Journal of Inflammation Research

Dovepress
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REVIEW

Deciphering the Role of CD36 in Gestational Diabetes Mellitus: Linking Fatty Acid Metabolism and Inflammation in Disease Pathogenesis

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Abstract: Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications which exerts detrimental effects on mothers and children. Emerging evidence has pointed to the important role of the fatty acid transporter protein CD36 in the pathogenesis of GDM. As a heavily glycosylated transmembrane protein, CD36 is widely expressed in diverse cell types, including placental trophoblasts, monocytes/macrophages, adipocytes, and pancreatic cells et al. CD36 plays a key role in lipid metabolism and signal transduction in the pathophysiological mechanism of GDM. The modified expression and functionality of CD36 may contribute to inflammation and oxidative stress in maternal tissues, interfere with insulin signaling, and subsequently influence maternal insulin sensitivity and fetal growth, increasing the risk for GDM. This review provides an overview of the current knowledge regarding the expression and function of CD36 in various tissues throughout pregnancy and explores how CD36 dysregulation can activate inflammatory pathways, worsen insulin resistance, and disrupt lipid metabolism, thereby complicating the necessary metabolic adjustments during pregnancy. Furthermore, the review delves into emerging therapeutic approaches targeting CD36 signaling to alleviate the impacts of GDM. Understanding the involvement of CD36 in GDM could yield crucial insights into its mechanisms and potential interventions for enhancing maternal and fetal health outcomes.

Keywords: CD36, gestational diabetes mellitus, lipid metabolism, inflammation, insulin resistance, treatment

Introduction

Gestational diabetes mellitus (GDM) is one of the most common disorders associated with pregnancy, characterized by the recognition of abnormal glucose tolerance during pregnancy for the first time, lacking the classic symptoms of polyphagia, polydipsia, polyuria, and weight loss observed in other forms of diabetes. Unlike those with type 1 or type 2 diabetes mellitus (T2DM), pregnant women with GDM frequently normalize after childbirth. The incidence of GDM exhibits geographical variation, with the Middle East and North Africa showing the highest prevalence at 27.6%, and North America recording the lowest at 7.1%. The average estimated prevalence rate stands at 14%.[1,2] There has been a steady increasing trend in GDM prevalence, mainly caused by the rising obesity epidemic and advancing maternal age.[3] Women with GDM are at an increased risk of shoulder dystocia, birth injuries, hypertensive disorders of pregnancy, postpartum depression, and subsequent development of T2DM. Fetuses of GDM women also face a greater risk of macrosomia, birth injuries, hypoglycemia, erythrocytosis, and hyperbilirubinemia.[4,5]

Received: 22 October 2024
Accepted: 27 January 2025
Published: 4 February 2025

The pathophysiology of GDM encompasses several pathological mechanisms, such as compromised lipid transport across the placenta, persistent low-level oxidative stress, inflammation, and disrupted lipid metabolism. CD36, a multiligand receptor involved in fatty acid transport, plays a pivotal role in these processes.[6,7] This receptor mediates lipid transport in the placenta, linking maternal metabolic health with fetal development. Moreover, the interaction between CD36 and agonists like free fatty acids (FFAs) is thought to potentially activate adipocytes and macrophages, thereby generating reactive oxygen species (ROS), heightening oxidative stress, and stimulating the release of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), among others.[8,9] Studies have reported that modulation of CD36 expression in endothelial and parenchymal cells has been shown to have a positive impact on GDM.[10]

This review focuses on the impact of CD36 in placental fatty acid transport, oxidative stress and inflammation, insulin resistance and abnormal lipid metabolism in GDM. In addition, it will discuss how changes in CD36 expression are linked to some of the adverse pregnancy reactions associated with GDM. This article also provides insights on current therapeutic approaches targeting CD36 for GDM.

CD36: Structure and Function

CD36, an 88-kDa heavily glycosylated fatty acid translocase (FAT/CD36), was first identified in platelets. It belongs to the class B2 scavenger receptor family, which encompasses low-density lipoprotein (LDL), high-density lipoprotein (HDL)-bound scavenger receptor B1, and HDL-bound scavenger receptor B3.[11–14] CD36 is widely expressed in various cell types, such as mononuclear cells, tissue macrophages, placental membranes, microvilli, placenta basement membranes, lymphatic endothelial cells (LECs), adipocytes, hepatocytes, platelets and skeletal myocytes (Table 1).[10,15–18]

Table 1 Localization and Functions of CD36 in the Human Body

CD36-Expressing Cells or Tissues	Main Ligands of CD36	Role of CD36	Related Diseases	References
Platelets	Thrombospondin-1, Oxidized low-density lipoprotein (ox-LDL)	Activate platelets	Heart attack, stroke	[19,20]
Macrophages and monocytes	ox-LDL, phosphatidylinositol, glycolipids and some bacterial components	Amplifies and initiates inflammatory pathways	Atherosclerosis, Alzheimer's, diabetes	[21–23]
Skeletal muscle and cardiomyocytes	Long chain fatty acids (LCFA)	Transfers LCFA that support muscle contraction	Diabetes	[24,25]
Pancreatic β-cells	LCFA	Increases the influx of free fatty acids into pancreatic β-cells to influence glucotoxicity dysfunction	Diabetes	[26]
Endothelial cells	LCFA, malaria parasite	Participate in inflammation and oxidative stress, promoting the expression of various cytokines and inflammatory factors, induce apoptosis	Atherosclerosis, Alzheimer's, diabetes, cerebral malaria	[27,28]
Immune lymphocyte	Lipid molecules, glycolipids	Mediates phagocytosis of apoptotic cells infected with Plasmodium falciparum	Malaria	[29]
Adipose tissues	LCFA and their derivatives	Adjust lipoprotein lipase (LPL) expression to mediate fatty acids (FAs) uptake	Diabetes	[30]
Liver	ox-LDL, FAs	Involved in ox-LDL being processed by the liver and involved in FAs uptake	Fatty liver disease, non-alcoholic fatty liver disease	[31,32]

The CD36 gene is positioned on chromosome 7 (7q11.2) and is composed of 17 exons and 18 introns. The gene encodes a 472-amino acid protein that is folded into a single peptide chain. This protein contains two transmembrane domains, two very short cytoplasmic domains, and a large glycosylated extracellular domain with a hairpin-like membrane topology.[33] The extracellular domain of CD36 contains multiple binding sites enabling the recognition of various endogenous and exogenous ligands, such as FFAs, collagen, thrombospondin (TSP), and oxidized low-density lipoproteins (ox-LDL). Furthermore, it has the ability to participate in inflammation through its signal transduction capabilities.[7,34–38] The amino-terminal region harbors binding domains for hexarelin, fatty acids (FAs), ox-LDL, phospholipids, TSP, and P. falciparum-infected erythrocytes, while the carboxyl tail facilitates signal transduction by interacting with multiple tyrosine kinases.[35–38]

Lipid Transport and Signaling Functions of CD36 in the Pathogenesis of GDM

In the pathological process of GDM, changes in CD36 levels in different types of cells will not only change the metabolism of the cells themselves, but also affect the progression of GDM (Table 2).

CD36 in Placenta and Trophoblasts

The placenta is differentiated from the cells of the trophoblast of the blastocyst and its substance is a structure located between the chorionic villi (the fetal side of the placenta) and the basement membrane (the maternal side of the placenta). The placenta functions as an intermediary for the exchange of materials between the mother and the fetus[43–46], facilitating the regulation of various nutrient transporters, including those for glucose, FAs, amino acids, and vitamins, to support fetal development.[43] Prior to crossing the placenta, lipids, including triglycerides, require hydrolysis to transform into FFAs.[47] The presence of lipoprotein lipase (LPL) activity in isolated placental trophoblasts suggests that the placenta is capable of metabolizing triglyceride-packaged lipid species into non-esterified FAs.[39,48] The trophoblast facilitates the transport of FAs through the placenta using specific binding and transport proteins (Figure 1, the right part). Notably, proteins like the 40-kDa placenta plasma membrane fatty acid binding protein (p-FABPpm), a family of 63–70-kDa fatty acid transport proteins (FATP 1–6), and FAT/CD36 are pivotal in this mechanism.[47,49–53] Segura et al demonstrated that placental FAT/CD36 expression is significantly elevated in pregnant women with GDM. This alteration is associated with an increased content of long-chain polyunsaturated fatty acids (LCPUFAs), including docosahexaenoic acid (DHA, 22:6 n-3), which is crucial for placental angiogenesis.[39,54–56] DHA has the ability to

Table 2 The Effect of CD36 on Different Cells and Progression of GDM

Cells	Expression of CD36	Effect on Cells	Effect on GDM	Reference
Placental trophoblasts	Upregulation*	Increases the transport of fatty acids	Increases the supply of fetal fatty acids	[39]
Vascular smooth muscle cells	–	Increases the production of reactive oxygen species	Aggravates oxidative stress	[40]
Adipocytes	Upregulation*	Increase the transport of fatty acids	Aggravates oxidative stress	[41]
	Deficiency**	Reduces PPARγ levels	Promotes local tissue insulin resistance	[30]
Monocyte-derived macrophages	Upregulation*	Initiates the inflammatory cascade	Increases inflammation	[7]
Hepatocytes	Upregulation*	Inhibits β-oxidation of fatty acids and increase triglyceride synthesis	Promotes the occurrence of hypertriglyceridemia	[31,42]

Notes: *: CD36 levels are pathologically up-regulated in GDM; **: Genetic deletion of CD36.
Abbreviations: GDM, gestational diabetes mellitus; PPAR, peroxisome proliferator-activated receptor.

https://doi.org/10.2147/JIR.S502314

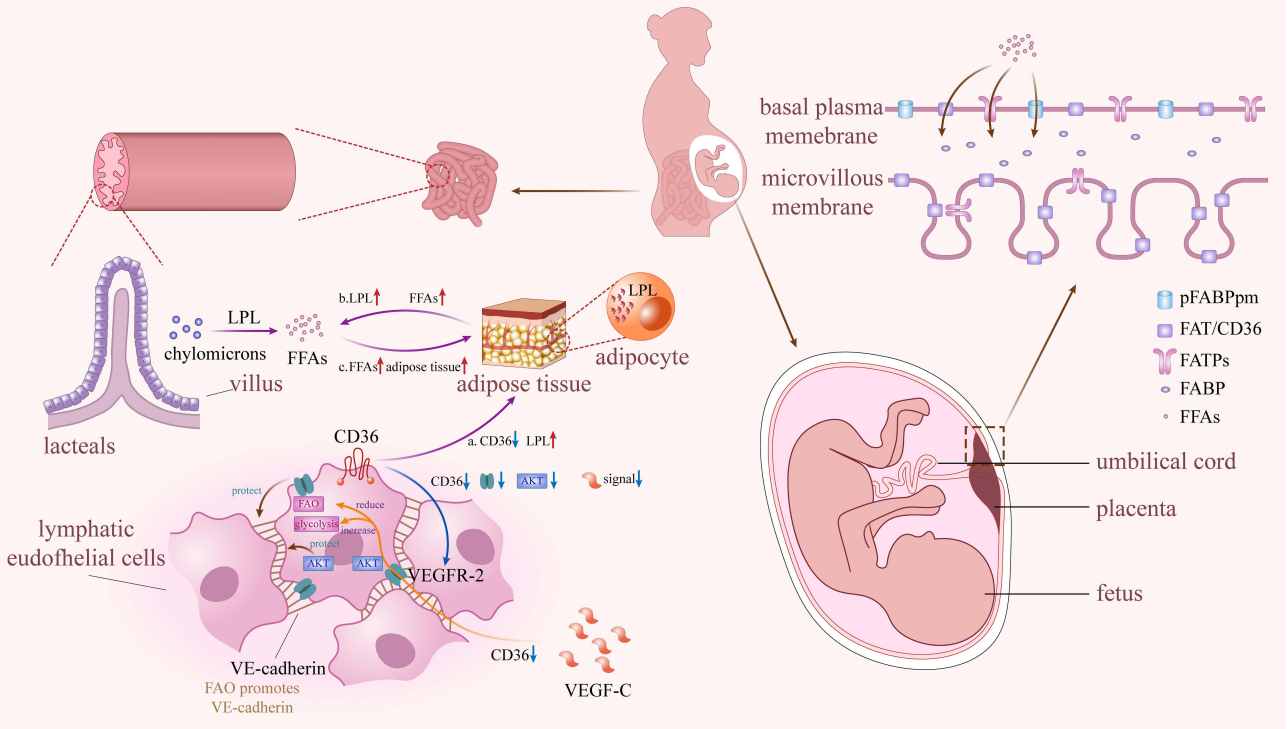

Figure 1 The role of CD36 in insulin resistance and fetal nutrient supply. (The left part) The expression level of CD36 in lymphatic endothelial cells (LECs) has a direct impact on the development of insulin resistance. When CD36 expression is absent in small intestinal lymphatic (ie, lacteals) endothelial cells, it has different effects on insulin resistance in endothelial cells and adipocytes. For endothelial cells, deletion of CD36 expression on LECs inhibits the signaling of vascular endothelial growth factor-C (VEGF-C), thereby enhancing glycolysis, weakening fatty acid oxidation, and reducing the expression of vascular endothelial-calcium adhesion (VE-cadherin), ultimately destroying the integrity of the endothelial monolayer. For adipocytes, (a) CD36 deficiency in LECs would induce lipoprotein lipase (LPL) expression. (b) Increased expression of LPL increases the reaction with chylomicrons, resulting in the production of more free fatty acids (FFAs). (c) Excess FFAs promote the growth of adipose tissue, leading to the accumulation of visceral fat, inflammation, and ultimately insulin resistance in adipose tissue. (The right part) CD36 is expressed as a fatty acid transporter protein in various cells of the placenta. Fatty acids (FAs) bound to proteins and other substances are broken down into FFAs by enzymes in placental tissues before being transported by fatty acid transporter proteins. This allows for the transportation of FAs to the fetus through the placenta, providing the necessary supply. On the placental basal plasma membrane, there are three fatty acid transporter proteins: placenta plasma membrane fatty acid binding protein (p-FABPpm), fatty acid transport proteins (FATP), and fatty acid translocase (FAT/CD36). Cytoplasmic fatty acid binding protein (FABP) may facilitate translocation to the fetal circulation through placental basal plasma membranes. On the microvillous membrane, there are only two transporter proteins: FATPs and FAT/CD36. This distribution facilitates the unidirectional transfer of FAs from the mother to the fetus.
Abbreviations: FAO, fatty acid oxidation; VEGFR-2, vascular endothelial growth factor receptor-2.

selectively enhance the expression of vascular endothelial growth factor (VEGF), thereby elevating VEGF levels in the placenta and consequently stimulating blood vessel formation.[55]

CD36 Promotes Oxidative Stress and Inflammation

Oxidative Stress

CD36 promotes inflammation and oxidative stress,[57] pathogenic processes strongly implicated in GDM. CD36 functions as both a fatty acid transporter and an essential signaling receptor, transducing intracellular cascades. In women with GDM, there is an increase in levels of oxidative stress markers in maternal circulation compared to those in normal pregnancy.[58,59] During pregnancy, physiological changes lead to increased production of placenta-derived ROS in the blood, promoting the occurrence of oxidative stress.[60] Elevated glucose oxidation occurs in pregnant women experiencing hyperglycemia, leading to an increased availability of electron donors for the electron transport chain. Consequently, more electrons are transferred to molecular oxygen, resulting in an escalation of ROS production, exacerbating oxidative stress.[61] CD36 on vascular smooth muscle can also promote the production of ROS by activating NADPH oxidase.[40] Excessive concentrations of ROS lead to irreversible oxidative damage to a broad spectrum of biomolecules, including DNA, proteins, and lipids, thereby compromising a multitude of cellular functions. Nakamura et al believe that the increased production of ROS in cardiomyocytes and the activation of tumor suppressor p53 (p53 participates in the regulation of mitochondrial respiration through cytochrome c oxidase 2 (SCO2)) may lead to p53 enhanced

transcriptional regulation of CD36.[62] For adipocytes, the expression of CD36 in adipocytes of obese people is up-regulated, and adipose tissue promotes fatty acid flow through CD36, leading to fat overload and oxidative stress.[41,63] Pancreatic β-cells are especially susceptible to ROS due to their low levels of free radical-quenching antioxidant enzymes.[64] Therefore, oxidative stress triggers β-cell dysfunction by promoting apoptotic processes, disrupting ATP-sensitive potassium channels (KATP channels), and suppressing transcription factors related to β-cell neogenesis, ultimately reducing insulin secretion.[65]

Inflammation

An imbalance between the body's antioxidant capacity and oxidative stress leads to an increase in ox-LDL within the endothelium of the blood vessels.[66] At this juncture, monocytes can easily migrate into the vascular intima and differentiate into macrophages within the tissue. CD36 exhibits a strong binding affinity for ox-LDL on the membranes of macrophages. The upregulation of CD36 on monocyte-derived macrophages is thought to be a consequence of increased glucose-mediated translation efficiency of CD36 mRNA, closely correlated with diabetes and obesity.[7,21,67] Over-expressed CD36 on macrophages initially interacts with ox-LDL, serving as a Toll-like receptor (TLR) agonist that triggers the inflammatory cascade. Subsequently, CD36 binds to Lyn, a tyrosine kinase, at the MISY motif (amino acids 460–463) located at the C-terminus of CD36.[7] FFAs have been postulated as TLR agonists, potentially playing a role in the initiation of inflammatory signaling pathways under the coexistence of GDM and obesity.[68] Through Lyn-mediated phosphorylation modification of TLR, CD36 binds to TLR and participates in the activation and amplification of downstream pro-inflammatory signaling pathways.[6,7] Upon interaction with ox-LDL, CD36, expressed on macrophages, initiates the formation of a complex between Toll-like receptor-4 (TLR-4) and Toll-like receptor-6 (TLR-6), thereby triggering the activation of the downstream adaptor protein myeloid differentiation primary response protein (MYD88). Simultaneously, CD36 also binds to FFAs, indirectly promoting MYD88 activation by zinc finger-aspartate-histidine-cysteine 6, a specific palmitoyl-acyl transferase of MYD88. The activated MYD88 leads to the release of nuclear factor-κB (NF-κB) from another complex, enabling its translocation into the nucleus. Within the nucleus, NF-κB binds to DNA, initiating transcription and resulting in the production of pro-inflammatory cytokines such as TNF-α and IL-6 (Figure 2).[68–72] Moreover, oxidative stress induces apoptosis in hypertrophic adipocytes, attracts macrophages for dead cell and waste product removal, and stimulates the release of inflammatory factors, leading to localized inflammation. Simultaneously, oxidative stress promotes the release of pro-inflammatory and inflammatory factors through the signal pathway mediated by TLR, which aggravates systemic inflammation.[73]

CD36 and Insulin Resistance

Insulin resistance refers to the impaired biological response of target tissues to insulin stimulation. While all tissues with insulin receptors can develop insulin resistance, the primary ones affected are adipose tissue, skeletal muscle, and the liver. The onset of insulin resistance typically hinders the disposal of glucose into insulin-resistant tissues, leading to inadequate energy provision to the body. Consequently, higher levels of insulin are needed to transport glucose into these tissues. This resultant hyperinsulinemia exacerbates insulin resistance, perpetuating a vicious cycle. Ultimately, the pancreatic β-cell activity becomes insufficient to meet the heightened insulin demand caused by insulin resistance, resulting in hyperglycemia.[74] During normal pregnancy, placental hormones coordinate a significant rise in insulin resistance, leading to increased postprandial glucose levels and a 2- to 3-fold increase in insulin production.[47] The majority of GDM cases (~80%) occur against a backdrop of chronic insulin resistance and develop into pancreatic β-cell damage, often influenced by genetic factors.[75]

The fatty acid transporter protein CD36 is implicated in the uptake of FAs by adipocytes, the promotion of adipogenesis, and the accumulation of visceral fat.[76,77] Recent studies have revealed its dual role as both a transporter protein and a signaling molecule in adipose tissue, implicated in insulin resistance. In adipocytes, the expression of CD36 could potentially influence the expression of peroxisome proliferator-activated receptor gamma (PPARγ), a key nuclear factor in adipogenesis.[78] CD36, as a downstream target of PPARγ, is also implicated in adipogenesis. Furthermore, CD36 is involved in adipocyte differentiation by regulating mitotic clonal expansion in the initial phase and modulating the expression of genes related to lipid biosynthesis.[79,80] The regulation of PPARγ expression by CD36 levels could play

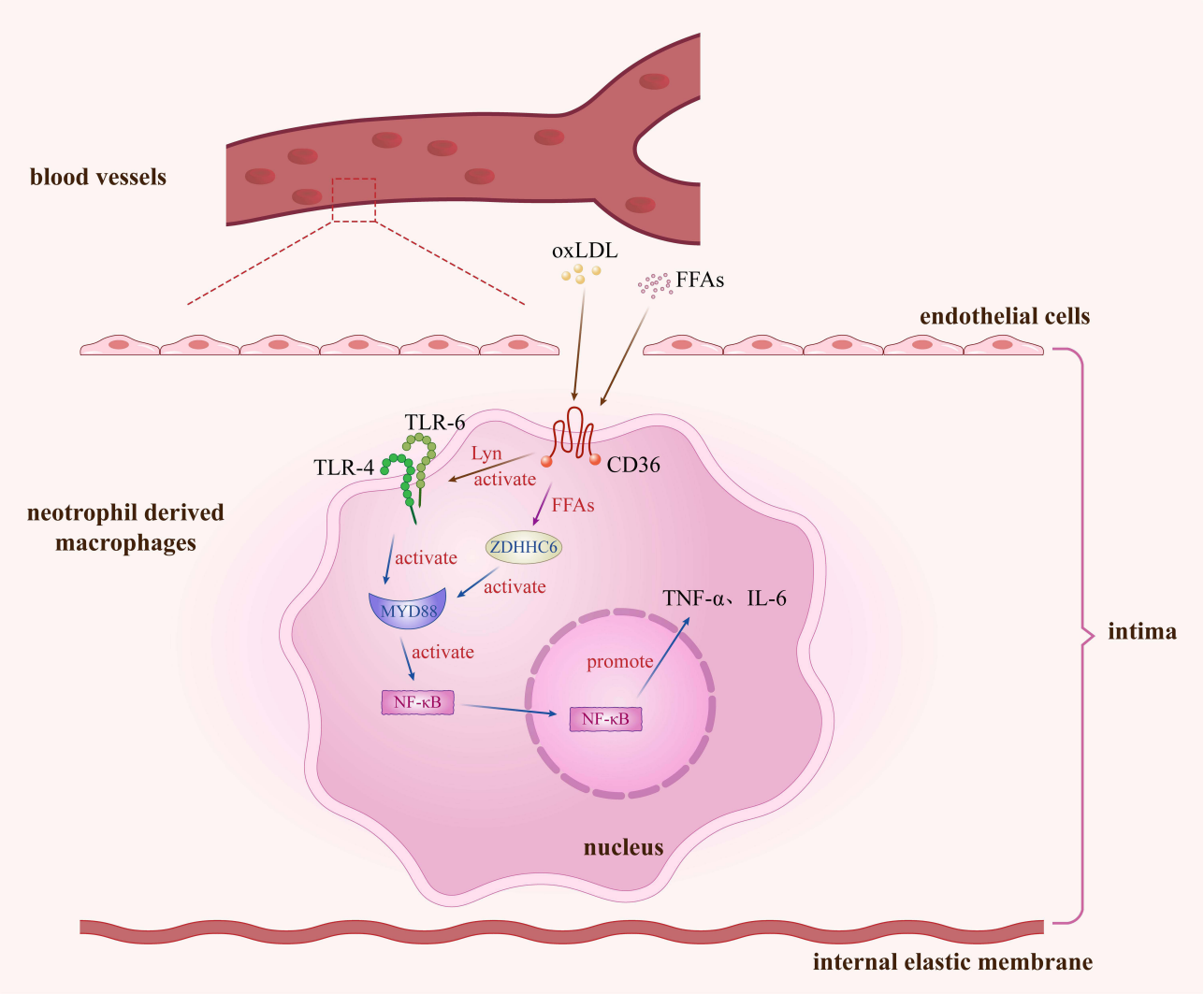

Figure 2 CD36 is involved in inflammatory signaling. Serving as a high-affinity receptor for exogenous fatty acids (FAs), CD36 mediates the cellular uptake of FAs, enabling the activation of myeloid differentiation primary response protein (MYD88) by zinc finger-aspartate-histidine-cysteine 6 (ZDHHC6). Participation of CD36 in the recruitment of the MYD88 adaptor protein by Toll-like receptor (TLR) for nuclear factor-κB (NF-κB) activation exacerbates the inflammatory state, leading to increased production of pro-inflammatory cytokines and elevated expression levels.
Abbreviations: FFAs, free fatty acids; IL-6, interleukin-6; oxLDL, oxidized low-density lipoproteins; TNF-α, tumor necrosis factor-α.

a role in the onset of insulin resistance in adipocytes. Nakamura et al argue that adiponectin, when stimulated by PPARγ, serves as a spacer between adipocytes by binding to T (truncated)-cadherin on the adipocyte surface. A decline in adiponectin production is proposed to reduce inter-cellular space, thereby restricting interstitial fluid perfusion, resulting in reduced metabolic activity in adipocytes and promoting insulin resistance.[30] Thus the absence of CD36 on adipocytes results in reduced PPARγ levels, subsequently decreasing PPARγ-induced lipocalin expression. This hinders the differentiation of adipocytes and promotes the onset of insulin resistance in adipocytes.

Cifarelli et al found that mice with deletion of CD36 in LECs ($Cd36^{\Delta LEC}$) showed heightened permeability of mesenteric lymphatics, accumulation of inflamed visceral fat, and impaired glucose disposal. This deletion also increased the gene expression of LPL in the visceral adipose tissue of mice, potentially leading to increased availability of FAs from chylomicrons in the leaked lymph, resulting in adipocyte hypertrophy, inflammation, and glucose intolerance.[17] When CD36 expression is absent in small intestinal lymphatic (ie, lacteals) endothelial cells, it has different effects on insulin resistance in endothelial cells and adipocytes. For endothelial cells, deletion of CD36 expression on LECs is associated with reduced biological activity of vascular endothelial growth factor receptor-2 (VEGFR-2) and AKT (a key

regulatory molecule in the insulin signaling pathway), which in turn affects vascular endothelial growth factor-C (VEGF-C) signaling. Inhibition of VEGF-C signaling leads to decreased expression of enzymes related to fatty acid oxidation in LECs, resulting in the inhibition of fatty acid oxidation. At the same time, the expression of enzymes related to glycolysis is elevated in LECs, which enhances glycolysis. These changes in cellular activities can alleviate insulin resistance in endothelial cells and reduce the expression of vascular endothelial-calcium adhesion proteins, ultimately disrupting the integrity of the endothelial monolayer (Figure 1, the left part).[81] For adipocytes, CD36 deficiency in LECs has the potential to directly impact lipid metabolism in adipocytes. Consequently, visceral adipose accumulates, promoting inflammation of adipose tissue and insulin resistance.[17]

CD36 and Abnormal Lipid Metabolism

CD36 can be distributed in the plasma membrane and cytoplasm of liver cells and adipocytes,[82] so there are potential differences in the subcellular distribution of CD36. This difference has implications for normal fat metabolism in the liver.[31] It has been reported that factors affecting CD36 expression levels (CD36 transcript levels) and factors affecting CD36 subcellular translocation (such as insulin levels and palmitoylation levels) are related to membrane-bound CD36 levels.[83–85] When a pregnant woman is under the conditions of a diabetic pregnancy, the level of membrane-bound CD36 is increased due to the gestational state, along with chronically high levels of insulin.[86] This translocation of CD36 to the plasma membrane in response to the metabolic state allows for increased FAs uptake by hepatocytes.[87] As a result of insulin action, CD36 on the mitochondria of hepatocytes is transferred to the plasma membrane in large quantities, leading to the inhibition of β-oxidation of FAs in the mitochondria in which CD36 is involved, as well as an increase in the synthesis of hepatocyte triglycerides.[31,88] This ultimately leads to the development of lipid overload in the liver, as well as hypertriglyceridemia, which is manifested in most pregnant women with diabetic pregnancies.[31,42]

GDM-Related Adverse Pregnancy Outcomes

Preeclampsia

Preeclampsia is described as the occurrence of hypertension along with significant proteinuria after 20 weeks of gestation, and it represents the foremost contributor to severe maternal complications and fetal demise on a global scale.[89,90] Vascular endothelial injury, mediated by oxidative stress from increased placental ROS or decreased antioxidant activity, is thought to be the fundamental pathology of preeclampsia. Thrombospondin −1 (TSP-1) functions as a ligand for CD36, dampening platelet sensitivity to activation signals at the vascular injury site. This modulation occurs through a tyrosine kinase-dependent mechanism downstream of CD36, thereby impacting platelet activation at the injury site and indirectly fostering vascular endothelial injury.[91,92] One of the specific markers for preeclampsia is VEGF, and the expression of VEGF-C is also decreased in CD36-deficient LECs.[17] This implies a potential role for CD36 in regulating the expression of the preeclampsia biomarker.

Macrosomia

Newborns are often classified as having "macrosomia" when their birthweight exceeds a specific threshold, commonly defined as 4000g.[93,94] Numerous articles have demonstrated the association between GDM and the incidence of macrosomia. High maternal serum glucose levels allow for the passage of glucose to the fetus through the placenta, yet the heightened maternal insulin cannot be conveyed to the fetus via the placenta. By the second trimester, the fetal pancreas is capable of independently secreting insulin and commences its response to elevated blood glucose. When hyperinsulinemia and hyperglycemia coexist, it can lead to increased fetal fat and protein storage, ultimately resulting in macrosomia.[95–97] The placental fatty acid transporter enzyme, FAT/CD36, exhibits heightened expression in patients with GDM, along with increased expression of FABPpm, FATP, and other proteins linked to placental fatty acid transport.[98] Consequently, there is an increase in the supply of FAs from the mother to the fetus, thereby heightening the risk of macrosomia.

Fetal Retina and Nervous System

DHA constitutes approximately 80% of all polyunsaturated FAs in the retina, and about 60% of the brain's dry weight comprises FAs, with DHA being the primary omega-3 fatty acid.[99] Despite the increased expression of FAT/CD36 in the placenta of pregnant women with GDM, leading to heightened placental DHA content,[39] María et al observed a notable reduction in the major facilitator superfamily domain containing 2A (MFSD2A) in the placenta of women with GDM. This reduction impeded the transfer of DHA from the placenta to the fetus,[100,101] resulting in an inadequate supply of fetal DHA. Such insufficiency may lead to visual symptoms in the fetus and could even impact the offspring's learning and cognitive abilities later in life.[102–105]

CD36-Related Potential Treatments for GDM

Targeting CD36 shows therapeutic promise, both interrupting the fueling of inflammatory pathways and allaying the disruptive effects of redox imbalance on insulin action and β-cell viability in GDM (Table 3).

Targeting Redox Imbalance

Metformin is widely utilized as an oral medication in clinical practice for the treatment of GDM. Moon et al exposed INS-1 islet cell tumor cells from mice to a high-glucose environment for a specific duration. This exposure led to an increase in FFAs uptake by promoting CD36 expression and downregulating insulin and pancreatic duodenal homeobox1 (Pdx1) mRNAs. Consequently, this inhibition of glucose-stimulated insulin secretion (GSIS) occurred alongside an elevation in ROS levels.[106] Treatment with metformin in high glucose conditions suppressed the increased CD36 mRNA expression by significantly reducing ROS production and reversed the decreased insulin mRNA expression. Inhibiting CD36 suppressed high glucose-induced activation of c-Jun amino terminal kinases (JNKs), potentially averting cell apoptosis, and reversed high glucose-induced activation of cleaved Caspase-3, thereby alleviating inflammation and apoptosis, ultimately reducing pancreatic cell damage.[106,111,112]

Targeting Inflammatory Pathways

PPAR Receptor Agonist

The PPAR family of transcription factors, as transcription factors with important roles in the transcription of CD36, has so far identified three different PPAR isoforms in mammals, namely PPAR-α, PPAR-β/δ, and PPAR-γ.[113] PPAR-α is a key transcription factor for the transcription of key enzymes in the βoxidation pathway occurring in, among others, hepatocyte mitochondria, including acyl CoA oxidase, carnitine palmitoyl transferase I, mitochondrial hydroxymethyl-glutaryl CoA synthase.[114,115] PPAR-α agonists, such as CP775146 and fenofibrate, increase the expression of CD36 in hepatocytes,[107,108] which perhaps can alleviate the inhibition of fatty acid β-oxidation caused by the lack of CD36 in the mitochondrial membrane of hepatocytes due to high levels of insulin in pregnant women with GDM, prevent the

Table 3 Compounds for the Treatment of Diseases Associated With CD36

Compounds	Type of Compounds	Effect on CD36	Target Organs of CD36	Related Diseases	References
Metformin	Non-target Biguanide	Blocks the increase of CD36mRNA expression and CD36 protein expression	Pancreas	Diabetes	[106]
Fenofibrate	PPAR-α agonists	Increases FAs oxidation and increase the expression of CD36	Liver	–	[107,108]
Thiazolidinediones	PPAR-γ agonists	Engages the expression of insulin receptor substrates	Adipose	Insulin resistance	[109]
miR-135a mimics	microRNA	Inhibits level of CD36 and variety of inflammatory related molecules	–	–	[110]

Abbreviations: GDM, gestational diabetes mellitus; PPAR, peroxisome proliferator-activated receptor; FAs, fatty acids.

accumulation of lipids in the cells, and attenuates inflammation. PPAR-γ agonists such as thiazolidinediones can enhance insulin sensitivity in adipose tissue and prevent the development of insulin resistance in adipose tissue by directly engaging the expression of insulin receptor substrates.[109]

Receptor for Advanced Glycation End Product (RAGE) Inhibiting Drugs

Advanced glycation end products (AGEs), are products of nonenzymatic reactions between the aldehyde groups of sugars and the free amino groups of proteins, lipids, and DNA, and are highly cytotoxic; hyperglycemia leads to the accumulation of AGEs.[116–118] Nε-(carboxymethyl)lysine (CML) is the key active component of AGEs that promotes the activation of ligands for AGEs (eg, TLR4 and RAGE) and modulates downstream inflammatory responses.[119] Bharathidevi et al proposed that RAGE silencing can inhibit TLR4 signaling and reduce TLR-involved inflammation, and the way to inhibit TLR signaling may be through down-regulating the expression of the adapter protein MYD88. Treating endothelial cells with CML can directly activate the expression of CD36.[120] RAGE silencing may be able to reduce CD36 involvement with TLR4-mediated inflammatory responses, which can also directly reduce the risk of damage to the body of pregnant women with GDM due to the cytotoxicity of AGEs.

miR-135a Mimics

miR-135a is a type of microRNA that has been recognized to be abnormally expressed in a variety of tumors.[121,122] Du et al found that miR-135a mimics can significantly overexpress miR-135a in vitro, resulting in significant inhibition of CD36 levels, a variety of inflammatory related molecules and TLR4 levels, thus inhibiting TLR4-mediated inflammatory response.[110]

Targeting the Subcellular Distribution of CD36

Palmitoyltransferases containing the Asp-His-His-Cys (DHHC) motif, including DHHC4 (localized in the Golgi apparatus) and DHHC5 (localized in the plasma membrane), have distinct roles in the translocation of CD36 from the cytoplasm to the plasma membrane.[123] Wang et al proposed that when CD36 protein reaches the Golgi apparatus, DHHC4 performs palmitoylation modification on CD36, and then translocates from the Golgi apparatus to the cytoplasm under the general sorting effect of ADP-ribosylation factors 6 (ARF6) on palmitoylated membrane proteins.[124,125] Wang et al believe that DHHC5 protects CD36 on the plasma membrane from depalmitoylation to ensure the membrane localization of CD36 and maintain the uptake of FAs by adipocytes through CD36.[124,125] Inhibiting DHHC4/5 may reduce plasma membrane-associated CD36 levels in adipocytes and prevent inflammation caused by lipid accumulation.

Conclusion

GDM, a metabolic disorder occurring during pregnancy, has implications for both maternal health and fetal growth and development, and its global prevalence is steadily increasing each year. During pregnancy, CD36 expression increases in tissues and organs including the placenta, adipose tissue, and pancreas. As a protein and signaling molecule facilitating fatty acid transport, CD36 plays a role in triggering and intensifying oxidative stress and inflammation, leading to insulin resistance, compromised β-cell function and abnormal lipid metabolism. Nonetheless, there is limited knowledge regarding the specific mechanism through which CD36 contributes to GDM. Subsequent studies may provide insight into the specific molecular mechanisms of CD36 in these processes and explore how to effectively regulate CD36 activity to treat or prevent GDM. Furthermore, it is crucial to consider the interactions between CD36 and other metabolic regulators and how these interactions influence metabolic status during pregnancy.

Disclosure

The authors report no conflicts of interest in this work.

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