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CD36 and Lipid Metabolism in the Evolution of Atherosclerosis

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Abstract

Introduction or background: CD36 is a multifunctional class B scavenger receptor, which acts as an important modulator of lipid homeostasis and immune responses.

Sources of data: This review uses academic articles.

Areas of agreement: CD36 is closely related to the development and progression of atherosclerosis.

Areas of controversy: Both persistent up-regulation of CD36 and deficiency of CD36 increase the risk for atherosclerosis. Abnormally up-regulated CD36 promotes inflammation, foam cell formation, endothelial apoptosis, macrophage trapping and thrombosis. However, CD36 deficiency also causes dyslipidemia, sub-clinical inflammation and metabolic disorders, which are established risk factors for atherosclerosis.

Growing points: There may be an 'optimal protective window' of CD36 expression.

Areas timely for developing research: In addition to traditionally modulating protein functions using gene overexpression or deficiency, the modulation of CD36 function at post-translational levels has recently been suggested to be a potential therapeutic strategy.

Keywords: CD36, atherosclerosis, hyperlipidemia, inflammation, endothelial dysfunction, macrophage migration, foam cell, thrombosis

1. INTRODUCTION

Atherosclerosis is a chronic inflammatory disease of the arterial wall and a major cause of vascular death worldwide. Its primary clinical manifestations include coronary heart disease (CHD), ischemic stroke and peripheral artery disease. In the United States, the prevalence of CHD in adults is estimated to be 6.2%, and the annual cost of CHD and strokes is approximate $317 billion. Atherosclerotic lesions begin with endothelial dysfunction in arterial vasculature, which leads to focal permeation and trapping of circulating monocytes and lipoprotein particles in the sub-endothelial space (intima). Intimal monocytes differentiate into macrophages and internalise modified lipoproteins to form foam cells, which is the hallmark of early fatty streak lesions. The activated macrophages produce and secrete multiple cytokines/chemokines and growth factors, which act on smooth muscle cells to induce proliferation and synthesis of extracellular matrix components within the intimal space, thus generating a fibromuscular plaque. Progressive structural remodelling of developing lesions results in the formation of complex plaques containing a fibrous cap, a lipid-rich, necrotic core and a rich population of inflammatory cells, including activated macrophages, T-cells, natural killer T-cells and dendritic cells, accompanied by varying degrees of matrix remodelling and calcification.

As the fat-laden foam cell is the earliest visible characteristic of the atherosclerotic lesion, the underlying molecular mechanisms for their formation have attracted much interest for decades. Almost 40 years ago, Goldstein et al. demonstrated that the uptake of oxidised low-density lipoprotein (ox-LDL) by scavenger receptors could trigger macrophage foam cell formation in vitro.[1] Following this line, much interest has been focused on the role of scavenger receptor in atherosclerosis. To date, the class B scavenger receptor CD36, a key mediator of ox-LDL uptake in macrophages,[2] has received the most attention. Numerous studies have demonstrated its importance in hyperlipidemia, inflammation, endothelial dysfunction, macrophage migration, foam cell formation and thrombosis,[3] which are clearly related to the development and progression of the atherosclerotic lesion. In this review, we summarise the knowledge gained regarding the roles of CD36 in atherosclerosis.

2. THE STRUCTURE, LIGANDS AND FUNCTIONS OF CD36

CD36 is expressed in various cells, including skeletal and cardiac myocytes, adipocytes, microvascular endothelial cells, macrophages, platelets, epithelial cells in the gut, kidney and breast, and microglia. It is an integral membrane glycoprotein, which has a hairpin-like membrane topology with two transmembrane domains, two very short intracytoplasmic domains, and a large heavily glycosylated extracellular domain. The extracellular domain of CD36 proteins contains binding sites for ligands. It has been demonstrated that fatty acid (FA)-binding site in CD36 (amino 127-279) overlaps with the binding sites (amino 157-171) of ox-LDL and oxidised phosphatidylcholine. The carboxyl tail of CD36 can be interacted with Src-family

tyrosine kinases and is necessary for signal transduction.[4]

CD36 independently binds and recognises multiple exogenous or endogenous ligands, including molecules presented on pathogens or pathogen-infected cells, apoptotic cells, long-chain fatty acid (LCFA), modified low-density lipoprotein (LDL) and high-density lipoprotein (HDL), glycated proteins, β-amyloid protein, serum amyloid A and thrombospondin-1 (TSP1). These ligands can be categorised into three major classes: LCFA; pathogen-associated molecular patterns (PAMPs) and endogenously derived hazardous molecules (e.g. ox-LDL); TSP1 and proteins that contain the TSP1 structural homology region (TSR). Through the interaction with diverse ligands, CD36 can modulate multiple physiologic and pathologic processes, including FA transport and lipid metabolism, scavenger receptor functions (e.g. uptake of apoptotic cells and modified lipid), angiogenesis, adhesion, inflammation, cardiomyopathy, diabetes and atherosclerosis.

3. THE ROLES OF CD36 IN HYPERLIPIDEMIA

A strong link between hypercholesterolemia and atherogenesis was established over 40 years ago, based on abundant experimental and clinical relationships between hypercholesterolemia and atheroma.[5] Hypertriglyceridemia is also a risk factor for atherosclerosis. In a cohort of 500 survivors of myocardial infarction, Goldstein and colleagues demonstrated that elevation in triglyceride levels with or without an associated elevation in cholesterol levels was three times more common in cardiovascular disease (CVD) patients than high cholesterol levels alone.[6] In patients with familial hypertriglyceridemia (FHTG), baseline triglyceride levels can predict subsequent cardiovascular disease mortality.[7] Furthermore, triglyceride reduction in clinical trials using fibric acid drugs has been suggested for reduction of CVD events in hypertriglyceridemic (HTG) subjects.[8]

Patients with the CD36 deficiency or CD36 gene polymorphism often display postprandial hyperlipidemia with high levels of plasma apoB48, triglyceride, FA and chylomicron (CM) remnants.[9, 10] These observations suggest the importance of CD36 in hyperlipidemia and related atherosclerosis. CD36 is involved in multiple processes of lipid metabolisms, including dietary lipid intake, lipoprotein production and transport, lipid utilisation, storage and lipolysis, which will be discussed below.

3.1. CD36 and dietary lipid intake: Dietary lipid is an important source of lipids in the blood. As a lifestyle with high-fat diet consumption is closely related to increased risk of dyslipidemia and atherosclerosis, the role of CD36 in lipid sensing and its regulation on lipid intake has drawn much attention in the recent decade. CD36 in taste bud cells can recognise dietary FA and induce the rise of cytosolic calcium, resulting in neurotransmitter release and central fat perception.[11] CD36 in hypothalamic metabolic-sensing neurons is also crucial for neuronal FA sensing.[12] In addition, obese patients carrying a single-nucleotide polymorphism in the CD36 gene (rs1761667 involving A/G substitution), which reduces CD36 expression in monocytes and platelets,[13] have lower sensitivity for fat perception and have increased

preference for food with high-fat content.[14]

3.2. CD36, CM formation and clearance: CD36 plays an essential role in coordinating the incorporation of FA and cholesterol into CM (82% triglyceride, 9% cholesterol, 7% phospholipid, and 2% protein),[15] which is responsible for transporting dietary lipids from gut to the blood. The particle size of CM in CD36-null mice is smaller than in wild-type mice. More importantly, CD36 deficiency impairs clearance of CM from the blood, which induces hyperlipidemia in the postprandial and fasting states.[16] Postprandial hyperlipidemia with high levels of CM remnants is also observed in humans with CD36-deficiency.[17]

3.3. CD36, lipid utilisation, lipid storage and lipolysis: In heart and skeletal muscle of rodents and humans, CD36 has been recognised as a major FA transporter and serves to supply the cells with an energy source for beta-oxidation. Patients with mutations in the CD36 gene, in which the expression of the CD36 protein was not detected on either platelets or monocytes membranes, display total lack of LCFA accumulation in the heart.[18] In adipose tissue, CD36 regulates the process of lipid storage and lipolysis. CD36 is a marker of human adipocyte progenitors and cells with a high CD36 level have pronounced adipogenic and triglyceride accumulation potential. CD36 gene silencing attenuates adipocyte adipogenesis in vivo and in vitro. The level and trafficking of CD36 are also associated with lipolysis and FA re-esterification. CD36 deletion increases the cAMP level through interaction with Src and ERK signaling, which results in triglyceride hydrolysis and an increase of free FA into plasma.[19]

Thus, CD36 is necessary for the maintenance of lipid homeostasis. In patients with CD36-deficiency or CD36 gene polymorphism, multiple factors may contribute to the occurrence of dyslipidemia, including their preference for food with high-fat content, impaired CM formation and clearance, reduced lipid utilisation and lipid storage, as well as increased lipolysis (Figure 1).

4. THE ROLE OF CD36 IN CHRONIC INFLAMMATION

Several new lines of evidence support the model of atherosclerosis as an inflammatory disease [20]: 1) Patients with chronic systemic inflammatory disorders, e.g., systemic lupus erythematosus, dialysis, obesity, type 2 diabetes and ageing have significantly increased the risk of atherosclerosis. 2) Inflammatory biomarkers including C-reactive protein, myeloperoxidase (a marker of leukocyte activation), and antibodies to ox-LDL are associated with risk and prognosis of atherosclerosis. 3) Tissue studies demonstrate that leukocyte recruitment and expression of pro-inflammatory cytokines characterize early atherogenesis, and malfunction of inflammatory mediators mutes atheroma formation in mice. Moreover, inflammatory pathways promote thrombosis, responsible for myocardial infarction and strokes. 4) Atherosclerosis is absent in animal models lacking monocytes or monocyte recruitment as well as T-cell–derived pro-inflammatory cytokines.

As a member of the class B scavenger receptor family, CD36 can recognise multiple endogenously derived hazardous molecules (e.g. ox-LDL), resulting in the activation of sterile inflammation. Although this process originally evolved to eliminate hazardous molecules, persistent inflammation contributes to a broad range of chronic metabolic disorders, including atherosclerosis, type 2diabetes and Alzheimer's disease. Thus CD36 up-regulation is closely related to chronic inflammation and the development of atherosclerosis. However, recent studies also support an important role of CD36 in the regulation of immune and inflammatory responses. The function of CD36 in mediating the pro-inflammatory and anti-inflammatory response will be discussed below.

4.1. Pro-inflammatory effects of CD36

CD36 and Toll-like receptor (TLR): CD36 ligands (e.g. ox-LDL) triggers the assembly of a CD36–TLR4–TLR6 heterotrimeric complex, activating transcription factor nuclear factor κB (NF-κB) and boosting sterile inflammation in macrophages and microglia cells.[21] Atherogenic lipid mediators such as ox-LDL, oxidised phospholipids, lipoproteins and FAs, also trigger an oxidative burst through the CD36–TLR2–TLR6 pathway, resulting in apoptosis of endoplasmic reticulum-stressed cholesterol-overloaded foam cells.[22] Defective clearance of apoptotic cells then causes secondary necrosis, triggering a pro-inflammatory response from macrophages. Furthermore, CD36 protein expression is up-regulated by pro-inflammatory cytokines at post-transcriptional level through modulating its translation in the ribosome, which may enlarge the inflammatory response in a feed-forward loop.

The mechanisms by which CD36 promotes TLRs activation remain incompletely understood. Few studies suggested that the interaction between CD36 and TLRs may be mediated by the activation of the Src family pathway. CD36 ligands recruit Lyn kinase to CD36,[21] which may contribute to TLR4 and TLR6 phosphorylation and activation.

CD36 and NLRP3-inflammasome: The nucleotide-binding domain and leucine-rich repeat pyrin domain containing 3 (NLRP3) inflammasome is a large multi-protein complex which comprises of the NLRP3 protein, the adapter apoptosis-associated speck-like protein (ASC) and pro-caspase-1. The NLRP3-Inflammasome catalyses the cleavage of pro-IL-1β and pro-IL-18 into their biologically active forms, which has been linked to the pathogenesis of several chronic inflammatory diseases such as atherosclerosis, type 2 diabetes (T2D) and Alzheimer's disease.

CD36 is involved in both NLRP3-inflammasome priming and activation. Sheedy et al. found that ox-LDL sequestered by macrophage CD36 activated NF-κB, downstream of the heterotrimeric CD36-TLR4-TLR6 complex, thereby up-regulating NF-κB-driven NLRP3 expression.[23] In addition, CD36-mediated ox-LDL uptake results in the intracellular accumulation of cholesterol crystals that cause lysosomal disruption and NLRP3-inflammasome activation.[23] This finding highlights the role of

the CD36 act as a central regulator of inflammasome activation.

4.2. Anti-inflammatory effects of CD36

CD36 and IL-10: IL-10 is an important anti-inflammatory cytokine that plays a multitude of roles in regulating both innate and adaptive immune responses. A subset of the peripheral blood mononuclear cell (PBMC) isolated from healthy individuals has readily detectable intracellular IL-10, and there is a linear relationship between IL-10 production and surface CD36 expression levels in these cells.[24] Interaction of CD36 on monocytes and immature dendritic cells with apoptotic cells is also associated with the secretion of IL-10. Binding of the apoptotic cells to CD36 on macrophages triggers Src family, p38 mitogen-activated protein kinase (MAPK) activation and phosphorylation of Pbx regulating protein-1 (Prep-1), thereby increasing pre-B cell leukaemia transcription factor-1 (Pbx-1) binding to the ACRE of the IL-10 promoter and up-regulating IL-10 transcription.[25] These findings support the importance of CD36 in the process of IL-10 induction and imply its anti-inflammatory effects in the microvasculature.

CD36 and the clearance of neutrophils: Effective elimination of neutrophils is essential for the resolution of the inflammatory process. Ballesteros et al. found that in a CD36-dependent manner, the peroxisome proliferator–activated receptor (PPAR) gamma agonist increases the microglia/macrophage-mediated phagocytosis of infiltrated neutrophils and contributes to the resolution of inflammation in stroke. Cifarelli et al. also reported that CD36-null mice exhibit chronic neutrophil infiltration of the gut and impaired epithelial barrier integrity, accompanied by an increase in circulating neutrophils and endotoxin levels as well as a depletion of Ly6Clow anti-inflammatory monocytes.[26] Loss of CD36 on endothelial cells, but not on enterocytes, causes neutrophil infiltration and epithelial barrier leakage in small intestines, reproducing notable abnormalities identified in germline CD36KO mice.[26]

Together, the current results suggest that CD36 is important in the maintenance of immune homeostasis. The interaction of CD36 with different ligands may trigger different signaling pathways, resulting in wholly different phenomena (the pro- and anti-inflammatory responses) (Figure 2). In considering its importance in maintaining the balance between inflammation and anti-inflammation responses, both abnormal up-regulation and deficiency of CD36 may disrupt homeostasis and cause persistent inflammation in vivo.

5. CD36 AND ENDOTHELIAL DYSFUNCTION

Several studies have linked CD36 to endothelial dysfunction. In vitro, glucose increased CD36 mRNA and protein levels in microvascular endothelial cells, accompanied by an increase of ox-LDL uptake, haemoxygenase-1 (HO-1) and endothelin-1 (ET-1) expression.[27] These glucose-induced changes are prevented by CD36 gene silencing in endothelial cells.[27] Jimenez et al. demonstrated that the interaction between endothelial cell CD36 and TSP1 leads to phosphorylation of the

Src kinase Fyn, followed by phosphorylation of p38 MAPK.[28] This signaling pathway leads to cellular apoptosis of endothelial cells, and thus efficiently prevents angiogenesis.[28] However, CD36 is reported to be required for activation of endothelial nitric oxide (NO) synthase in response to high-density lipoprotein.[29] CD36-null mice exhibited higher arginase activity in adipose tissues,[30] which may contribute to decreased production of NO, causing reduced endothelial NO bioavailability and endothelial dysfunction. These findings suggest that CD36 is physiologically necessary for the maintenance of endothelial function; the abnormal up-regulation of CD36 under pathological conditions, such as hyperglycemia, may also lead to endothelial dysfunction.

6. THE ROLE OF CD36 IN MACROPHAGE MIGRATION

The migration of circulating monocyte into the arterial intima is a critical event in the development of atherosclerosis. However, the role of CD36 in monocyte/macrophage migration is complicated since both CD36 overexpression and down-regulation may regulate macrophage migration through different mechanisms.

Park et al. found that treatment of macrophages with ox-LDL activates (FAK) and inactivates Src homology 2-containing phosphotyrosine phosphatase, inducing actin polymerisation and cell spreading, thereby inhibiting cellular migration in a CD36-dependent manner.[31] The authors thus conclude that up-regulation of CD36 by ox-LDL inhibits macrophage migration and may contribute to macrophage trapping in the atherosclerotic lesion.

Paradoxically, however, Harb et al. reported that EP80317, a CD36-binding peptide which competes for the binding domain with ox-LDL on CD36, reduces phosphorylation of the focal adhesion kinase (FAK) Pyk2, resulting in reduced recruitment of radiolabeled macrophages to atherosclerotic lesions in ApoE$^{-/-}$ mice, but not in CD36-deficient mice.[32] Kuchibhotla et al. also reported that CD36-deficient macrophages display reduced chemotaxis towards the chemokine CCL2.[33] These studies thus support that the inhibition of CD36 on macrophages inhibits macrophage migration.

In addition, we recently found that while CD36 genetic silencing in macrophages inhibits cellular migration, CD36 genetic silencing in hepatic parenchyma cells promotes macrophage migration.[34] CD36 deficiency inactivates nuclear histone deacetylase 2 (HDAC2) and activates MCP-1 transcription in hepatic parenchyma cells, thereby promoting macrophages migration through a paracrine loop.[34] Interestingly, CD36 deficiency in macrophages does not alter the histone modification of MCP-1 promoter, at least in part, due to low levels of HDACs in macrophage nuclei.[34] Thus our findings provide the first evidence that CD36 is involved in the epigenetic modification of MCP-1 gene in a cell-specific manner. This also highlights the importance of CD36 in regulating the cross-talk between parenchyma cells and macrophages migration.

7. THE ROLE OF CD36 IN FOAM CELL FORMATION

It is well-recognised that macrophage scavenger receptors mediate the uptake of ox-LDL. Although this process is originally evolved to be homeostatic (i.e. clearance of modified lipoproteins from the vessel wall), the persistent uptake of ox-LDL "loads" the cells with excess cholesterol, resulting in what is called "foam cells", the earliest visible characteristic of the atherosclerotic lesion.

It is noteworthy that ox-LDL can increase CD36 expression through activating the nuclear hormone receptor PPAR gamma, a transcription factor that regulates the expression of CD36. Thus ox-LDL promotes further cellular ox-LDL uptake, and this feed-forward loop presumably accelerates foam cell formation in the arterial intima. The CD36 expression is also up-regulated at the transcriptional level by FA and its metabolite, e.g. 13-hydroxy octadecadienoic acid (13-HODE), through activating the nuclear transcription factors testicular orphan nuclear receptor 4 (TR4) and/or PPAR gamma,[35] thereby promoting cellular uptake of ox-LDL and causing foam cell formation (Figure 3). Hyperglycemia promotes CD36 expression and contributes to a pro-atherosclerotic state in patients with diabetes.

CD36 deficiency in human monocyte-derived macrophages significantly reduced its binding and uptake capacity for ox-LDL.[2] The absence of CD36 expression is associated with a lack of foam cell formation in vitro when macrophages are exposed to ox-LDL.[36] However, the in vivo result of the CD36 function in foam cell formation is controversial. There appears to be no deficiency in foam cell formation in $ApoE^{-/-}$ mice deficient in either CD36 or scavenger receptor A, or both.[37] This remarkable observation suggests that foam cell formation may occur via pathways that are independent of scavenger receptors or ox-LDL uptake in vivo.

8. CD36 AND THROMBOSIS

Atherothrombotic events are severe adverse complications of atherosclerosis. Platelet CD36 mediates ox-LDL-induced platelet activation and the release of granules including IL-1β.[38] It renders platelets hypersensitive to aggregation stimuli by for example ADP, thereby contributing to platelet aggregation and atherothrombosis in vivo and in vitro. The underlying mechanism is dependent on ox-LDL-mediated activation of the CD36 signal cascade, which induces recruitment of the Src family proteins Fyn and Lyn to CD36.[39] This then leads to the phosphorylation and activation of JNK family members and extracellular signal-regulated kinase 5 (ERK5), thereby promoting platelet aggregation and thrombosis.[40] CD36-null mice have significantly prolonged thrombotic occlusion times in response to vascular injury.[41] Thus CD36 is an important link between lipid metabolism, atherosclerosis and thrombosis.

9. THE COMPLEXITY OF CD36 IN ATHEROSCLEROSIS

The roles of CD36 in atherosclerosis are both complex and conflicting in both rodents and humans. It seems that both CD36 overexpression and complete CD36 deficiency predispose to metabolic complications.

Spontaneously hypertensive rats (SHR) genetically deficient in CD36 display several features of human metabolic syndromes, including hypertension, type 2 diabetes, obesity, and hyperlipidemia.[42] Transgenic overexpression of CD36 in SHR ameliorates insulin resistance and lowers serum FAs.[43] These findings thus support CD36 as a protective factor for atherosclerosis in rat models.

In mice models, the function of CD36 in atherosclerosis is controversial. Febbraio et al. reported that CD36 deficiency reduced aortic lesion formation by 76% in ApoE deficient mice.[33, 36] Bone-marrow-specific deletion of CD36 has similar protective effects on atherosclerosis in ApoE$^{-/-}$ mice, suggesting CD36 on macrophages act as the key pro-atherogenic mediator of atherosclerosis.[44] Genetic deletion of CD36 also protects ApoE$^{-/-}$mice from the hyper-coagulability and the prothrombotic state.[45] Thus these findings support the pro-atherosclerotic and pro-thrombotic potential of CD36. Paradoxically, however, Freeman and colleagues found in ApoE$^{-/-}$ mice that deletion of either CD36 or the related scavenger receptor A, or both had little impact on aortic lesion area in their experimental system.[37, 46] To date, explanations of these different findings remain unclear.

Likewise, the results from studies of CD36 function in human atherosclerosis are both complex and controversial. Levels of soluble CD36 are positively correlated with plaque instability and symptomatic carotid atherosclerosis.[47] The expression of CD36 on macrophages was significantly increased in atherosclerotic plaques of the human aorta.[48] The mRNA expression of CD36 on human PBMCs was significantly higher in hypercholesterolemic than normocholesterolemic patients. These findings thus suggest CD36 overexpression is perhaps a biomarker for the development and progression of atherosclerotic lesions.

However, the studies of human populations with the CD36 deficiency or CD36 gene polymorphism raise the possibilities that CD36 deficiency is as much a risk factor as CD36 overexpression for atherosclerosis. CD36 deficiency is rare in Caucasians but is relatively common (3-6%) in Asian and African populations. A genetic CD36 deficiency is closely associated with an increased prevalence of metabolic abnormalities, including hyperlipidemia, hypertension, and elevated fasting glucose contents.[49] So far, there is no definitive evidence supporting the direct relationship between human CD36 deficiency and altered cardiovascular risk although hit has been reported that the frequency of CD36-deficiency was three times higher in CHD patients than in healthy subjects.[17]

Overall, these findings support that there may be an ‘optimal protective window’ of CD36 expression that either abnormal up-regulation or deficiency of CD36 may

increase the risk for atherosclerosis. We proposed that different mechanisms are involved in these processes. When CD36 is persistently up-regulated by pathological factors, for example, ox-LDL and TSP1, it promotes inflammation induced by NF-κB and inflammasome activation, foam cell formation, endothelial apoptosis, macrophage trapping and thrombosis. On the other hand, in subjects with the CD36 deficiency or CD36 gene polymorphism, multiple factors may contribute to the development of atherosclerosis, including hyperlipidemia, subclinical inflammation caused by impaired apoptotic cells clearance, increased neutrophils and endotoxin levels, impaired endothelial NO bioavailability, and increased macrophage migration through a paracrine-loop (Figure 4). Therefore, the maintenance or restoration of CD36 function is important for prevention or treatment of atherosclerosis.

Traditionally, we modulate protein functions at translational levels using gene overexpression or deficiency. Recently, increasing amounts of data have suggested that in addition to this, the post-translational modifications may be a novel mechanism to modulate the location and function of CD36.[50] These post-translational modifications on CD36 proteins include phosphorylation, glycosylation, palmitoylation, and ubiquitination. Glycosylation is necessary for CD36 location in plasma membranes. Inhibition of palmitoylation decreases the incorporation of CD36 into plasma membrane rafts, thereby reducing the efficiency of uptake of ox-LDL in vitro.[51] Furthermore, we recently found that the blocking of CD36 palmitoylation reducing FA uptake and inflammatory response in mice models (unpublished data). These data suggest that modulation of CD36 functions at post-transcriptional levels may provide a new therapeutic strategy for the treatment of atherosclerosis.

10. CONCLUSION

CD36 is a multi-functional immuno-metabolic receptor. It functions physiologically as an important modulator in lipid homeostasis and immune homeostasis. Both abnormal and persistent up-regulation of CD36 and CD36 deficiency are involved in the development and progression of atherosclerosis. Thus there may be an 'optimal protective window' of CD36 expression. The modulation of the CD36 function at post-translational levels may provide a new potential therapeutic strategy for treatment of atherosclerosis.

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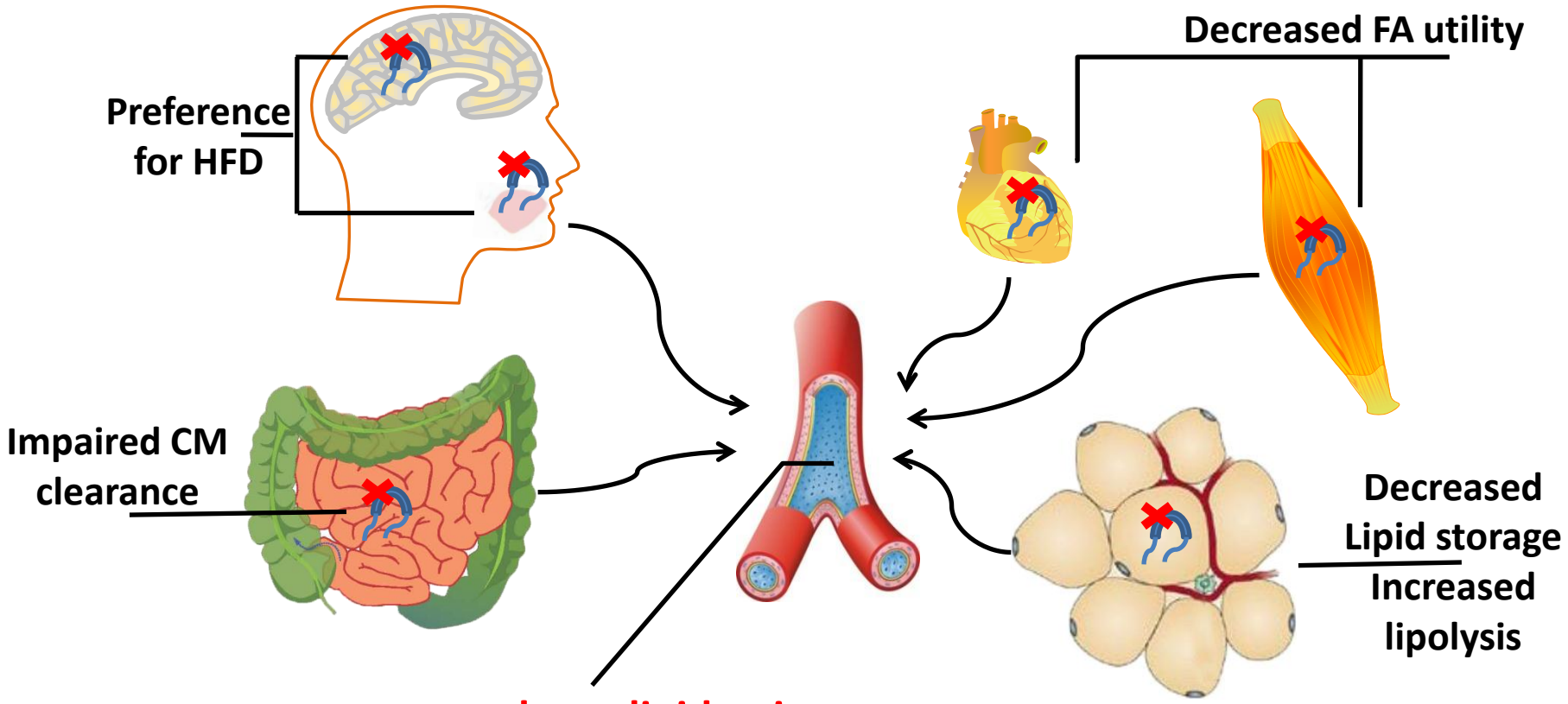
Figure legends

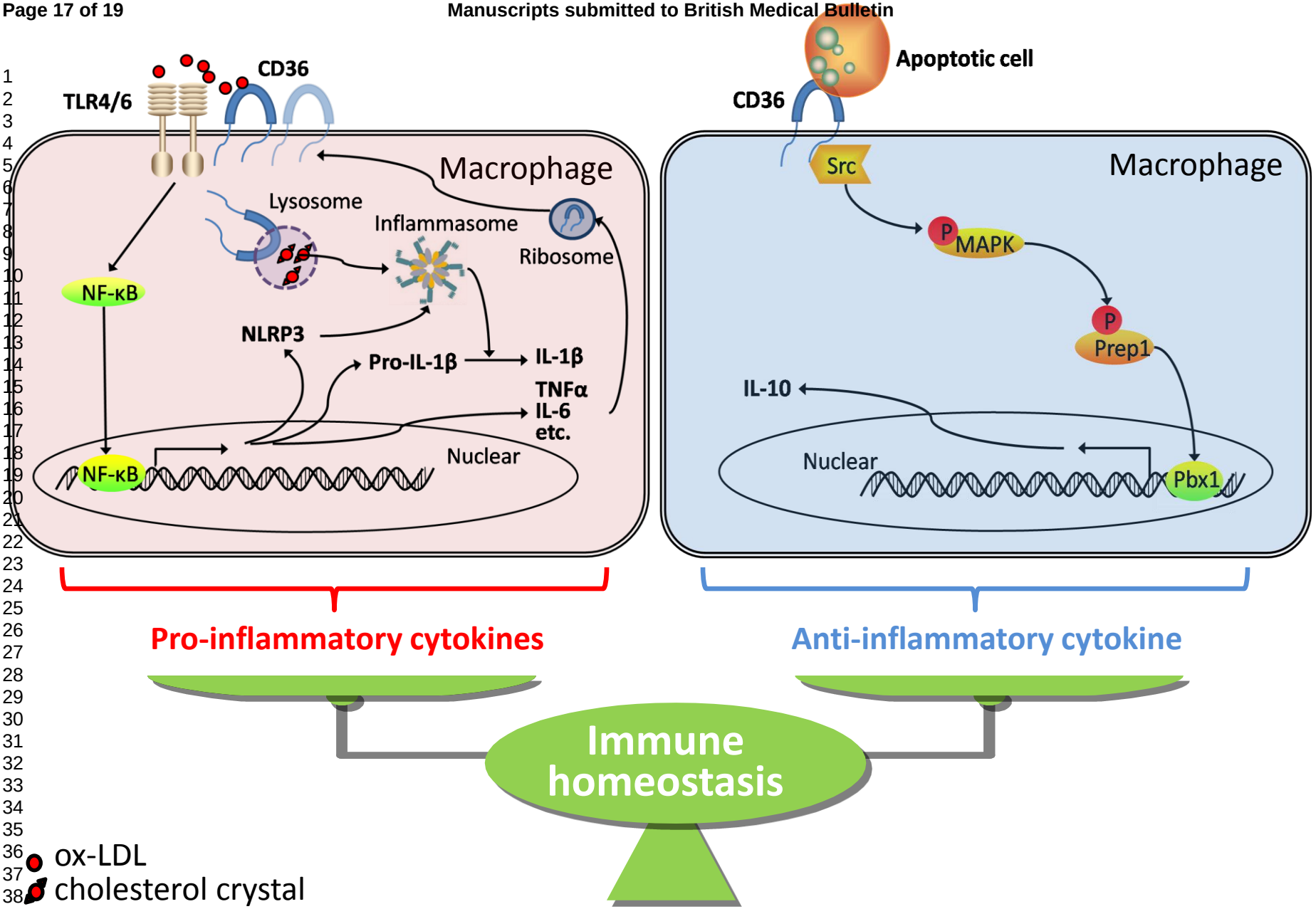
Fig1. The mechanisms of hyperlipidemia in patients with CD36 deficiency. CD36-deficiency may cause the preference for food with high-fat content. The impairment of CM clearance, the reduction of lipid utilisation and lipid storage, as well as the increase of lipolysis contribute to the occurrence of dyslipidemia in patients. TG, triglyceride; FA, fatty acid; CM, chylomicron.

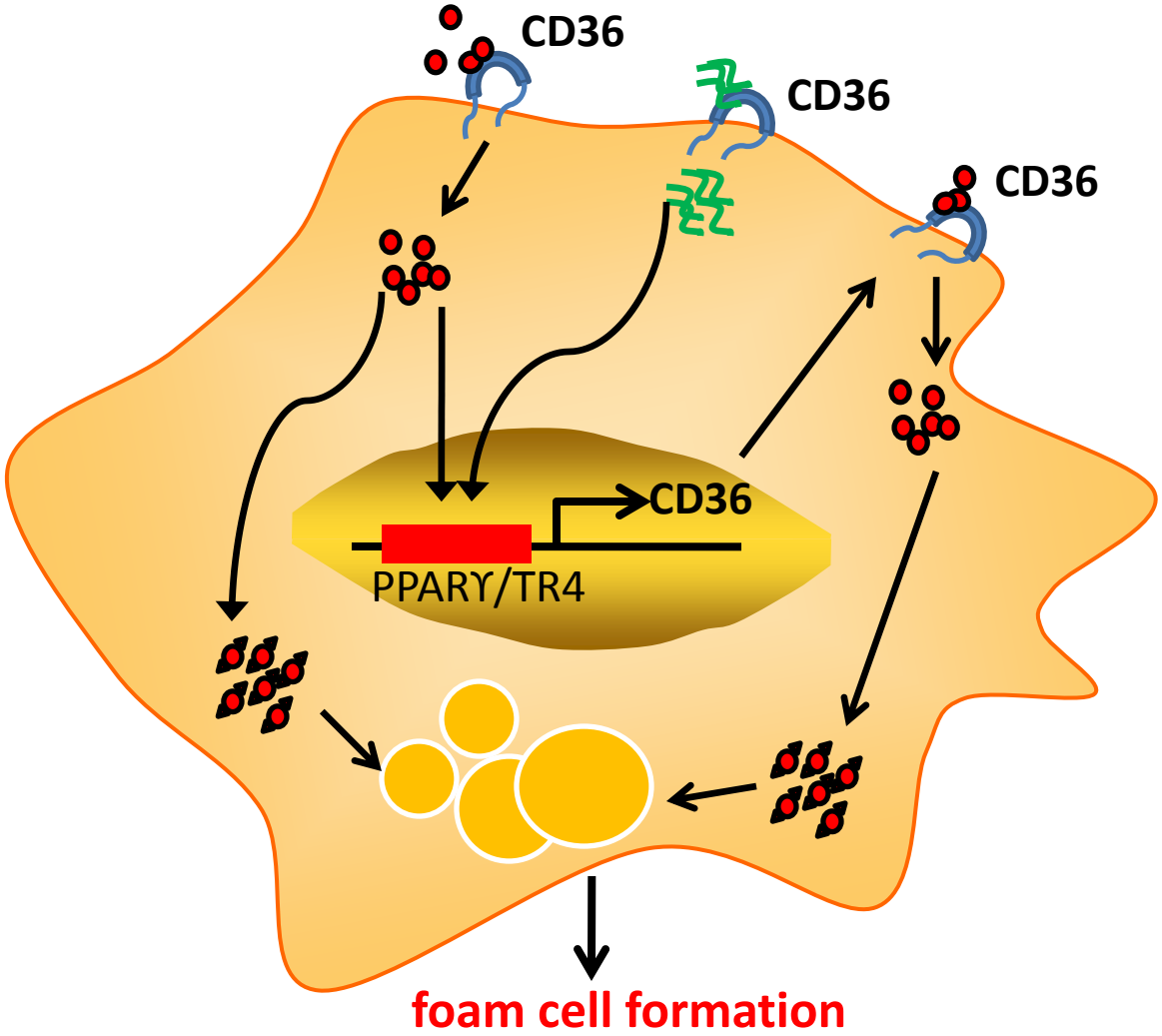
Fig2. The molecular mechanisms of CD36 modulation in inflammatory response and immune homeostasis. With the interaction with ox-LDL, CD36 mediates the activation of NF-κB and NLRP3-inflammasome, boosting sterile inflammation in macrophages. However, binding of the apoptotic cells to CD36 on macrophages up-regulates IL-10 expression, resulting in an anti-inflammatory response. Thus CD36 is important in the modulation of the pro- and anti-inflammatory responses. ox-LDL, oxidative low density lipoprotein; TLR, toll-like receptor; NLRP3, nucleotide-binding domain and leucine-rich repeat pyrin domain containing 3; NF-κB, nuclear factor kappa B; TNFα, tumor necrosis factor alpha; IL-1β, interleukin 1β; IL-6, interleukin 6; IL-10, interleukin 10; MAPK, mitogen-activated protein kinase; Prep1, Pbx regulating protein-1; Pbx1, pre-B cell leukemia transcription factor-1.

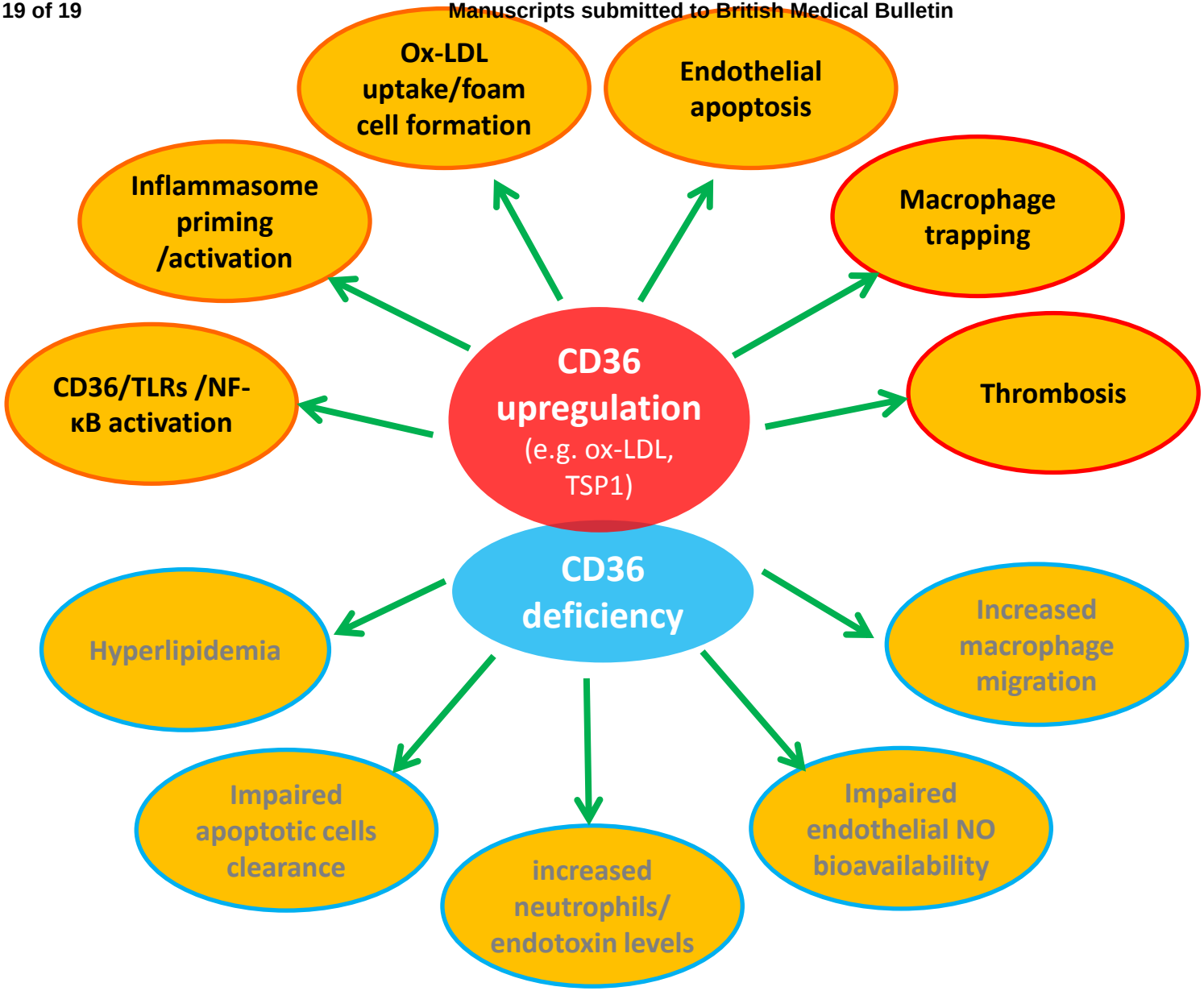
Fig3. The role of CD36 in foam cell formation. Macrophages uptake ox-LDL in a CD36-dependent manner. Furthermore, ox-LDL and FA activate the nuclear transcription factors TR4 and PPAR gamma, increasing CD36 expression. This feed-forward loop promotes further cellular uptake of ox-LDL and causing foam cell formation. ox-LDL, oxidative low-density lipoprotein; FA, fatty acid; PPARϒ, peroxisome proliferator–activated receptor gamma; TR4, testicular orphan nuclear receptor 4.

Fig4. A proposed hypothesis for the potential link between CD36 and atherosclerosis. When CD36 is persistently up-regulated, it promotes inflammation, foam cell formation, endothelial apoptosis, macrophage trapping and thrombosis. On the other hand, in subjects with the CD36 deficiency or CD36 gene polymorphism, hyperlipidemia, subclinical inflammation, impaired endothelial NO bioavailability, and increased macrophage migration may also increase the risk of atherosclerosis. ox-LDL, oxidative low-density lipoprotein; TSP1, thrombospondin-1; TLR, toll-like receptor; NF-κB, nuclear factor kappa B.


Preference for HFD
Decreased FA utility
Impaired CM clearance
Decreased Lipid storage
Increased lipolysis
hyperlipidemia with high levels of plasma TG, FA and CM remnants
CD36 deficiency


TLR4/6
CD36
Macrophage
Lysosome
Inflammasome
Ribosome
NF-κB
NLRP3
Pro-IL-1β
IL-1β
TNFα
IL-6
etc.
Nuclear
NF-κB
Apoptotic cell
CD36
Src
Macrophage
P
MAPK
P
Prep1
IL-10
Nuclear
Pbx1
Pro-inflammatory cytokines
Anti-inflammatory cytokine
Immune homeostasis
ox-LDL
cholesterol crystal


CD36
CD36
CD36
CD36
PPARγ/TR4
foam cell formation
ox-LDL
FA
cholesterol crystal


Ox-LDL uptake/foam cell formation
Endothelial apoptosis
Inflammasome priming /activation
Macrophage trapping
CD36/TLRs /NF-κB activation
CD36 upregulation (e.g. ox-LDL, TSP1)
Thrombosis
CD36 deficiency
Hyperlipidemia
Increased macrophage migration
Impaired apoptotic cells clearance
increased neutrophils/ endotoxin levels
Impaired endothelial NO bioavailability