

The role of CD36 receptor in the pathogenesis of atherosclerosis

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Abstract

Atherosclerosis is a progressive, chronic inflammation in artery walls. Oxidized low density lipoproteins (ox-LDL) play an important role in atherosclerotic plaque formation. ox-LDL are taken up by macrophages mainly through scavenger receptors, among which CD36 is considered to be the most important. Animal studies have shown that crossing atherogenic mice with a strain lacking the expression of CD36 prevented the development of atherosclerosis despite a diet rich in saturated LCFA. In humans, autopsy studies performed in obese patients have demonstrated increased expression of CD36 receptor on macrophages, comprised within atherosclerotic plaques. Until recently it had been believed that CD36 is a major player in atherosclerosis progression in humans. However, recent studies challenge this conviction, showing increased incidence of coronary heart disease in the subgroup of patients with decreased expression of CD36. This article reviews the role of CD36 receptor in the development of atherosclerosis. The authors also discuss current possibilities to interfere with CD36, their potential benefits and hazards.

Key words: atherosclerosis, CD36 receptor, ox-LDL

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Cardiovascular diseases are the main cause of death in Poland. It is often the process of atherosclerosis which leads to heart attack, stroke, heart failure or arrhythmias. Atherosclerosis is a multifactorial, progressive disease involving endothelial dysfunction and chronic inflammation of the arteries. Monocytes transformed into macrophages accumulate oxidized low-density lipoproteins (ox-LDL) in the vessel wall, forming foam cells. Monocytes and macrophages express plasmalemmal receptors participating in the uptake of ox-LDL. When overloaded with fatty acids, macrophages transform into foam cells. These cells are the most important in the development of atherosclerosis.

CD36 receptor, its structure and role

CD36 belongs to class B scavenger receptors, which chemically or oxidatively bind modified lipoproteins, polyanions and apoptotic cells.^{1,2} It is a membrane glycoprotein with a mass of 88 kDa, composed of a single protein chain.^{3,4} CD36 is present on the surface of a number of cells, such as adipocytes, monocytes, macrophages, platelets, endothelial, cardiac, skeletal and smooth muscle cells, dendritic cells, retinal pigment epithelium and hematopoietic precursors of red cells (Table 1).^{1,2,5,6} It is a multifunctional receptor with the independent ability to bind to three major classes of ligands (modified phospholipids, long chain fatty acids (LCFA) and proteins containing structural domains of thrombospondin homologs) which include: ox-LDL, oxidized and negatively charged phospholipids, thrombospondin, collagen, apoptotic cells, hexarelin, red cells infected with plasmodium malariae or the outer segment of the retinal pigment epithelium.^{1,2,7}

CD36 has 85% homology with FAT/CD36 protein – fatty acid translocase. It belongs to the transmembrane transporter proteins, facilitating the transport of LCFA.⁸

Pro-atherosclerotic effect of CD36 receptor

Excessive uptake of LCFA results in their accumulation in the cells, contributing to lipotoxicity and secondarily to the development of metabolic diseases like obesity, atherosclerosis or diabetes, with their consequences such as coronary heart disease and ischemic stroke. CD36 binds ox-LDLs after recognizing them through lipid components, namely negatively charged phospholipids. Lack of the lipid component of ox-LDLs inhibits their uptake by CD36 receptor and, as a result, reduces lipoprotein accumulation in macrophages.² After entering monocytes or macrophages, LCFA are bound by cytoplasmic fatty acid binding proteins (FABPc) and then, depending on the needs of the cell, they are targeted to suitable intracellular locations for rendering: oxidation in mitochondria and peroxisomes or storage (mainly esterified) in the endoplasmic reticulum and the cytoplasm.⁹

In vitro, macrophages devoid of CD36 receptor, incubated with increased concentrations of ox-LDL, did not show increased intracellular transport of ox-LDL. These macrophages did not accumulate cholesterol esters and they did not undergo transformation into foam cells.¹⁰ CD36 facilitates translocation of LCFA in adipocytes, hepatocytes, and heart and skeletal myocytes, where LCFA are important substrates for energy production.¹ Thus CD36 receptor participates in lipid utilization within muscles, fat energy storage and fat absorption in the intestines.⁴

Table 1. The role of CD36 receptor in different cells

Cell type	Role of CD36 receptor
Adipocytes	CD36 receptor is 85% homology with FAT/CD36 protein – fatty acid translocase. It takes part in long-chain fatty acid uptake. ⁸
Macrophages	Uptake of ox-LDL on the surface of macrophages and cholesterol esters accumulation. ⁵¹ CD36 removes death cells. ¹ It takes part in destruction of dying neutrophils by monocytes. It supports macrophages phagocytic abilities through creation of complexes with vitronectin receptors (α_v , β_3). It recognizes specific oxidated phospholipids and lipoproteins on fagocytic cells through its functions as a scavenger receptor. ³
Platelets	Activation of blood platelets in response to ox-LDL through signaling events that include the activation of c-Jun N-terminal kinas, Src kinases, and extracellular signal-regulated kinase. ⁵²
Erythrocytes	CD36 receptor activates erythrocytes infected with plasmodium malaria. ¹ CD36 receptor was identified as a receptor for the sequence of plasmodium malaria infected erythrocytes which affects the adhesion of infected blood cells to the endothelium of vessels in various organs such as heart, lung, liver and brain. Membrane protein-1 of plasmodium malaria infected erythrocytes is one of the main ligands for CD36 receptor. ⁵³
Endothelial cells	CD36 is a mediator in activity of thrombospondin and collagen in the process of angiogenesis inhibition. ² It was identified as a receptor of endothelial cells for TSP-1 and -2 (thrombospondin 1 and 2) which is necessary for TSP antiangiogenic activity. Angiogenic activity of CD36 in endothelial cells is a result of its ability to activate specific cascade signal caused by proangiogenic response directed to apoptotic response. ^{3,54,55}
Muscle cells	CD36 receptor is 85% homology with FAT/CD36 protein – fatty acid translocase. Its main role is cellular transportation of longchain fatty acids. ⁸

Upon interaction with ox-LDL, CD36 initiates a signaling cascade, leading to ox-LDL uptake and foam cell formation. Cytoskeletal changes and inhibition of cell migration contribute to the trapping of foam cells within the atherosclerotic plaque. Interaction of ox-LDL with CD36 localized on macrophages triggers signals for the reaction, which is pro-inflammatory and pro-atherosclerotic. The signaling pathway involves activation of MAP kinases, Src family kinases and Vav family guanine nucleotide exchange factors, leading to internalization of the ligand, foam cell formation and inhibition of migration.¹¹

In vivo, the impact of CD36 on the development of atherosclerosis has been studied in mice with congenital deficiency of this receptor on macrophages. A significant reduction in atherosclerotic lesions (by 88%) was demonstrated.¹⁰ In order to assess the importance of CD36, an atherogenic strain of mice lacking apolipoprotein E, was crossed with mice deficient in CD36. Mice deficient both in apolipoprotein E and CD36 showed no tendency to the development of atherosclerotic plaques, despite a diet rich in saturated LCFA. The extent of atherosclerotic lesions in the aorta was on average lower by 77% as compared to the mice lacking only apolipoprotein E.¹²

In addition to inhibition of lipid storage by macrophages, mice deficient in CD36 receptor demonstrated improved insulin signaling.¹³ This implies the role of CD36 receptor in insulin resistance development.

Animal studies have shown that CD36 participates in the inflammatory process by regulating membrane calcium influx. CD36 takes part in the activation of membrane calcium channels in response to endoplasmic reticulum stress. This results in phosphorylation of cytoplasmic phospholipase A2 and its translocation to membranes in a CD36-dependent manner. The subsequent release of arachidonic acid from phospholipids contributes to the generation of eicosanoids mediating the pleiotropic inflammatory effects. A major prostanoid metabolite of arachidonic acid formed with the participation of cyclooxygenases – prostaglandin E2 – is a potent proinflammatory mediator.¹⁴ This study suggests that CD36 takes part in the development of atherosclerosis by regulating the intracellular influx of calcium and synthesis of prostaglandin E2 from arachidonic acid.

In humans, autopsy studies performed on atherosclerotic arteries in obese people with dyslipidemia showed increased expression of CD36 receptor on macrophages comprised within atherosclerotic plaques. In contrast, the expression of CD36 on macrophages present in the walls of arteries without atherosclerotic lesions was negligible.¹⁵

The stimulation of macrophages with oxLDL induced foam cell formation and cytokine secretion. Rios et al. showed that blocking CD36 and PAFR (Platelet Activating Factor) decreases oxLDL uptake and IL-10 production by macrophages as well as PAFR and CD36 are colocalized in human atherosclerotic plaques.¹⁶ They found that uptake of oxLDL and IL-10 production induced by oxLDL

in macrophages requires PAFR and CD36 recruitment into the same specific membrane microdomains (lipid rafts). oxLDL induced the expression of IL-10 mRNA only in HEK293T expressing both receptors CD36 and PAFR. In their experiments, they also observed a decrease of IL-10 production and oxLDL uptake caused by lipid raft disruption by treatment with methyl- β -cyclodextrin and an increase of oxLDL uptake when both receptors were present.¹⁶ By contrast, the blockage of CD36 reduced the secretion of IL-1 β , IL-6 and IL-8 and foam cell formation in human macrophages.¹⁷

Based on the results of the above studies, it can be concluded that reduction of CD36 receptor expression on macrophages prevents the development of atherosclerosis. This has opened up the scope for further research on the regulation of CD36 expression to prevent atherosclerosis in humans.

However, Moore et al. showed that CD36 deficiency does not necessarily lead to a reduction in atherosclerotic lesions.¹⁸ They showed increased accumulation of foam cells at the aortic sinus in CD36-ApoE double knockout mice compared to ApoE-KO mice.¹⁸ Further confusion was caused by a Japanese study in 40 humans deficient in CD36 receptor. They were shown to have significantly higher incidence of coronary heart disease than the general population, suggesting that CD36 deficiency might in fact be atherogenic.¹⁹

Factors regulating the expression of CD36 receptor

Expression of the CD36 gene is mainly controlled by the lipogenic transcription factor PPAR γ , liver X receptor (LXR), nuclear pregnane X receptor (PXR) and testicular orphan nuclear receptor 4 (TR4).^{4,20}

PPAR γ (nuclear peroxisome proliferator-activated receptor gamma) has ligands such as 15-deoxy Δ 12,14-prostaglandin J2 and thiazolidinediones (drugs used to treat type 2 diabetes). PPAR γ together with CD36 function by positive feedback: the increased activity of PPAR γ leads to increased expression of CD36 in macrophages.²¹ What is more, studies in recent years show that PPAR directly affects CD36 expression and mediate oxLDL uptake in monocytes, which promotes foam cell formation.¹⁷ It is known that HDL has anti-atherogenic properties, however, the mechanism has not been fully elucidated. HDL probably reduces the accumulation of lipids in adipocytes by phosphorylation of PPAR.²² In contrast, Zhong et al. suggest that HDL may increase oxLDL uptake in inflammatory adipocytes stimulated by endotoxin lipopolysaccharide, which causes an increase in the expression of PPAR and CD36.²³

Another factor regulating the expression of CD36 receptor is HDL (high density lipoproteins). At higher concentrations, HDL decrease the expression of CD36 by

increasing the phosphorylation of PPAR γ . This results in reduced transcription of CD36 mRNA.²⁴

Expression of CD36 is enhanced by such pro-inflammatory cytokines as IL-1 (interleukin-1), IL-4 and IL-18, as well as M-CSF (macrophage colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor).^{25–29} And increased concentration of pro-inflammatory cytokines leads to increased expression of CD36 on the surface of macrophages and stimulates the accumulation of ox-LDL.^{21,24,30}

CD36 expression is reduced by TGF- β (transforming growth factor beta) through phosphorylation of MAPK (mitogen-activated protein kinases), followed by phosphorylation of PPAR γ and reduced gene transcription of CD36 in macrophages.³¹ Also bacterial lipopolysaccharides (LPS) and interferon gamma (IFN- γ) inhibit CD36 synthesis by reduction in mRNA expression in macrophages.^{26,27,32} The reduced accumulation of cholesterol in macrophages treated with IFN- γ and TNF- α , was also showed. This combined treatment of IFN- γ and TNF- α in mRNA reduced the CD36 expression on macrophages.³³

Recent studies indicate that human neutrophil peptides (HNPs) take part in atherosclerosis development.^{34,35} Quinn et al.³⁶ suggest that the HNP induces increase of CD36 expression in the surface of macrophages and as a result contributes to the increased amount of foam cell formation.

Research on double knockout nuclear pregnane X receptor (PXR) and ApoE mice showed the influence of PXR on the expression of CD36. Deficiency of PXR did not change the plasma levels of cholesterol and triglyceride in ApoE mice, but PXR and ApoE deficient mice had significantly decreased atherosclerotic lesions in the arteries.³⁷ Moreover, expression of CD36, lipid accumulation and CD36-mediated oxidized LDL uptake in the peritoneal macrophages of PXR and ApoE mice were reduced by PXR deficiency. One of the human PXR antagonists is bisphenol A (a chemical substance used in many consumer products). In PXR-humanized ApoE deficient mice, exposure to bisphenol A significantly increased the atherosclerotic lesion area in the aortic root and brachiocephalic artery as well as increased CD36 expression and lipid accumulation in macrophages.³⁸ This suggests that deficiency of PXR reduces the risk of atherosclerosis development which may be due to decreased CD36 expression and reduced lipid uptake in macrophages.³⁷

Méndez-Barbero et al. found that CD36 expression also depends on RCAN1 (regulator of calcineurin 1 activity).³⁹ RCAN1 genetic deletion decreased the expression of CD36 receptor on macrophages, reduced oxLDL uptake and inhibited macrophage migration, which contributes to reducing the size and severity of atherosclerosis in ApoE deficient mice.³⁹

Interestingly, AdipoR2 (adiponectin receptor 2) deficiency results in reduced atherosclerosis in the brachiocephalic artery in ApoE deficient mice. The macrophages

from AdipoR2^{-/-}ApoE^{-/-} mice had lower expression of CD36 compared to AdipoR2^{+/+}ApoE^{-/-} after incubation with oxidized LDL.⁴⁰

The authors have suggested that IRGM1 (a member of the immunity-related small GTPase family) plays a role in the regulation of oxLDL uptake by macrophages as a regulator for the CD36 receptor in the pathogenesis of atherosclerosis.⁴¹ IRGM1 regulates CD36 function by controlling F-actin polymerization, and loss of IRGM/IRMG1 (IRGM in humans) significantly decreases ox-LDL uptake in both mice and humans.⁴¹

Drugs modifying CD36 expression

Statins

Drugs lowering blood cholesterol concentration i.e., statins – indirectly decrease CD36 expression on monocytes and macrophages through reduction in the activity of PPAR γ . Statins also exert their anti-atherogenic action by inhibiting cholesterol synthesis and their anti-inflammatory and antithrombotic activity.⁴² The effect of reducing the expression of CD36 by the statins is also confirmed by other researchers who have evaluated the expression of CD36 in monocytes isolated directly from the fresh anticoagulated blood of patients with acute coronary syndromes (ACS), and then repeated the test after 6 months of treatment with atorvastatin patients (administration of a statin). They showed significantly lower expression of CD36 after treatment with atorvastatin, which suggests that atorvastatin significantly reduces the expression of CD36. These studies also indicate the participation of CD36 in the development of both atherosclerosis and ACS in humans.⁴³ Further studies have provided information that statins can activate PPAR γ not only in macrophages but in other vascular cells. Fukuda et al. have observed that statins (fluvastatin and pitavastatin) can activate PPAR γ in smooth muscle cells from the human aorta, thereby confirming the anti-atherogenic effects of this drug group.⁴⁴

Thiazolidinediones

Thiazolidinediones are synthetic PPAR γ ligands which increase the activity and expression of PPAR γ and lead to enhanced expression of CD36 resulting finally in increased intracellular transport of ox-LDL.^{24,45,46} Despite this, thiazolidinediones inhibit atherosclerosis, probably by decreasing expression of other scavenger receptors, e.g. class A, so that the total uptake of ox-LDL does not change.⁴⁷ Some clinical trials indicate that thiazolidinediones decrease triglycerides and LDL-cholesterol in serum and at the same time increase serum levels of HDL-cholesterol in type 2 diabetes.⁴⁸ These drugs stimulate the expression of proteins controlling the ejection of

cholesterol from the cells with the involvement of apolipoprotein A1. As a result, thiazolidinediones reduce the accumulation of cholesterol esters in macrophages and inhibit their transition into foam cells.⁴⁹ These drugs also inhibit the activation of macrophages by reducing the secretion of pro-inflammatory factors such as TNF- α (tumor necrosis factor alpha), IL-4 (interleukin-4) and IL-6 (interleukin-6) and the decreased activity of some transcription factors.^{45,47,49}

Studies on testicular orphan nuclear receptor 4 (TR4) knockout mice indicate that it affects the expression of CD36. Transcription factor TR4 directly associated with CD36 regulates gene expression on macrophages. TR4-knockout mice showed reduced CD36 expression on macrophages. Thus TR4 can affect foam cell formation by modulating the expression of CD36. Moreover, it was shown that polyunsaturated fatty acids (PUFAs) such as omega-3 and -6 and thiazolidinediones (rosiglitazone) can enhance CD36 activation through TR4.²⁴

Arginine

Arginine, whose supplementation protects endothelial function, also has an indirect effect on the development of atherosclerosis. Arginine contributes to the reduction of platelet aggregation and adhesion of mononuclear endothelial cells in hypercholesterolemia.⁷ The authors observed an increase of CD36 protein expression in the aorta of fat diet rats compared to a control group of rats, and a decrease in the arginine group compared to the fat diet group of rats.⁵⁰ Similar results were obtained in rat blood mononuclear cell experiments. CD36 mRNA expression increased in blood mononuclear cells in fat diet rats compared to control rats and decreased in the arginine group compared to the fat diet rats. CD36 mRNA expression in rats in both the arginine and control groups was similar. Based on these results, the authors suggest that, indirectly, arginine may reduce the development of atherosclerosis by reducing CD36 expression in blood mononuclear cells and the aorta of fat diet rats.⁵⁰

Conclusions

Atherosclerosis is a chronic progressive disease that begins in childhood. Knowledge about its exact pathomechanism might produce a tool to prevent it and perhaps also to treat it. CD36 is a major protein involved in ox-LDL uptake into macrophages. Animal studies suggest an important role of CD36 receptor in the development of atherosclerosis. Lack of CD36 expression on the surface of macrophages has prevented the development of atherosclerosis in mice.⁴ However, recently, the methods of these studies have been challenged and contradictory results have been described. Therefore, it is important to discover the exact role of CD36 receptor in the develop-

ment of atherosclerosis on animal models as this knowledge will allow us to conduct human-targeted research and establish more effective methods of treatment. The incidence of coronary heart disease has been described to be higher in patients with decreased CD36 expression than in the general population. These findings define the urgent need to clarify the involvement of CD36 receptor in atherosclerosis initiation and progression in humans.

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