REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Cluster of differentiation (CD-36) as promising marker for many diseases

Morkoss M. Fakhry[a], Asmaa R. Abdel-Hamed[b], Dina M. Abo-elmatty[b], Noha M. Mesbah[b], Ahmed Al-Sawaf [c], Omnia Ezzat[a], Hussein AL-Sawaf [a]

[a.] *Department of Biochemistry , Faculty of Pharmacy, Egyptian Russian University. Cairo - Egypt*

[b.] *Biochemistry Department, Faculty of Pharmacy, Suez Canal University. Ismailia- Egypt*

[c.] *Gynacology and obstetrics Department, Faculty of Medicine, Cairo University. Cairo- Egypt*

Received on: 16. 06. 2020

Revised on: 23. 10. 2020

Accepted on: 29. 10. 2020

*Correspondence Author:

Tel: +201010202433

E-mail address:

morkoss-medhat@eru.edu.eg

Abstract

CD36 is a transmembrane protein involved in fatty acid translocation, scavenging for oxidized fatty acids acting as a receptor for adhesion molecules. It is expressed on macrophages, as well as other types of cells, such as endothelial and adipose cells. CD36 participates in muscle lipid uptake, adipose energy storage, and gut fat absorption. Recently, several preclinical and clinical studies demonstrated that the upregulation of CD36 is a prerequisite for tumor metastasis. Cancer metastasis-related research emerged much later and has been less investigated, though it is equally or even more important. CD36 protein expression can be modified by epigenetic changes and post-transcriptional interference from non-coding RNAs. Some data indicate modulation of CD36 expression in specific cell types by epigenetic changes via DNA methylation patterns or histone tails, or through miRNA interference, but this is largely unexplored. The few papers addressing this topic refer mostly to lipid metabolism-related pathologies, whereas in cancer research, data are even more scarce. The aim of this review was to summarize major epigenetic and post-transcriptional mechanisms that impact CD36 expression in relation to various pathologies while highlighting the areas in need of further exploration.

Key words: CD-36, Marker, Cluster

1.Cluster of differentiation (CD-36)

1. 1. Cluster of differentiation (CD-36) and its different names.

Cluster of differentiation 36 is a membrane glycoprotein present on the surfaces of many cells like platelets, mononuclear phagocytes, adipocytes, hepatocytes, myocytes, and epithelia (Silverstein & Febbraio, 2010).There are other names of CD-36 such as platelet glycoprotein 4, fatty acid translocase (FAT),and scavenger receptor class B member 3 (SCARB3). Cluster determinant 36 (CD36) gene is up-regulated in patients who suffer from essential hypertension(Liu, et al, 2013). CD-36 has other names like, GPIV, GPIIIb, PAS IV, or FAT(Abumrad,et al, 1993) (PrabhuDas et al., 2014).

1.2. Structure, sites and other names of CD-36:

Cd-36 was first isolated from platelets (Tandon,et al, 1989). It is also present in immune cells, adipocytes, myocytes, enterocytes, enteroendocrine cells, retinal and mammary epithelial cells, and microvascular endothelial cells., CD36 has distinctive structural features including a hairpin-like membrane topology with double transmembrane domains and with both termini in the cytoplasm**.** The heavily glycosylated extracellular domain of CD36 contains three disulfide bridges in the carboxyl-terminal half that are critical for CD36 membrane function. The amino-terminal half contains binding sites for hexarelin, FA, oxidized LDL or phospholipids, thrombospondin, and Plasmodium falciparum–infected erythrocytes(Collot-Teixeira,et al, 2007)**.** (Figure 2).

1.3 Pathologies involving CD-36

A- CD-36 and athrosclerosis :

Cluster of differentiation 36 is involved in the progression of atherosclerosis so if we make a genetic deletion of CD36 or blockage of the CD36-induced signalling cascade it will reduce atherosclerotic lesion formation. CD36 has significant roles in many stages of the atherogenic process and consequently can be regarded as an important molecule in the progression of atherosclerosis (Park, 2014).

B- CD36 and Metastasis:

Cluster of differentiation 36 proposed as a prognostic marker in various cancers, mostly of epithelial origin (breast, prostate, ovary, and colon) and also for hepatic carcinoma and gliomas. Data from clinical models of various cancers showed that blocking CD36 might prove beneficial in stopping metastasis spread (Enciu et al., 2018)

C- CD36 and cerebral amyloid angiopathy

CD36 involved in vascular amyloid deposition in brain. This suggest that CD-36 receptor is a putative therapeutic target for cerebral amyloid angiopathy and related conditions (Sarnyai et al., 2000)

D- CD-36 and Malaria

Cluster of differentiation 36 plays an important roles in immunity to malaria, including the sequestration of parasite-infected erythrocytes in microvascular capillaries (Gowda et al., 2013).

1.4 CD-36 gene location in human genome

Cytogenetic Location: 7q21.11, which is the long (q) arm of chromosome 7 at position 21.11 and encoded by 15 exons.
Molecular Location: base pairs 80,602,188 to 80,679,277 on chromosome 7 (Fakhry et al., 2020) (Rać, et al, 2007) (Figure1) .

1.5 Function of CD-36

Functions of CD-36 differ from cell to cell as shown in this table (Silverstein & Febbraio, 2009)

1.6 Polymorphisms of the CD 36 gene and relations to many diseases.

The fatty acid translocase CD36 has been the subject of much of the research related to long chain fatty acid (LCFA) taste perception. CD36 is expressed in human (Simons,et al, 2011a), and has a strong affinity for LCFA (Baillie, et al, 1996a). CD36 knockout mice are unable to detect LCFA in behavioral tests (Sclafani,et al, 2007). The oral 7 perception of linoleic acid (an n-6 polyunsaturated fatty acid), α-linolenic acid (an n-3 polyunsaturated fatty acid), and oleic acid (an n-9 monounsaturated fatty acid) have been attributed to the CD36 TBC receptor (Hochheimer et al., 2014). Additionally, a GPCR has been found to bind LCFA and influences the perception of lipids in the oral cavity. GPCR120-null mice show decreased preference for LCFA-enriched solutions in eating behavioral tests compared to wild type (Cartoni et al., 2010). Thus, LCFA as gustatory stimuli are more complex than initially understood. The consumption of energy-dense foods may be linked to enhanced palatability of dietary fats which predispose individuals to metabolic complications (Stewart, et al, 2011). The relationship between sensory fat perception and predisposition to weight gain has been shown in adult human studies (Liang et al., 2012). This relationship outlines the remarkable difference in obese and lean subjects with respect to fat intake and taste sensitivity.

In an obese rat model, an inverse correlation between gustatory sensitivity to LCFAs and dietary preference for fat was observed (Liang et al., 2012). Correspondingly, a higher sensitivity to tasting LCFA has been correlated to reduced fat intake, total caloric intake, and body mass index (BMI). Similarly, a high-fat diet decreased the taste sensitivity to oleic acid in lean, but not obese patients (Stewart & Keast, 2012). These observations suggest that a lack of sensitivity to fat taste increases fat intake and may partly explain why obese adult individuals seem to consume fatty foods more frequently than lean patients. Therefore, the implications of these findings on eating patterns and health have potential significance. A study by Ma et al. investigated associations between common SNPs in the CD36 gene and lipid and glucose metabolism, and risk for cardiovascular disease (Ma et al., 2004). This group genotyped 21 polymorphisms which evenly spanned the CD36 gene, revealing 2 linkage disequilibrium (LD) blocks represented by a haplotype. The haplotype comprised the following five SNPs: 1) -33137A/G (rs1984112; MAF (Major allale frequency)=0.3468), 2) -31118G/A (rs1761667; MAF=0.3904, 3) 25444G/A (rs1527483; MAF=0.1018), 4) 27645 deletion /insertion (del /in) (rs3840546; MAF not reported) and 5) 30294G/C (rs1049673; MAF=0.3832). In humans and pigs CD36 is the putative orosensory receptor for dietary LCFA and may be involved in the preference for fatty foods. (Simons,et al, 2011b) A similar increase in plasma FFA levels was seen in men carrying the -33137A and -31118G polymorphisms. In the order of SNPs

listed above, the haplotype of an individual can be represented by sequentially naming the nucleotide bases. Men with the AGGIG haplotype had 31% higher FFA and 20% higher plasma triglycerides (TG) than non-carriers. CD36 modulated lipid metabolism and CVD risk in adults of European descent. However, it is unclear whether this modulation occurred at the level of taste perception or metabolism. Further research is required to discern the effects of taste perception and lipid transport on the levels of FFA and TG in the plasma, or if this modulation would also be seen in other ethnicities. CD36 plays an important role in lipid metabolism and polymorphisms within the CD36 gene have been linked to CVD risk factors (Noel et al., 2010).

The relationship between genotypes and haplotypes of five SNPs in the CD36 gene (-33137G, -31118A, -22674C (rs2151916; MAF=0.3339), 27645 del/ins and 30294C) with lipid levels were examined in young normal-weight subjects (Ramos-Arellano et al., 2013). High-density lipoprotein cholesterol (HDL-C) levels were lower in -22674C carriers than -22674T carriers, and TT homozygotes had lower oxidized low-density lipoprotein cholesterol (LDL-C) levels compared to -22674C allele carriers. LDL-C levels were higher in carriers of the CC genotype for the 30294C polymorphism compared to non-carriers. Subjects carrying the AATDC haplotype had 3.2 times higher risk of LDL-C > 100 mg/dL than those carrying the AGTIG haplotype, whereas subjects carrying the AATIC haplotype had 2.0 times higher risk of total cholesterol > 200 mg/dL than the AGTIC haplotype. Therefore, genetic variation in CD36 may modulate CVD risk by affecting lipid metabolism. Single nucleotide polymorphisms in the CD36 gene have also been associated with metabolic disorders related to excess fat depots in adult populations (Corpeleijn et al., 2006), and a (TG)-repeat in intron 3 has been linked to elevated BMI in Korean patients with coronary heart disease (Min Yun,et al, 2007). Bokor et al. assessed the link between CD36 SNPs and the risk of obesity in a case–control study comprising 307 obese (age = 15.0 ± 1.1 years) and 339 normal-weight (age = 14.6 ± 1.1 years) adolescents (Bokor et al., 2010). Four SNPs (rs3211867, rs3211883, rs3211908, and rs1527483) were associated with increased obesity risk, higher BMI, and higher percent body fat. A haplotype consisting of the minor alleles of these SNPs was also linked to obesity and excess adiposity (i.e., higher BMI and percent body fat).

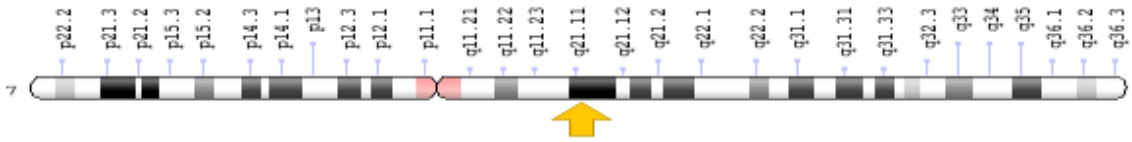
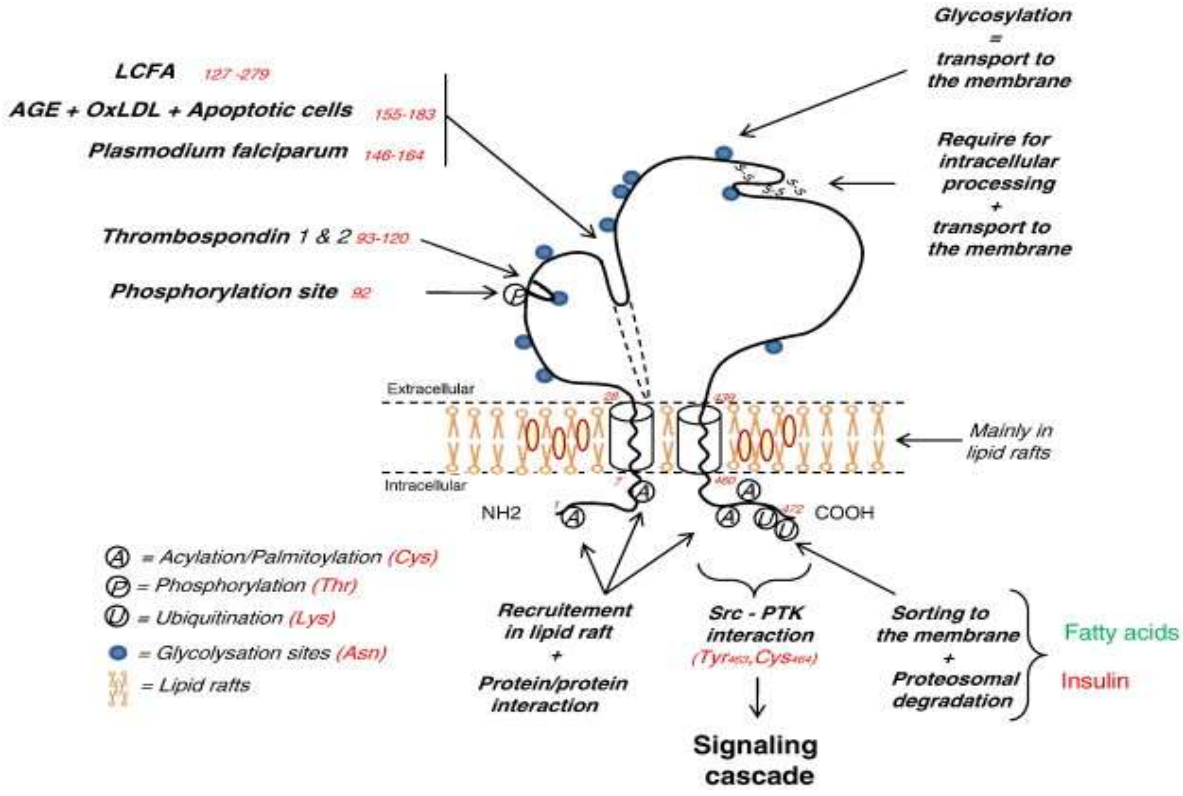


Figure (1) Location of CD-36 gene on the human genome (Adopted from ncbi.nlm.nih.gov)

Table (1): Functions of CD-36

Site of CD-36	Function of CD-36
Myocytes	Involved in Beta-oxidation by supplying the source of energy to the cell
Adipocytes	Have an important role in lipid storage by up taking of lipid molecule with hydrophobic pocket in CD-36
Gut	Involved in absorption of fat - soluble vitamins



Figure(2): Structure related activity of CD-36 (Luiken,et al, 2016)

Reference:

Abumrad, N.A., El-Maghrabi, M.R., Ez-Zoubir, A., Lopez, E., Grimaldill, P.A., 1993. Cloning of a Rat Adipocyte Membrane Protein Implicated in Binding or Transport of Long-chain Fatty Acids That Is Induced during Preadipocyte Differentiation. J. Biol. Chem. 268, 17665–17668. https://doi.org/http://dx.doi.org/10.1002/pd.4617

Baillie, A.G.S., Coburn, C.T., Abumrad, N.A., 1996. Reversible Binding of Long-chain Fatty Acids to Purified FAT, the Adipose CD36 Homolog. J. Membr. Biol. 153, 75–81. https://doi.org/10.1007/s002329900111

Bokor, S., Legry, V., Meirhaeghe, A., Ruiz, J.R., Mauro, B., Widhalm, K., Manios, Y., Amouyel, P., Moreno, L.A., Molnr, D., Dallongeville, J., 2010. Single-nucleotide polymorphism of cd36 locus and obesity in European adolescents. Obesity 18, 1398–1403. https://doi.org/10.1038/oby.2009.412

Cartoni, C., Yasumatsu, K., Ohkuri, T., Shigemura, N., Yoshida, R., Godinot, N., le Coutre, J., Ninomiya, Y., Damak, S., 2010. Taste preference for fatty acids is mediated by GPR40 and GPR120. J. Neurosci. 30, 8376–82. https://doi.org/10.1523/JNEUROSCI.0496-10.2010

Collot-Teixeira, S., Martin, J., McDermott-Roe, C., Poston, R., McGregor, J.L., 2007. CD36 and macrophages in atherosclerosis. Cardiovasc. Res. 75, 468–477. https://doi.org/10.1016/j.cardiores.2007.03.010

Corpeleijn, E., van der Kallen, C.J.H., Kruijshoop, M., Magagnin, M.G.P., de Bruin, T.W.A., Feskens, E.J.M., Saris, W.H.M., Blaak, E.E., 2006. Direct association of a promoter polymorphism in the CD36/FAT fatty acid transporter gene with Type 2 diabetes mellitus and insulin resistance. Diabet. Med. 23, 907–911. https://doi.org/10.1111/j.1464-5491.2006.01888.x

Enciu, A.M., Radu, E., Popescu, I.D., Hinescu, M.E., Ceafalan, L.C., 2018. Targeting CD36 as Biomarker for Metastasis Prognostic: How Far

risk in Caucasians. Hum. Mol. Genet. 13, 2197–2205. https://doi.org/10.1093/hmg/ddh233

Min Yun, Y., Young Song, E., Hoon Song, S., Song, J., Kim, J.Q., 2007. CD36 polymorphism and its relationship with body mass index and coronary artery disease in a Korean population. Clin. Chem. Lab. Med. 45, 1277–1282. https://doi.org/10.1515/CCLM.2007.270

Noel, S.E., Lai, C.-Q., Mattei, J., Parnell, L.D., Ordovas, J.M., Tucker, K.L., 2010. Variants of the CD36 gene and metabolic syndrome in Boston Puerto Rican adults. Atherosclerosis 211, 210–215. https://doi.org/10.1016/J.ATHEROSCLEROSIS.2010.02.009

Park, Y.M., 2014. CD36, a scavenger receptor implicated in atherosclerosis. Exp. Mol. Med. https://doi.org/10.1038/emm.2014.38

PrabhuDas, M., Bowdish, D., Drickamer, K., Febbraio, M., Herz, J., Kobzik, L., Krieger, M., Loike, J., Means, T.K., Moestrup, S.K., Post, S., Sawamura, T., Silverstein, S., Wang, X.-Y., El Khoury, J., 2014. Standardizing Scavenger Receptor Nomenclature. J. Immunol. 192, 1997–2006. https://doi.org/10.4049/jimmunol.1490003

Rać, M.E., Safranow, K., Poncyljusz, W., 2007. Molecular basis of human CD36 gene mutations. Mol. Med. 13, 288–96. https://doi.org/10.2119/2006–00088.Raæ

Ramos-Arellano, L.E., Salgado-Bernabé, A.B., Guzmán-Guzmán, I.P., Salgado-Goytia, L., Muñoz-Valle, J.F., Parra-Rojas, I., 2013. CD36 haplotypes are associated with lipid profile in normal-weight subjects. Lipids Health Dis. 12, 167. https://doi.org/10.1186/1476-511X-12-167

Sarnyai, Z., Sibille, E.L., Pavlides, C., Fenster, R.J., McEwen, B.S., Tóth, M., 2000. Impaired hippocampal-dependent learning and functional abnormalities in the hippocampus in mice lacking serotonin1A receptors. Proc. Natl. Acad. Sci. U. S. A. 97, 14731–14736. https://doi.org/10.1073/pnas.97.26.14731

Sclafani, A., Ackroff, K., Abumrad, N.A., 2007. CD36 gene deletion reduces fat preference and intake but not post-oral fat conditioning in mice. Am. J. Physiol. Integr. Comp. Physiol. 293, R1823–R1832. https://doi.org/10.1152/ajpregu.00211.2007

Silverstein, R.L., Febbraio, M., 2010. NIH Public Access. Cell 2, 1–16. https://doi.org/10.1126/scisignal.272re3.CD36

Silverstein, R.L., Febbraio, M., 2009. CD36, a Scavenger Receptor Involved in Immunity, Metabolism, Angiogenesis, and Behavior. Sci. Signal. 2, re3–re3. https://doi.org/10.1126/scisignal.272re3

Simons, P.J., Kummer, J.A., Luiken, J.J.F.P., Boon, L., 2011a. Apical CD36 immunolocalization in human and porcine taste buds from circumvallate and foliate papillae. Acta Histochem. 113, 839–843. https://doi.org/10.1016/J.ACTHIS.2010.08.006

Simons, P.J., Kummer, J.A., Luiken, J.J.F.P., Boon, L., 2011b. Apical CD36 immunolocalization in human and porcine taste buds from circumvallate and foliate papillae. Acta Histochem. 113, 839–843. https://doi.org/10.1016/J.ACTHIS.2010.08.006

Stewart, J.E., Feinle-Bisset, C., Keast, R.S.J., 2011. Fatty acid detection during food consumption and digestion: Associations with ingestive behavior and obesity. Prog. Lipid Res. 50, 225–233. https://doi.org/10.1016/J.PLIPRES.2011.02.002

Stewart, J.E., Keast, R.S.J., 2012. Recent fat intake modulates fat taste sensitivity in lean and overweight subjects. Int. J. Obes. 36, 834–842. https://doi.org/10.1038/ijo.2011.155

Tandon, N.N., Lipsky, R.H., Burgess, W.H., Jamieson, G.A., 1989. Isolation and characterization of platelet glycoprotein IV (CD36). J. Biol. Chem. 264, 7570–7575.