Adipose and Muscle Tissue Profile of CD36 Transcripts in Obese Subjects Highlights the Role of CD36 in Fatty Acid Homeostasis and Insulin Resistance

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**OBJECTIVE**

Fatty acid (FA) metabolism is tightly regulated across several tissues and impacts insulin sensitivity. CD36 facilitates cellular FA uptake, and *CD36* genetic variants associate with lipid abnormalities and susceptibility to metabolic syndrome. The objective of this study was to gain insight regarding the in vivo metabolic influence of muscle and adipose tissue CD36. For this, we determined the relationships between CD36 alternative transcripts, which can reflect tissue-specific CD36 regulation, and measures of FA metabolism and insulin resistance.

**RESEARCH DESIGN AND METHODS**

The relative abundance of alternative *CD36* transcripts in adipose tissue and skeletal muscle from 53 nondiabetic obese subjects was measured and related to insulin sensitivity and FA metabolism assessed by hyperinsulinemic–euglycemic clamps and isotopic tracers for glucose and FA.

**RESULTS**

Transcript 1C, one of two major transcripts in adipose tissue, that is restricted to adipocytes predicted systemic and tissue (adipose, liver, and muscle) insulin sensitivity, suggesting adipocyte CD36 protects against insulin resistance. Transcripts 1B and 1A, the major transcripts in skeletal muscle, correlated with FA disposal rate and triglyceride clearance, supporting importance of muscle CD36 in clearance of circulating FA. Additionally, the common *CD36* single nucleotide polymorphism rs1761667 selectively influenced *CD36* transcripts and exacerbated insulin resistance of glucose disposal by muscle.

**CONCLUSIONS**

Alternative *CD36* transcripts differentially influence tissue CD36 and consequently FA homeostasis and insulin sensitivity. Adipocyte CD36 appears to be metabolically protective, and its selective upregulation might have therapeutic potential in insulin resistance.

The appropriate regulation of fatty acid (FA) metabolism is important for normal energy homeostasis, insulin sensitivity, and metabolic health. FA utilization is regulated across multiple tissues. Dietary-derived FAs taken up by adipose tissue are primarily converted to triglycerides (TGs) for storage in cytosolic lipid droplets.
During periods of fasting and exercise, there is increased FA mobilization from adipocytes and FA delivery to tissues, particularly skeletal muscle, for uptake and oxidation (1). However, excessive plasma FA availability can result in FA fluxes that exceed the tissues’ capability for FA utilization, leading to liver (2) and skeletal muscle insulin resistance (3). The scavenger receptor, CD36, plays an important role in facilitating cellular FA uptake and utilization (4,5). In mice, CD36 deletion impairs FA uptake and adaptive fuel flexibility by heart and skeletal muscle. In adipocytes, CD36 is important for FA uptake and FA release in response to lipolytic stimuli (6), influencing both energy storage and mobilization. Mutations in the cd36 gene in the spontaneously hypertensive rat result in hyperlipidemia and insulin resistance (7).

In humans, complete CD36 deficiency (~6% of populations of Asian or African ancestry) results in reduced myocardial (8) and adipose tissue FA uptake (9) and in abnormalities of plasma lipid levels (10,11). Common single nucleotide polymorphisms (SNPs) in the CD36 gene identified in African Americans and Caucasians influence levels of plasma lipids (11,12) and risk of metabolic syndrome (11) and diabetes (13). High levels of soluble CD36 in plasma (14) and increased monocyte CD36 expression (15) correlate with inflammation and insulin resistance. Increased hepatic CD36 expression is also observed in subjects with nonalcoholic fatty liver disease (16). The above observations indicate that both deficiency and high levels of CD36 can associate with negative metabolic effects in humans.

We hypothesized that the association of CD36 to metabolic disease might reflect its influence at the level of various organs, notably adipose and muscle tissues, which have high metabolic impact. The objective of this study was to gain insight into the relationship of muscle and adipose CD36 to serum FA homeostasis and organ insulin sensitivity in vivo. For this, we examined how tissue-specific alternative CD36 transcripts, which inform on local regulation of CD36 gene expression, relate to metabolic phenotypes of subjects who underwent a hyperinsulinemic-euglycemic clamp.

Tissue-specific distribution of many mammalian genes is driven by alternate promoter usage (17) and in the case of the human CD36 gene, several independently regulated promoters (18–20) yield six transcripts that encode the same protein. These transcripts can serve as indicators of tissue-specific gene expression and regulation in health and disease situations. We determined the relationships of alternative CD36 transcripts in muscle and adipose tissues to FA metabolism and insulin resistance in a cohort of obese subjects. Our findings provide novel insight into the importance of CD36 in tissue FA partitioning and insulin sensitivity.

**RESEARCH DESIGN AND METHODS**

**Study Subjects**

This study used adipose and muscle samples collected from 53 subjects who underwent metabolic phenotyping (21,22). Subcutaneous adipose tissue was available from all subjects (38 women and 15 men; 10 African American, 40 Caucasian American, 2 American Indian, and 1 Asian) and skeletal muscle from 36 of the subjects (26 females and 10 men; 6 African American, 27 Caucasian, 2 American Indian, and 1 Asian). The exclusion criteria included history of consuming >20 g/day of alcohol, use of medications that affect glucose or lipid metabolism, or type 2 diabetes (confirmed by 2-h oral glucose tolerance test). All subjects provided written informed consent, and the study was approved by the Washington University Institutional Review Board.

**Metabolic Characterization of Subjects**

Study designs and methodology have been described (21,22), and the protocol followed is shown in Supplementary Fig. 1. Briefly, subjects were admitted to the clinical research unit at Washington University School of Medicine on the evening before the clamp procedure. Body fat mass (FM) and fat-free mass (FFM) were determined with dual-energy X-ray absorptiometry (Delphi W densitometer, Hologic, Waltham, MA). Intra-abdominal and abdominal subcutaneous adipose tissue volumes were quantified by magnetic resonance imaging (Siemens, Iselin, NJ; ANALYZE 7.0 software, Mayo Foundation, Rochester, MN). Intrahepatic TG (HTIG) content was measured using localized proton magnetic resonance spectroscopy (Siemens Magneton Vision Scanner, Siemens, Erlanger, Germany) as described (23). To determine hepatic, skeletal muscle, and adipose tissue insulin sensitivity [6,6-2H2]glucose, [2,2-2H2]palmitate, and 20% dextrose enriched with labeled glucose were infused (22,24). Blood samples were obtained before beginning the tracer infusion for background plasma glucose and palmitate tracer-to-tracer ratios (TTRs) then every 10 min during the final 30 min of the basal period and of the insulin clamp stage 1 (insulin infused at 20 mU/m2 body surface area; 3–6 h) and stage 2 (50 mU/m2 body surface area; 6–9 h) to determine glucose, free FA (FFA), and insulin concentrations and substrate kinetics.

Tissue samples were obtained from subcutaneous abdominal adipose tissue and from the quadriceps femoris muscle 60 min after starting the glucose tracer during the basal period (Supplementary Fig. 1). Tissues were immediately rinsed with ice-cold saline, frozen in liquid nitrogen, and stored at −80°C. For studying kinetics of very LDLs (VLDLs), after a 12-h overnight fast, subjects were given an intravenous bolus of [1,1,2,3,3-2H3]glycerol and a primed constant infusion of [5,5,5-2H3]leucine was started and maintained for 12 h (22). Blood samples were obtained before the start of tracer infusions to determine plasma concentrations of substrates, insulin, and background isotopic enrichments of glycerol and leucine in plasma, VLDL-TG, and VLDL apolipoprotein B (apoB) 100. Samples were then obtained at regular time points throughout to determine VLDL-TG and VLDL-apoB kinetics. Plasma glucose, palmitate and leucine TTRs, glycerol TTR in VLDL-TG, and leucine TTR in VLDL-apoB were determined with gas chromatography mass spectrometry.

**Calculations**

Metabolic and isotopic steady states were achieved during the last 30 min of the basal period and stages 1 and 2 of the clamp procedure, and the Steele equation for steady-state conditions was used to calculate substrate kinetics (25). Glucose rate of disappearance (Rd) from plasma was assumed to equal the glucose rate of appearance (Ra) during basal conditions; during the clamp...
procedure, glucose Rd was assumed to equal the sum of endogenous glucose Ra and the rate of infused glucose. Hepatic insulin sensitivity index (HISI) was determined by calculating the reciprocal of the hepatic insulin resistance index (product of basal endogenous glucose production rate, in \( \mu \text{mol/kg FFM} \cdot \text{min}^{-1} \) and fasting plasma insulin in \( \mu \text{U/L} \)) (26). Skeletal muscle insulin sensitivity was assessed as the relative increase in glucose Rd during insulin infusion (24). The suppression of palmitate Ra during stage 1 of the clamp procedure was used as a measure of adipose tissue insulin sensitivity. Total FFA Ra was calculated by dividing palmitate Ra by the proportional contribution of palmitate to total plasma FFA concentration. FFA Rd was expressed in \( \mu \text{mol/kg FFM} \) per min, which indicates the amount of FFA released into the circulation in relation to the amount of lean tissues that use FFA (i.e., index of FFA availability).

Hepatic secretion rates of VLDL-TG and VLDL-apoB were calculated by multiplying plasma VLDL-TG or VLDL-apoB concentration by VLDL-TG or VLDL-apoB fractional turnover rate, determined by fitting the TTR data to a compartmental model. Plasma VLDL-TG clearance rate was calculated as VLDL-TG Rd divided by VLDL-TG concentration (22).

**RNA Isolation and Quantitative RT-PCR**

Total RNA was extracted from the tissue biopsies and from normal human dermal microvascular endothelial cells (HMVECs; Lonza) using TRIzol (Invitrogen) and quantified (NanoDrop ND1000). For tissue distribution, total RNA from various human tissues was purchased from Stratagene for liver (catalog number 540017), heart (540011), skeletal muscle (540029), and pancreas (540023); Agilent for tongue (540149), and Clontech for adipose tissue (636558). Synthesis of cDNA (SuperScript III, Invitrogen) using random hexamer primers was followed by quantitative RT-PCR (qRT-PCR) in triplicate (SYBR Green PCR Master Mix on the ABI 7500 RT PCR System, Applied Biosystems) as described (22). Relative expression of CD36, peroxisome proliferator–activated receptor (PPAR)-\( \gamma \) and CEB/Px was normalized to the human acidic ribosomal phosphoprotein P0 (RPLP0). Human CD36 alternative transcript assays were detected using forward primers unique to the first exons (untranslated 5’ sequence), and reverse primers were positioned at exon 2, which is common to all the transcripts (18,19). The primers for qRT-PCR are shown in Supplementary Table 1. The average reaction efficiency (slope = 10(−1/slope)−1) for each primer pair was 96 ± 0.05%.

Human THP-1 monocytes (ATCC, Rockville, MD) were cultured in RPMI 1640 (ATCC 30–2001) with 10% heat-inactivated FBS, 100 \( \mu \text{g/mL} \) penicillin/streptomycin and 0.05 mmol/L 2-mercaptoethanol. Cells (4 \( \times 10^5 \) cells/well) were treated (18–24 h) with phorbol myristic acid (50 ng/mL) to drive differentiation into macrophages and switched to fresh medium for 24 h prior to RNA isolation. Simpson–Golabi–Behmel syndrome (SGBS) human preadipocytes (27) were differentiated in serum-free Dulbecco's modified Eagle's medium with 2 \( \mu \text{mol/L} \) rosiglitazone, 250 nmol/L dexamethasone, 0.5 mmol/L 3-isobutyl-1-methylxanthine, 1 \( \mu \text{mol/L} \) cortisol, 0.2 nmol/L triiodothyronine, and 10 nmol/L insulin. RNA was isolated 14 days later for exon qRT-PCR. Adipose tissue CD36 protein levels were determined as previously described (22).

**Statistical Analysis**

Distribution normality for transcripts and metabolic variables was assessed using the Shapiro–Wilk test. Correlations were calculated using Spearman rank-order coefficients. The data were adjusted for the effects of age, sex, BMI, and visceral adipose tissue (VAT) on insulin sensitivity. Neither of these variables significantly impacted the observations, and the data presented are unadjusted correlation coefficients with corresponding \( P \) values. Differences between rs1761667 genotypes were determined by Student t tests with significance at \( P < 0.05 \) (two-tailed).

**RESULTS**

**Tissue Distribution of Alternative CD36 Transcripts in Humans**

The human CD36 gene exhibits six alternative promoters yielding transcripts 1A–1F, with distinctive tissue distribution as shown in Fig. 1A and B. The most ubiquitous transcript is 1B, which is nearly exclusive in liver, monocytes, and macrophages. In adipose tissue and skeletal muscle, 1B transcripts are expressed several fold higher relative to 1C and 1A. Transcripts 1D, 1E, and 1F are orders of magnitude less abundant (Supplementary Fig. 2), except for exon 1D in microvascular endothelial cells (HMVEC) (Fig. 1D). We focused our analysis on the predominant transcripts in adipose and muscle tissues 1A–1C. Transcript 1C is not present in human macrophages or endothelial cells (Fig. 1C and D), thus in adipose tissue, 1C expression would provide an in vivo assessment of adipocyte CD36. In contrast, 1B expression reflects adipocytes and resident macrophages in addition to a minor contribution from endothelial cells. As shown in Fig. 1C and E, differentiation of monocytes to macrophages and of preadipocytes to adipocytes associated with general increases in all transcripts expressed by each cell type.

**Adipose Tissue Transcript 1C Strongly Associates With Insulin Sensitivity**

To determine metabolic relevance of tissue CD36, levels of total CD36 mRNA and alternative transcripts 1A–1C were determined in adipose (\( n = 53 \)) and skeletal muscle (\( n = 36 \)) biopsies from obese individuals who underwent body composition measurements and hyperinsulinemic–euglycemic clamps (Table 1). In adipose tissue, transcripts 1B and 1C both correlated with total CD36 mRNA and protein. These correlations were stronger with 1C despite its lower abundance as compared with 1B (Table 2), supporting contribution of both transcripts to CD36 mRNA and protein abundance.

Total adipose tissue CD36 mRNA inversely correlated with IHTG content (Table 2), and modest positive correlations were observed with the HISI and with insulin suppression of lipolysis (palmitate Ra), an index of adipose tissue insulin sensitivity.

Interestingly, the 1B and 1C adipose CD36 transcripts displayed strikingly different relationships to measures of insulin sensitivity. There were no associations with transcript 1B despite its abundance in adipose tissue. On the other hand, strong correlations were observed with transcript 1C (Table 2 and Supplementary Fig. 3). Transcript 1C negatively correlated with IHTG content (\( P < 0.001 \)) and positively with liver (\( P < 0.001 \)), adipose tissue (\( P < 0.001 \)), and skeletal muscle (\( P < 0.0001 \)) insulin sensitivity. Expression of transcript 1A did not relate to insulin sensitivity systemically or at the
organ level. These findings suggest that adipocyte-specific transcript 1C is a sensitive marker of multiorgan (adipose, muscle, and liver) insulin sensitivity.

Adipose Transcript 1C Inversely Correlates With Visceral Fat Tissue

Our study cohort did not include lean subjects and had a relatively narrow BMI range (Table 1), which should minimize the confounding effects of BMI on metabolic parameters. However, equally obese subjects differ in the amount of VAT (21,22). Consistent with the strong relationship of this depot to insulin resistance, VAT volume inversely correlated ($P = 0.009$) to adipose tissue transcript 1C. Total adipose tissue CD36 mRNA showed a modest relationship to the percentage of FM, reflecting associations by both 1C and 1B transcripts (Table 2). Overall, all relationships observed between total and 1C adipose CD36 transcripts and measures of insulin sensitivity were not affected when the data were adjusted for BMI or VAT. This suggested that the correlations obtained were not driven by adiposity in this cohort.

Muscle CD36 Transcripts Associate With FA and VLDL Kinetics but Not With Insulin Sensitivity

Total adipose tissue CD36 mRNA negatively correlated with secretion rate of VLDL-TG and VLDL-apoB. Transcripts 1A,
1B, and 1C all negatively related to apoB-100 production rate, but only 1C showed a negative correlation with VLDL-TG production rate.

In skeletal muscle, there were no significant relationships between total or individual CD36 transcripts and measures of skeletal muscle or systemic insulin sensitivity (data not shown). However, muscle transcripts 1A and 1B and total CD36 mRNA correlated with FFA Rd, and a weaker correlation was observed with VLDL-TG clearance (Table 2).

Overall, the data presented in Table 2 showed a differential relationship between adipose and muscle CD36 transcripts as related to metabolic phenotypes. Adipose tissue transcripts positively correlated with multiple organ insulin sensitivity and inversely with hepatic secretion of VLDL while muscle transcripts positively associated with uptake of FFA and VLDL clearance.

Table 1—Characteristics of the study subjects

| Characteristic         | Mean (SD) |
|------------------------|-----------|
| Age, years             | 41 ± 2    |
| BMI, kg/m²              | 35.9 ± 0.6|
| Glucose, μU/mL          | 94 ± 0.93 |
| Insulin, μIU/mL         | 14.5 ± 1.2|
| IHTG, % liver volume   | 13 ± 2    |
| TGs, mg/dL             | 136 ± 9   |
| Total cholesterol, mg/dL| 170 ± 4   |
| HDL cholesterol, mg/dL  | 45 ± 2    |
| LDL cholesterol, mg/dL  | 100 ± 3   |

Values are mean ± SEM unless otherwise noted.

Table 2—CD36 transcripts in adipose tissue correlate positively with measures of insulin sensitivity while transcripts in skeletal muscle correlate with FFA Rd and VLDL clearance

| CD36 Transcripts | Total  | 1A     | 1B     | 1C     |
|------------------|--------|--------|--------|--------|
| Adipose tissue   |        |        |        |        |
| IHTG, %          | -0.39* | 0.08   | -0.24  | -0.49**|
| HSI              | 0.45*  | -0.02  | 0.27   | 0.47** |
| Insulin stimulation of glucose Rd, % | 0.27    | 0.23   | 0.22   | 0.57***|
| Insulin suppression of palmitate Ra, % | 0.52*   | 0.22   | 0.30   | 0.56** |
| VLDL-TG production rate, μmol/min | -0.45*  | -0.14  | -0.20  | -0.40* |
| VLDL-apoB100 production rate, μmol/min | -0.44*  | -0.49* | -0.55**| -0.49* |
| CD36 total mRNA  | —      | 0.27   | 0.58** | 0.68***|
| CD36 protein, %   | 0.75***| 0.32   | 0.46   | 0.58** |
| VAT, cm²          | -0.09  | -0.39* | -0.10  | -0.47* |
| FM, %             | 0.43*  | 0.05   | 0.47*  | 0.36*  |

Skeletal muscle

| CD36 Transcripts | Total  | 1A     | 1B     | 1C     |
|------------------|--------|--------|--------|--------|
| VLDL-TG clearance, mL/min | 0.35*  | 0.38*  | 0.40*  | -0.16 |
| FFA Rd, μmol/kg FFM/min | 0.58** | 0.45*  | 0.54** | -0.32 |

Shown are Spearman r correlations and corresponding P values. Protein expression level in arbitrary units. *P < 0.05. **P < 0.001. ***P < 0.0001. †n = 36. ‡n = 26 for skeletal muscle.
are common for mammalian genes (17). For CD36, alternative promoter usage confers tissue and cell-specific CD36 distribution and differential sensitivity to regulation. From a clinical perspective, aberrant use of a particular CD36 promoter could be a factor in metabolic abnormalities and might be relevant to disease mechanisms. Determining the CD36 tissue transcript profile in the context of obesity could provide useful clues related to the metabolic status of various tissues and to the potential mechanisms underlying obesity-associated complications such as metabolic syndrome, diabetes, and cardiovascular disease. CD36 downregulation has been proposed as an effective target in hyperlipidemia, insulin resistance, and inflammation (35,36). As more knowledge becomes available related to the regulation of individual CD36 transcripts, this might allow for the design of therapies that target select CD36 transcripts and specific tissues.

Our data show that adipocyte CD36, which is uniquely represented by 1C, predicts insulin sensitivity while there is lack of association with adipose 1B. This difference might reflect the independent regulation of the two adipose transcripts. While both the 1B and 1C promoters contain PPARG sites, unlike 1C, 1B lacks proximal (within 1 kb) C/EBP motifs, perhaps accounting for the stronger relation of 1C to adipose tissue PPARG and CEBPA mRNA expression. In addition, 1B has several conserved response elements for factors that impair insulin sensitivity (glucocorticoids [37], interferon-γ [38]) or are linked to inflammation (NFKB, CK2, Spl-1/PU.1) (39).

In muscle, the positive correlations observed between the major CD36 transcripts and the FFA rate of disposal and VLDL-TG clearance support the important quantitative role of muscle CD36 in serum lipid utilization in humans. The lack of association between muscle CD36 transcripts and insulin sensitivity that we report in this study does not rule out involvement of muscle CD36 in the etiology of insulin resistance. Our data

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**Figure 2**—CD36 common promoter SNP rs1761667 influences skeletal muscle CD36 expression and muscle glucose uptake. Expression is compared between genotype groups: (A) total skeletal muscle CD36 mRNA, (B) skeletal muscle 1B, and (C) skeletal muscle 1A. Sample size n = 12 A/A and 15 G/-.

_D:_ Insulin-stimulated muscle glucose uptake. Rs1761667 G/- genotype further impairs insulin-stimulated glucose uptake in subjects with high IHTGs. Subjects were subdivided into those having lower or higher than 5% IHTG. Rs1761667 genotype distribution in the subgroups: IHTG <5%, n = 8 A/A, and n = 17 G/-. For IHTG >5%, n = 11 A/A and n = 17 G/-; see Supplementary Table 2 for subject characteristics in the subgroups. AU, arbitrary units. *P = 0.01.
focused on the contribution of transcriptional regulation to tissue CD36 levels and as a result do not consider the impact of posttranscriptional regulation. Previous studies have documented alterations in intracellular trafficking and posttranslational processing of CD36 in the diabetic muscle (5,39,40). The data suggest that transcriptional regulation might play a more important role in determining CD36 function in adipose tissue as compared with muscle.

Our study demonstrates that the effects of a disease-associated CD36 SNP might be tissue and transcript specific, and this should be considered when evaluating the functional impact of particular SNPs and their clinical utility as potential biomarkers of disease susceptibility. CD36 SNP rs1761667 (A/G) worsened insulin resistance of muscle glucose disposal, and this effect could be consequential to its impact on the CD36 transcript profile, which influences how tissue CD36 is regulated in response to metabolic challenges. The finding that the effect of rs1761667 was only significant in the insulin-resistant subgroup of our cohort would be consistent with earlier findings showing an association between the rs1761667 SNP with coronary disease only in diabetic subjects (31).

In summary, these novel findings shed light on the physiological role of human CD36 and its genetic variants and highlight the link between CD36 and insulin resistance. The findings will be useful for designing therapeutic approaches that target tissue-specific CD36 transcripts in order to improve FA homeostasis and insulin resistance.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. T.A.P. and T.S. performed the gene expression studies and analyzed the data. C.C. collated and analyzed the metabolic data. E.F. collated and analyzed the metabolic data and edited the manuscript. B.W.P. contributed to metabolic data analysis. S.K. reviewed the interpretation of the metabolic data and edited the manuscript. N.A.A. designed the study, reviewed the data, and wrote the manuscript. L.L.-G. reviewed all the data analyses, designed the study, reviewed the data, and wrote the manuscript. N.A.A. and L.L.-G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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