Molecular Basis of Human CD36 Gene Mutations

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CD36 is a transmembrane glycoprotein of the class B scavenger receptor family. The CD36 gene is located on chromosome 7 *q11.2* and is encoded by 15 exons. Defective CD36 is a likely candidate gene for impaired fatty acid metabolism, glucose intolerance, atherosclerosis, arterial hypertension, diabetes, cardiomyopathy, Alzheimer disease, and modification of the clinical course of malaria. Contradictory data concerning the effects of antiatherosclerotic drugs on CD36 expression indicate that further investigation of the role of CD36 in the development of atherosclerosis may be important for the prevention and treatment of this disease. This review summarizes current knowledge of CD36 gene structure, splicing, and mutations and the molecular, metabolic, and clinical consequences of these phenomena.
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INTRODUCTION

CD36 is a type B scavenger receptor located on the surface of many types of cells. More than 20 mutations in the coding sequence of the CD36 gene that lead to type I receptor deficiency have been described, but the molecular basis of type II CD36 deficiency is still unclear. Different systems of nucleotide numbering in the CD36 gene are used by individual authors; thus descriptions of mutation locations are ambiguous. This review summarizes current knowledge of CD36 gene structure, splicing, and mutations and the molecular, metabolic, and clinical consequences of these phenomena.

STRUCTURE OF THE HUMAN CD36 GENE

The CD36 gene is located on chromosome 7 *q11.2* (1). The structural organization of the human CD36 gene was described by Armesilla et al. (2,3). The CD36 gene is encoded by 15 exons (Table 1). Exons 1, 2, and 15 are noncoding. Exons 3 and 14 encode N-terminal and C-terminal domains of the CD36 protein, respectively (3). Interestingly, the 5′-untranslated region of CD36 mRNA is encoded by 3 exons. Exon 3 contains the last 89 nucleotides of the 5′-untranslated region and encodes the N-terminal cytoplasmic and transmembrane domains (2). The 3′-untranslated region is contained in exon 14 only or in exons 14 and 15 (3).

CD36 LOCATION

CD36 is present on the surface of platelets, endothelial cells, macrophages, dendrite cells, adipocytes, striated muscle cells, and hematopoietic cells (4–9).

CD36 GENE EXPRESSION REGULATION

CD36 gene expression is tissue dependent. In adipocytes, the nuclear peroxisome proliferation activator receptor γ (PPARγ) is the critical factor for feedback control of the CD36 gene (10–13). In monocytes, receptor expression can be upregulated by adhesion and by action of cytokines (such as M-CSF and GM-CSF), native and modified LDL, cellular cholesterol, interleukin-4, insulin, and glucose (14–17). Expression is inhibited by TGF-β, corticosteroids, HDL, and LPS (lipopolysaccharides) (14,17–19). CD36 expression in the heart and skeletal muscles is increased by triacylglycerides (TG) and fatty acids (FA) in plasma and regulated by energy requirements of the tissue (20).

ALTERNATIVE SPLICING

A marked feature of the CD36 gene is the presence of several (at least five) alternative and independent first exons and their promoters, which lack TATA-boxes and CpG islands (21). Another alternative promoter and first exon have recently been identified downstream of exon 2 (22). Alternative splicing of the first CD36 exon appears to be regulated differently in different tissues, indicating that the promoters are tissue specific. The alternative transcripts are all expressed in more than one human tissue, and their expression patterns are highly variable in skeletal muscle, heart, liver,

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Table 1. Exons, Introns, and Mutations in the Human CD36 Gene

Exon number	Next intron length	mRNA nucleotides[a]	Amino acids encoded	Change in nucleotide sequence[b]	Change in amino acid sequence	Ref.
1	7341 (43708)[c]	–289 to –184 (–356 to –184)[c]	None			
2	470	–183 to –90	None	del *exons 1–3*	no expression of CD36 protein	59
3	9679	–89 to +120	1–40			
4	4362	121–281	41–94	*C268T*	Pro90Ser	48
5	1779	282–429	94–143	319–324delGCTGAG	inframe del AA 107–108	55
				329–330del *AC*	frameshift at AA 110	55
				G367A	Glu123Lys	49
				C380T	Ser127Leu	50
				T411C	Ala137Val	51
6	1236	430–609	144–203	*560insT*	frameshift at AA 187	56
7	1945	610–701	204–234	619–624del *ACTGCA*/ins *AAAAC*	frameshift at AA 207	57
				691–696del *AAAGGT*	inframe del AA 231–232	53
8	3463	702–748	234–250			
9	954	749–818	250–273	*T760C*	Phe254Leu	52
10	757	819–1006	273–336	845–849del *ACGTT*	frameshift at AA 282	53
				949ins*A*	frameshift at AA 317	58
				T975G	Tyr325Term	53
11	729	1007–1125	336–375	*T1079G*	Leu360Term	54
12	511	1126–1199	376–400	Del tttagAT	skipping *exon 12*	56
				1140–1146delTTTACAA/ins*CCAAA*	frameshift at AA 380	53
				G1150C + 1155del*A*	Ala384Pro + frameshift at AA 385	53
13	573	1200–1254	400–418	del *tattacagAG*	skipping *exon 13*	56
				dupl. 1204–1246	frameshift at AA 416	56
				1218–1224del*GAGGAAC*	frameshift at AA 406	57
				1228-1239del*ATTGTGCCTATT*	deletion of Ile-Val-Pro-Ile	56,57
				A1237C	Ile413Leu	52
14	2236[d]	1255–1688 (1255–1419)[d]	419–472			
15[d]	—	1420–2044[d]	None			

[a]Genbank NM 000072; the first mRNA nucleotide encoding CD36 protein is +1.
[b]Lowercase nucleotides are located in an intron.
[c]Alternatively spliced exon 1 (Genbank NM 001001547).
[d]At position 1709 within exon 14, there is an internal splicing donor site that can join nucleotide 1419 to the first nucleotide of exon 15, thus generating an alternative CD36 mRNA form (Genbank NM 001001548) containing exon 15 (3).

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  1 ATG GGC TGT GAC CGC AAC TGT GGG CTC ATC GCT GGG GCT GTC ATT GGT
  1 Met Gly Cys Asp Arg Asn Cys Gly Leu Ile Ala Gly Ala Val Ile Gly

 49 GCT GTC CTG GCT GTG TTT GGA GGT ATT CTA ATG CCA GTT GGA GAC CTG
 17 Ala Val Leu Ala Val Phe Gly Gly Ile Leu Met Pro Val Gly Asp Leu

 97 CTT ATC CAG AAG ACA ATT AAA AAG CAA GTT GTC CTC GAA GAA GGT ACA
 33 Leu Ile Gln Lys Thr Ile Lys Lys Gln Val Val Leu Glu Glu Gly Thr

145 ATT GCT TTT AAA AAT TGG GTT AAA ACA GGC ACA GAA GTT TAC AGA CAG
 49 Ile Ala Phe Lys Asn Trp Val Lys Thr Gly Thr Glu Val Tyr Arg Gln

193 TTT TGG ATC TTT GAT GTG CAA AAT CCA CAG GAA GTG ATG ATG AAC AGC
 65 Phe Trp Ile Phe Asp Val Gln Asn Pro Gln Glu Val Met Met Asn Ser

241 AGC AAC ATT CAA GTT AAG CAA AGA GGT CCT TAT ACG TAC AGA GTT CGT
 81 Ser Asn Ile Gln Val Lys Gln Arg Gly Pro Tyr Thr Tyr Arg Val Arg
                                        Ser

289 TTT CTA GCC AAG GAA AAT GTA ACC CAG GAC GCT GAG GAC AAC ACA GTC
 97 Phe Leu Ala Lys Glu Asn Val Thr Gln Asp Ala Glu Asp Asn Thr Val

337 TCT TTC CTG CAG CCC AAT GGT GCC ATC TTC GAA CCT TCA CTA TCA GTT
113 Ser Phe Leu Gln Pro Asn Gly Ala Ile Phe Glu Pro Ser Leu Ser Val
                                            Lys               Leu

385 GGA ACA GAG GCT GAC AAC TTC ACA GTT CTC AAT CTG GCT GTG GCA GCT
129 Gly Thr Glu Ala Asp Asn Phe Thr Val Leu Asn Leu Ala Val Ala Ala
                                    Ala

433 GCA TCC CAT ATC TAT CAA AAT CAA TTT GTT CAA ATG ATC CTC AAT TCA
145 Ala Ser His Ile Tyr Gln Asn Gln Phe Val Gln Met Ile Leu Asn Ser

481 CTT ATT AAC AAG TCA AAA TCT TCT ATG TTC CAA GTC AGA ACT TTG AGA
161 Leu Ile Asn Lys Ser Lys Ser Ser Met Phe Gln Val Arg Thr Leu Arg
                                                T
529 GAA CTG TTA TGG GGC TAT AGG GAT CCA TTT TTG AGT TTG GTT CCG TAC
177 Glu Leu Leu Trp Gly Tyr Arg Asp Pro Phe Leu Ser Leu Val Pro Tyr
                                                          AAA AC
577 CCT GTT ACT ACC ACA GTT GGT CTG TTT TAT CCT TAC AAC AAT ACT GCA
193 Pro Val Thr Thr Thr Val Gly Leu Phe Tyr Pro Tyr Asn Asn Thr Ala

625 GAT GGA GTT TAT AAA GTT TTC AAT GGA AAA GAT AAC ATA AGT AAA GTT
209 Asp Gly Val Tyr Lys Val Phe Asn Gly Lys Asp Asn Ile Ser Lys Val

673 GCC ATA ATC GAC ACA TAT AAA GGT AAA AGG AAT CTG TCC TAT TGG GAA
225 Ala Ile Ile Asp Thr Tyr Lys Gly Lys Arg Asn Leu Ser Tyr Trp Glu

721 AGT CAC TGC GAC ATG ATT AAT GGT ACA GAT GCA GCC TCA TTT CCA CCT
241 Ser His Cys Asp Met Ile Asn Gly Thr Asp Ala Ala Ser Phe Pro Pro
                                                        Leu

769 TTT GTT GAG AAA AGC CAG GTA TTG CAG TTC TTT TCT TCT GAT ATT TGC
257 Phe Val Glu Lys Ser Gln Val Leu Gln Phe Phe Ser Ser Asp Ile Cys

817 AGG TCA ATC TAT GCT GTA TTT GAA TCC GAC GTT AAT CTG AAA GGA ATC
273 Arg Ser Ile Tyr Ala Val Phe Glu Ser Asp Val Asn Leu Lys Gly Ile

865 CCT GTG TAT AGA TTT GTT CTT CCA TCC AAG GCC TTT GCC TCT CCA GTT
289 Pro Val Tyr Arg Phe Val Leu Pro Ser Lys Ala Phe Ala Ser Pro Val

                                                A
913 GAA AAC CCA GAC AAC TAT TGT TTC TGC ACA GAA AAA ATT ATC TCA AAA
305 Glu Asn Pro Asp Asn Tyr Cys Phe Cys Thr Glu Lys Ile Ile Ser Lys

961 AAT TGT ACA TCA TAT GGT GTG CTA GAC ATC AGC AAA TGC AAA GAA GGG
321 Asn Cys Thr Ser Tyr Gly Val Leu Asp Ile Ser Lys Cys Lys Glu Gly
                    END

1009 AGA CCT GTG TAC ATT TCA CTT CCT CAT TTT CTG TAT GCA AGT CCT GAT
337 Arg Pro Val Tyr Ile Ser Leu Pro His Phe Leu Tyr Ala Ser Pro Asp

1057 GTT TCA GAA CCT ATT GAT GGA TTA AAC CCA AAT GAA GAA GAA CAT AGG
353 Val Ser Glu Pro Ile Asp Gly Leu Asn Pro Asn Glu Glu Glu His Arg
                                END
                                                C CAA A
1105 ACA TAC TTG GAT ATT GAA CCT ATA ACT GGA TTC ACT TTA CAA TTT GCA
369 Thr Tyr Leu Asp Ile Glu Pro Ile Thr Gly Phe Thr Leu Gln Phe Ala
                                                                Pro

1153 AAA CGG CTG CAG GTC AAC CTA TTG GTC AAG CCA TCA GAA AAA ATT CAA
385 Lys Arg Leu Gln Val Asn Leu Leu Val Lys Pro Ser Glu Lys Ile Gln

1201 GTA TTA AAG AAT CTG AAG AGG AAC TAT ATT GTG CCT ATT CTT TGG CTT
401 Val Leu Lys Asn Leu Lys Arg Asn Tyr Ile Val Pro Ile Leu Trp Leu
                                                    Leu

1249 AAT GAG ACT GGG ACC ATT GGT GAT GAG AAG GCA AAC ATG TTC AGA AGT
417 Asn Glu Thr Gly Thr Ile Gly Asp Glu Lys Ala Asn Met Phe Arg Ser

1297 CAA GTA ACT GGA AAA ATA AAC CTC CTT GGC CTG ATA GAA ATG ATC TTA
433 Gln Val Thr Gly Lys Ile Asn Leu Leu Gly Leu Ile Glu Met Ile Leu

1345 CTC AGT GTT GGT GTG GTG ATG TTT GTT GCT TTT ATG ATT TCA TAT TGT
449 Leu Ser Val Gly Val Val Met Phe Val Ala Phe Met Ile Ser Tyr Cys

1393 GCA TGC AGA TCG AAA ACA ATA AAA TAA
465 Ala Cys Arg Ser Lys Thr Ile Lys END
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Figure 1. cDNA nucleotide and amino acid sequences of CD36 with mutations indicated as follows: substitutions (underline), *deletions* (line over and usually italic), **insertions** (bold) (based on: http://snpper.chip.org).

adipose tissue, placenta, spinal cord, cerebrum, and monocytes (21).

Alternative splicing of 5′-untranslated and 3′-untranslated exons in CD36 pre-mRNA accounts for some of the heterogeneity in the molecular size of CD36 mRNA (23,24). All the splice acceptor and donor sequences conform to the consensus rule for splicing. Of the 11 splice junctions found around coding exons, type 0 occurs between codons, type 1 occurs after the first nucleotide, and type 2 occurs after the second nucleotide of a codon. Such diversity in the type of intron phase limits the number of mRNA forms that might arise by exon deletion while maintaining the same open reading frame (3). Alternatively spliced coding exons can be detected in CD36-expressing cells (24).

The functional diversity of CD36 may result from alternative splicing of CD36 pre-mRNA. Skipping of coding exons 4 and 5 gives rise to a CD36 isoform that lacks 103 amino acid residues, 41–143, and three potential N-glycosylation sites (25).

Andersen et al. have suggested that the molecular mechanisms regulating the CD36 gene expression are unusually complex, reflecting the multifunctional role of CD36 in different tissues and conditions (21).

PROTEIN STRUCTURE

CD36 is a transmembrane glycoprotein of the class B scavenger receptor family (26–28). Synonym names of CD36 are platelet glycoprotein, GPIV, glycoprotein IIIb, GPIIIB, leukocyte differentiation antigen CD36, CD36 antigen, SR-BI, PAS IV, PAS-4 protein, platelet collagen receptor, fatty acid translocase, FAT, and thrombospondin (TSP) receptor.

According to the nucleotide sequence, CD36 mRNA (Genbank: NM 000072) codes for 472 amino acids (AA) (SwissProt: P16671; Figure 1). The mature polypeptide is 471 AA long, beginning at the AA residue immediately following the initiator methionine (4). The molecular mass of the functional receptor is 78–88 kDa, depending on the cell type and on post-translational glycosylations (4,6,25). The receptor consists of 1 extracellular, 2

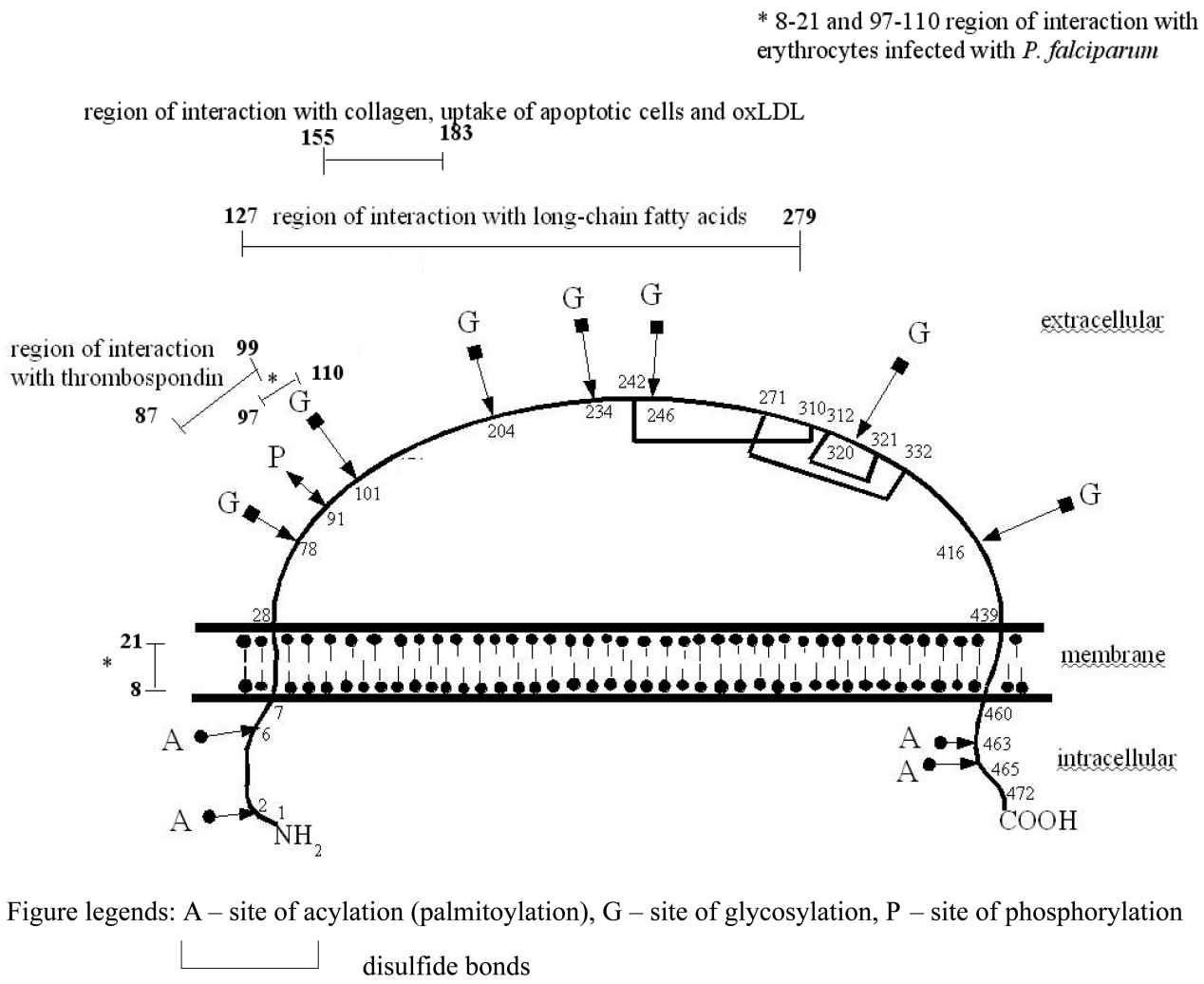

Figure 2. Diagram of CD36 structure, based on (23,39,41,49).

transmembrane, and two cytoplasmic fragments representing the C-terminal and N-terminal parts of the molecule (3). The cytoplasmic and transmembrane regions predicted at both terminal ends of the polypeptide chain are encoded by the single exons 3 and 14. The translation start codon is located 289 (or 356 with alternatively spliced exon 1) nucleotides downstream of the 5′-end of CD36 mRNA (25). The large number of exons encoding the highly glycosylated extracellular domain (exons 4–13 and part of exon 14) may be a consequence of the multiplicity of interactions in which CD36 seems to be involved (3).

There are no free cysteines in CD36, and the six centrally clustered cysteines are linked by disulfide bonds: Cys242/Cys310, Cys271/Cys332, and Cys312/Cys321, resulting in a 1-3, 2-6, and 4-5 arrangement of the disulfide bridges (3). A diagram of the CD36 structure is presented in Figure 2.

POSTTRANSLATIONAL MODIFICATIONS

The protein has two short intracellular segments (residues 1–6 and AA 461–472) that may undergo acylation (palmitoylation, Figure 2), and two transmembrane domains (residues 7–28 and AA 439–460) potentially acylated near the intracellular side of the membrane (29). The remaining part of CD36 is extracellular, comprising 7 glycosylation sites and 3 disulfide bridges (6,29,30).

CD36 FUNCTIONS

The CD36 functions presented in Table 2 include removal of oxidized LDL from plasma (in macrophages and monocytes) (10,31–34), apoptosis induction (together

Table 2. Functions of the CD36 receptor

Function	Type of cells[a]	Domain location (Ref)
Thrombospondin receptor	Monocytes, platelets, some cancer cells	87–99 AA (46) or 93–110 and 139–155 AA (45)
Receptor for erythrocytes infected with *Plasmodium falciparum*	Monocytes, endothelial cells, some cancer cells	8–21 and 97–110 AA (4,38)
Collagen receptor	Platelets	(?)155–183 AA (3,43)
Uptake of apoptotic cells	Macrophages	155–183 AA (35–37)
Receptor for oxidized LDL (oxLDL)	Macrophages, monocytes	155–183 AA (10,31–34)
Long-chain fatty acid receptor	Endothelial cells, adipocytes, platelets	127–279 AA (39,40)

AA amino acids. [a]The list of cell types is incomplete and mentions only the most studied ones.

with other membrane proteins such as $\alpha_v\beta_3$ integrin and thrombospondin 1) (35–37), and enhancement of cytoadherence of abnormally shaped erythrocytes (infected with *Plasmodium falciparum* or containing hemoglobin S) (4,38). CD36 is a long-chain fatty acid receptor (39,40) with a potential binding site for the fatty acids in its extracellular segment between residues 127 and 279 (39). CD36 is also an adhesion molecule capable of interacting with collagen type I and IV and with thrombospondin (5,41–44). Leung et al. reported that the CD36-TSP interaction is a two-step process; the AA 139–155 region of CD36 binds first to TSP (thrombospondin), triggering a change in TSP structure, which then reveals a second site that binds the AA 93–110 region of CD36 with high affinity (45). On the other hand, Asch et al. (46) reported that three functional sequences exist; one of these mediates TSP binding (AA 87–99) and two other support malarial cytoadhesion (AA 8–21 and AA 97–110). The data reported by Asch et al. also suggest that CD36 ligand specificity is directed by the extracellular release or activation of threonine phosphatase in response to a platelet agonist and that CD36 dephosphorylation may affect signaling. Phosphorylation was observed to inhibit TSP binding to the peptide by 60% (46). Ren et al reported that transfection of the macrophage adhesion molecule CD36 into human Bowes melanoma cells specifically conferred greatly increased capacity, comparable to that exhibited by macrophages, to ingest apoptotic neutrophils, lymphocytes, and fibroblasts (35).

CD36 GENE MUTATIONS

Different systems of nucleotide numbering in the CD36 gene are used by individual authors. Therefore, to standardize the nomenclature, we consistently use the numbering system in which the position of the first protein-encoding mRNA nucleotide is +1 (Figure 1). This position corresponds to nucleotide +211 according to the nomenclature used by Kashiwagi et al. (47).

The following mutations in the CD36 gene (presented in Table 1) have been described so far: nucleotide substitutions (47–54), small deletions (53,55–57), small insertions (56,58), small indels (53,57), gross deletion (59), duplication (56), complex rearrangements (53), and repeat variation, a dinucleotide repeat (TG)n in intron 3 (50,60), where the repeat number n = 12 is involved in the nonproduction of the variant CD36 transcript that lacks exons 4 and 5 (50).

MOLECULAR CONSEQUENCES OF CD36 GENE MUTATIONS

CD36 deficiency is divided into two subgroups according to the phenotypes. In type I deficiency, neither platelets nor monocytes express CD36, whereas in type II deficiency (very rare in whites, 0.3% of the population, more frequent in Asians and Afro-Americans, 3%–4% of the population), CD36 is expressed in monocytes but not in platelets (7,44).

TYPE I DEFICIENCY

The type I CD36 deficiency is most commonly detected in subjects who are homozygous or compound heterozygous for the following three mutations: *C268T*, *949insA*, and *329-330delAC* (18,61). A survey of the CD36 mutations in type I CD36 deficiency has revealed that *C268T* is the most common mutation, and is responsible for more than 50% of the mutated allele frequency in Asians (57). This mutation is the most frequent factor responsible for the absence of CD36 receptor expression in platelets and monocytes/macrophages (47,48). Substitution leads directly to CD36 deficiency via posttranslational modification defects (probably due to defective glycosylation of the 81 kDa protein). In an expression assay using the *C268* or *T268* form of CD36 cDNA-transfected cells, the substitution markedly impaired maturation of the 81-kDa precursor to the 88-kDa mature form of CD36 (47,48). The mutated precursor form of CD36 was subsequently degraded in the cytoplasm.

Another mutation responsible for type I deficiency—deletion of 12 bp, ATTGTGCCTATT, at *nt. 1228–1239* (exon 13)—is present with or without skipping of exon 9 (*nt. 749–818*). The mechanism of exon 9 skipping is unknown because there are no mutations at the junction sites of exon 9. The 12-bp deletion leads to an inframe 4-AA deletion, whereas exon 9 skipping leads to a frameshift and appearance of a premature stop codon. In an expression assay, both *1228–1239del* and exon 9 skipping directly caused impairment of the surface expression of CD36 (57).

Individuals with type I CD36 deficiency may be at risk of developing an

anti-CD36 isoantibody after receiving a transfusion or during pregnancy (44).

TYPE II DEFICIENCY

The genomic or molecular background of type II CD36 deficiency is not clearly understood and is probably heterogenous, leading to confounding interpretations of cause-and-effect relationships in human CD36 deficiency (18,51,61). Type II CD36 deficiency has been observed in individuals who lack a CD36 mutation but have a heterozygous mutation (most often *C268T*). The genotype-phenotype correlations indicated that the platelet CD36 protein expression level was regulated by other heritable platelet-restricted factors in addition to the CD36 coding region genotype (51). Kashiwagi et al. observed (47,55,57) that monocyte CD36 cDNA samples from two subjects with type II deficiency were heterozygous for the *C268* and *T268* forms, whereas their platelet CD36 cDNA consisted of only the *T268* form.

As reported by Lipsky et al., in the Japanese population 6 different alleles (*A1* to *A6*) of the CD36 gene were detected according to the size of a $(TG)_n$ repeat within intron 3 (60). To explain the tangled phenotype-genotype correlation in type II CD36 deficiency, Kashiwagi et al. hypothesized the "platelet-specific silent allele" and predicted its linkage to the *A5* allele, which encodes $(TG)_{12}$ (42,60). However, no DNA sequence corresponding to such a platelet-specific silent allele has yet been identified. Yanai et al. investigated the polymorphic site in the 5′-proximal flanking region and the 3′-untranslated region (61). According to these authors, an altered DNA sequence in or near the 3′-untranslated region may change the structure of mRNA and its stability in CD36 deficiency. Yanai et al. suggested that if the proposed platelet-specific silent allele exists, it may be remote to the CD36 gene, because the previously reported linkage with the *A5* allele was not confirmed.

METABOLIC CONSEQUENCES OF CD36 GENE MUTATIONS

CD36 may play an important role in the pathogenesis of some metabolic diseases. The receptor is responsible for the removal of approximately 50% of oxidatively modified LDL (ox-LDL) from plasma (10,31). Binding takes place in the 155–183 amino acid region of the protein (34). Long-chain fatty acids (FA) are the main ligand for the receptor (26). Reduced expression of CD36 protects the vessels, according to some authors (62,63), and some have pointed out that CD36 gene mutations are associated with increased serum concentrations of total cholesterol and LDL (18,64). Other investigators have reported significant decreases in binding and uptake of ox-LDL in peritoneal macrophages of null mutation mice (65). Kashiwagi et al. demonstrated a marked reduction in the uptake of ox-LDL by CD36-deficient macrophages, a finding that suggests that differences in atherosclerosis may occur in type I or type II CD36-deficient individuals and CD36-positive individuals. In type II–deficient subjects, alleles having hypothetical platelet-specific mRNA transcription defects may be involved (42). Type I and type II deficiencies are believed to differ in their effects on the course of atherogenesis. Ox-LDL plays a role in macrophage transformation to foam cells, but the absence of expression of the macrophage CD36 can cause retention of ox-LDL in plasma (8,31,66).

Other authors have observed abnormalities of glucose and lipid metabolism in type I CD36 deficiency. For example, increased plasma triglycerides, decreased HDL-cholesterol, impaired glucose tolerance, and delayed response of insulin secretion (57,67). Kadlecova et al. proposed that defective CD36 is probably a candidate gene for disordered fatty-acid metabolism, glucose intolerance, and insulin resistance in spontaneously hypertensive rats (SHR), but other genes may also play a role in the pathogenesis of the metabolic syndrome in *Prague* hereditary hypertriglyceridemic rats (68). As shown by Glazier, chromosomal deletion at the CD36 locus in SHR was mediated by unequal recombination between the CD36 gene and the second pseudogene CD36-ps2, and was induced by extensive homology between these sequences. This recombination resulted in the creation of a single chimeric gene in SHR. The trait of insulin resistance and defective fatty acid metabolism is probably caused by CD36 deficiency (69). Recently, CD36 has been reported to play an important role in atherogenicity. To understand the role of CD36, it is important to clarify the condition of CD36-deficient subjects. Some authors suggest that upregulation of class B scavenger receptors could have therapeutic potential for the treatment of atherosclerosis (70,71). CD36 expression in tissues with very active fatty acid metabolism (skeletal muscle, heart, mammary epithelium, and adipose tissue), and its involvement in foam cell formation (macrophages), suggest that lipoprotein binding to CD36 might contribute to the regulation of lipid metabolism and to the pathogenesis of atherosclerosis (72).

Long-chain fatty acids (LCFA) are the major energy substrate for the heart, and their oxidation is important to ensure maximum cardiac performance. CD36 acts as a major myocardial-specific LCFA transporter in humans (73,74). FA translocase/CD36 is probably involved in regulating FA oxidation along with the well-known regulator carnitine palmitoyltransferase I (74). Some authors suggest that polymorphisms at the CD36 gene modulate lipid metabolism and cardiovascular risk in whites (75,76). Homozygous or compound heterozygous mutations of the CD36 gene in humans result in severe defects of the uptake of long-chain fatty acids (LCFAs) in the heart (56,77). Type I CD36 deficiency is closely related to the absence of LCFA accumulation and metabolism in the myocardium (19,78). CD36 deficiency leads also to decreased myocardial accumulation of ^{123}I-BMIPP (iodine-123-(R,S)-15-(p-iodophenyl)-3-methylpentadecanoic acid) (79). Tanaka et al. hypothesized that this deficiency is a possible etiology of

hereditary hypertrophic cardiomyopathy (HCM) (80). Some patients with HCM demonstrate abnormal myocardial LCFA metabolism. Data reported by Okamoto et al. suggest that abnormal myocardial LCFA metabolism seen in HCM patients may be related to abnormality of the CD36 molecule, and that abnormalities of this molecule may be the cause of some HCM types. On the other hand, patients in the Okamoto et al. study with apical HCM showed normal CD36 molecule expression and no severe impairment of myocardial BMIPP accumulation. Thus, abnormalities of the CD36 molecules may be related to the pathogenesis of some HCM types (81). Moreover, some CD36 mutations found in persons in Thailand are associated with reduced risk of cerebral malaria (50,60). In Africans, such mutations may be maintained by unidentified selection pressures and probably protect against some infections other than malaria (53).

PERSPECTIVES

Since the CD36 receptor was first isolated in 1973 (82), its function has been associated with an increased risk of or protection against many pathological conditions, including metabolic diseases. There are indications that abnormalities of the CD36 gene are implicated in the pathogenesis of hypercholesterolemia, peripheral vessel atherosclerosis, arterial hypertension, diabetes, cardiomyopathy, Alzheimer disease, and malaria (9,10,16,25,83–86). An animal model revealed that lack of CD36 expression restrained atherosclerosis (87). Increased expression of CD36 was shown in atheroslerotic plaques and in damaged vascular tissue (88). Contradictory data (89–91) concerning the effects of antiatherosclerotic drugs on CD36 expression indicate the necessity for further investigation of the role of CD36 in the development of atherosclerosis. The results may be important for the prevention and treatment of this disease. The association between cardiovascular risk and CD36 deficiency should be analyzed in extensive prospective studies in various populations.

The spectrum of CD36 mutations differs in various populations. The influence on CD36 expression of polymorphisms in noncoding regions of the CD36 gene is currently under investigation. Further research is needed to characterize the roles of numerous alternative CD36 transcripts and tissue-specific promoters. The results of these studies may elucidate the still unclear molecular background of type II CD36 deficiency.

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