *et al.*, unpublished data). Further studies should help to document the role of FA utilization in insulin resistance and allow a better understanding of the molecular mechanisms involved.

Figure 1. Correlation between muscle CD36 expression and blood glucose levels in streptozotocin treated rats
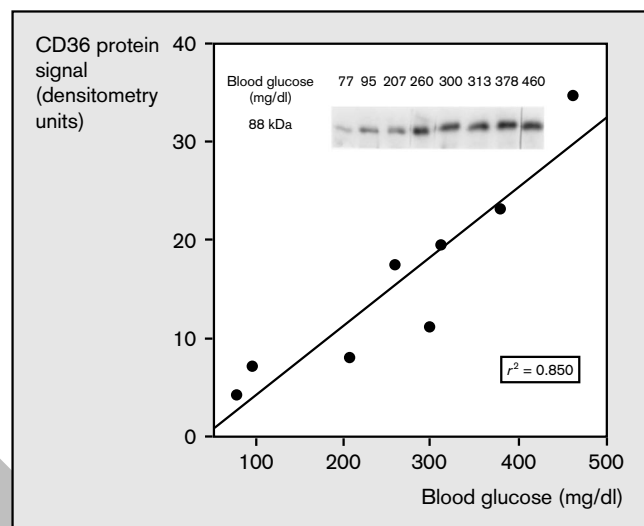
Sprague–Dawley male rats (approximately 200 g) were fasted for 12–14 h before receiving an intraperitoneal injection of streptozotocin (STZ; 85 mg/kg body weight). Rats (*n* = 4) were killed at days 0, 1, 2, 4, 5, 7, 8 and 10 after STZ injection. Plasma glucose was measured and membrane proteins were prepared from muscle tissue as previously described [25]. Triton solubilized membrane proteins (50 mg) were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis, and blotted to nitrocellulose for immunodetection using enhanced chemiluminescence (ECL, Amersham, Piscataway, NJ, USA). Signal for CD36 protein was scanned by densitometry and plotted as a function of blood glucose.

Data linking CD36 deficiency and insulin resistance in humans are currently limited and controversial [72–76]. Miyaoka *et al.* [73] studied a limited number of CD36-deficient patients using the euglycemic hyperinsulinemic clamp technique and documented abnormalities of glucose metabolism in all cases [72]. However, conclusions from this study were not supported by the findings of Yanai and coworkers [77,78] who reported that young CD36-deficient patients showed no sign of insulin resistance. As Chiba *et al.* [76] suggested, the data obtained by Miyaoka *et al.* might reflect the older age of the CD36-deficient patients studied (over 64 years old versus 60 years old for control individuals), who exhibited other abnormalities such as hypertension, hyperlipidemia and hyperglycemia. Our data with CD36-null mice (Hajri T *et al.*, unpublished data) are more consistent with the findings of Yanai and coworkers [77,78]. Based on our findings, our current interpretation is that the effect of CD36 deficiency on insulin responsiveness is strongly dependent on diet, and consideration of this interaction could help reconcile some of the divergent effects in humans.

Conclusion

Over the past several years, the identification of CD36 as a long-chain FA transporter has significantly contributed

to our understanding of the regulation of FA uptake and utilization. It will be important to gain a better understanding of the interactions between defects in CD36 expression or function and abnormalities in other proteins that are important for FA or glucose utilization. It is clear that most metabolic diseases are not caused by defects in a single gene, but probably involve a set of interactions between various genes, and these are in turn modulated by environmental factors. A better knowledge of the metabolic role of CD36 and of the tissue-specific alterations in its expression brought about by hormonal or nutritional factors should contribute valuable insight into the set of conditions that result in metabolic pathology. CD36 studies will probably make an important contribution to our ability to evaluate the role played by lipid metabolism in the etiology of diseases such as obesity, insulin resistance, heart hypertrophy and possibly heart failure.

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