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Lipids and the Endothelium: Bidirectional Interactions

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Abstract

The endothelium is often viewed solely as the barrier that prevents the penetration of circulating lipoproteins into the arterial wall. However, recent research has demonstrated that the endothelium both takes an important part in regulating circulating fatty acids and lipoproteins, and is in turn affected by these lipids/lipoproteins in ways that appear to have important repercussions for atherosclerosis. Thus, a number of potentially toxic lipids are produced during lipolysis of lipoproteins at the endothelial cell surface. Catabolism of triglyceride-rich lipoproteins creates free fatty acids that are readily taken up by endothelial cells, and, likely through the action of acyl-CoA synthetases, exacerbate inflammatory processes. In this article, we will review how endothelium participates in lipoprotein metabolism, how lipids alter endothelial functions, and how lipids are internalized, processed and transported into the subendothelial space. Finally, we will address the many endothelial changes that might promote atherogenesis, especially in the setting of diabetes.

Keywords

Acyl-CoA; Atherosclerosis; Diabetes; Endothelium; Fatty Acid; High-density lipoprotein; Lipoprotein lipase; Low-density lipoprotein; Metabolic Syndrome; Mouse models; Very low-density lipoprotein

Introduction

Cardiovascular (CVD) disease caused by atherosclerosis is the major cause of morbidity and mortality in subjects with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [1]. It also is common in subjects with the metabolic syndrome [2]. Mouse models have demonstrated that diabetes promotes both atherosclerotic lesion initiation and progression into advanced lesions [3–5] and slows regression of lesions [6**]. At least some of these effects are likely to be mediated by effects on the endothelium [7]. In this review, we will focus on the endothelial cell and its roles in lipoprotein metabolism. In addition, we will discuss studies of endothelial dysfunction that relate to CVD in the setting of diabetes and the metabolic syndrome. Special emphasis is placed on recent discoveries related to the

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roles of lipoproteins and fatty acids, and the mechanisms whereby lipoproteins and fatty acids modulate endothelial function and subsequent atherosclerosis. The discussed mechanisms are summarized in Figure 1.

How do endothelial cells modulate metabolism of triglyceride-rich lipoproteins?

Endothelial biology is almost certainly affected by circulating lipoproteins. T2DM and the metabolic syndrome are associated with abnormalities in circulating lipids, whereas T1DM does not usually result in lipid abnormalities, unless inadequately controlled. In poorly controlled subjects with T1DM, higher triglyceride levels are observed [8]. The most common lipid abnormalities in T2DM and the metabolic syndrome are hypertriglyceridemia, greater concentrations of small dense LDL, and changes in HDL cholesterol [8]. The relationship between circulating triglyceride levels and atherosclerosis is still unclear and the human epidemiologic and clinical intervention data has been reviewed recently [2,10]. In part, this controversy has continued because of a lack of definitive human intervention data and experimental animal models. Severe hypertriglyceridemic mice develop small amounts of atherosclerosis with aging [11–12]. However, these mice had defective lipolysis and therefore did not test whether local lipolysis is deleterious.

Endothelial cell toxicity can occur due to circulating lipids or lipolysis products that are generated at the endothelial surface. This latter process is due to the actions of lipoprotein lipase (LpL) anchored to the luminal surface of endothelial cells via its interactions with proteoglycans and a specific LpL binding protein, glycosyl inositol HDL binding protein 1 (GPIHBP1) [13] which also might allow transfer of LpL from the abluminal to luminal sides of endothelium [14]. Discovery of this protein by the Young laboratory was a major advance in our understanding of LpL metabolism as it showed that LpL binding to the endothelium was not a non-specific interaction with proteoglycans. It should be noted that humans with defects in GPIHPB1 have hypertriglyceridemia [15]. Aside from recent and on-going studies to understand the structure/function relationship of LpL-GPIHPB1 interaction, reviewed in [16], there are a number of still unanswered issues relating to this biology. Is part of the LpL binding to GPIHBP1 a necessary process to protect LpL from inactivation by angiopoietin-like protein 4, as recently suggested [17]? Are there alternative methods for LpL recruitment that are in play with high fat feeding or prolonged heparin administration, which has been shown to reduce triglyceride to normal in GPIHBP1 deficient patients [18]? Does the VLDL receptor, which is highly expressed in endothelial cells, also mediate LpL transport and is this the reason that VLDL receptor deficiency is associated with decreased LpL activity and hypertriglyceridemia in the setting of increased lipoprotein production [19–20]?

Lipolysis of triglyceride-rich lipoproteins liberates free fatty acids, lysolecithin and a number of epoxides and oxidized lipids [21]. Many of these lipids have been used in *in vitro* studies to mimic putative atherogenic events. These include increased expression of adhesion molecules by lysolecithin [22], and reduced activity of endothelial nitric oxide synthase (eNOS) and greater production of reactive oxygen species (ROS) [23]. However, it should be noted that increased LpL activity in humans is associates with lower circulating levels of triglycerides and higher HDL, which associates with less CVD [24], indicating that LpL has mixed actions. In agreement with a beneficial effect of LpL are studies demonstrating that local lipolysis provides ligands for activation of the transcription factors peroxisome proliferator-activated receptors (PPARs), which might have anti-inflammatory actions. These events appear to require local generation of lipolysis products. Experiments performed using medium that contains heparin, which leads to release of LpL from cells and lipolysis of triglyceride-rich lipoprotein at a distance from the cells, does not activate endothelial PPARs to the same extent as when triglyceride hydrolysis occurs at the endothelial cell surface [25]. Interestingly, when one of the PPARs, PPARγ, was deleted specifically in endothelial cells in a mouse model, the result was markedly increased

circulating free fatty acids and triglycerides [26]. It is likely that the increase in circulating fatty acids and triglycerides was due to changes in lipolysis, which could derive from defective endothelial cell uptake of locally produced free fatty acids, as has been suggested to be one reason for decreased triglyceride clearance in mice deficient in the fatty acid transporter and scavenger receptor CD36 [27]. Free fatty acids inhibit LpL and also cause its dissociation from the endothelial surface. These findings demonstrate that the endothelium is a cell type that has a major impact on metabolism of triglyceride-rich lipoproteins.

The exposure of the arterial wall to lipolysis products is dependent on a number of factors: the amount of LpL on the endothelial surface, the amount of substrate (i.e. the circulating triglyceride concentration) and the approximation of those lipoproteins to the luminal side of the blood vessel. *In vitro* and *in vivo* data suggest that LpL is saturated at a substrate concentration of 5 μM (~500 mg/dL) [28], therefore under most physiologic conditions local LpL actions are highly dependent on the circulating triglyceride level. Moreover, larger lipoproteins have a greater chance of contacting the vessel wall, are likely better LpL substrates, and create more lipolysis products. Besides production of atherogenic remnants [29], chylomicrons are potentially the source of more vascular damage as they create more products of lipolysis.

Another enzyme that produces fatty acids and lysolecithin is endothelial lipase (EL). Although EL was initially cloned from endothelial cells, its major sites of expression are the liver and thyroid gland [30–31]. EL is primarily a phospholipase and its preferred lipoprotein substrate is HDL. Although reduced EL activity is associated with higher HDL levels, EL gene variants do not correlate with CVD risk [32].

Together, these studies demonstrate that the endothelium takes an important part in regulating circulating levels of triglyceride-rich lipoproteins and fatty acids. The endothelium also reacts to these lipids in different ways that may contribute to vascular disease.

How do fatty acids interact with and cross the endothelium?

Locally produced fatty acids must cross the endothelial barrier to enable tissue uptake in muscle and adipose, and likely allow fatty acids to penetrate into the arterial wall. This trans-endothelial passage could occur via movement between or around endothelial cells. High local concentrations of free fatty acids disrupt the endothelial barrier as does active lipolysis, which can also enhance LDL movement into the artery [33]. Fatty acid uptake by endothelial cells is not completely understood; it might involve both receptor mediated uptake and non-specific uptake [34], which might occur in the presence of high local fatty acid concentrations, e.g. those that occur during chylomicron but not VLDL lipolysis [35].

The best characterized free fatty acid transporters are CD36 and members of the FATP family [34]. A recent report has localized the fatty acid binding site on CD36 [36]. Most importantly for our understanding of atherosclerosis, this binding site overlaps with that of oxidized LDL. These data suggest that fatty acids, which are likely to always be in higher molar concentration than oxidized LDL, are likely to compete for binding to CD36 and discourage uptake of some forms of atherogenic lipoproteins.

Regulation of endothelial fatty acid transport appears to involve vascular endothelial growth factor B (VEGF-B). This molecule promotes fatty acid uptake in endothelial cells by stimulating expression of the fatty acid transport proteins FATP3 (*Slc27a3*) and FATP4 (*Slc27a4*) [37**]. Accordingly, *Vegfb*$^{-/-}$ mice have defective fatty acid uptake into heart, muscle and brown adipose tissue after oral gavage of [^{3}H]-oleic acid, as compared to wildtype controls [38]. The fatty acid transport protein family consists of six members, as

reviewed in [34]. Endothelial cells express primarily FATP1 and FATP4, but other fatty acid transport proteins are expressed at lower levels [39]. These fatty acid transport proteins are believed to increase uptake of fatty acids, at least in part, through a process termed "vectorial acylation" [40] mediated by the linking of a FATP and an acyl-CoA synthetase (ACSL – see below). Once the fatty acid has reached the intracellular space, the ACSL links the free fatty acid to a hydrophilic CoA moiety, thereby "trapping" the fatty acid in the cell. Excess fatty acid uptake, as discussed below, could have untoward effects.

How do fatty acids affect endothelial biology?

In vitro, saturated fatty acids, such as palmitate (C16:0) and stearate (C18:0) induce generation/secretion of a number of pro-inflammatory molecules in endothelial cells that may be involved in recruitment of monocytes and other leukocytes into lesions of atherosclerosis. These include CCL2, CXCL1, CXCL8 [41*], IL-6 and CXCL3 [42]. This response is most likely mediated by an increased activation of NF-kB signaling and ER stress [42]. Saturated fatty acids have been proposed to generate inflammatory effects through extracellular actions in cells, by acting as ligands of toll-like receptor 2 (TLR2) and TLR4 [43]. More recently however, the ability of saturated fatty acids to activate TLR signaling has been attributed to an increased recruitment of TLRs into membrane lipid raft domains [44]. This process has been observed also in endothelial cells [45]. Thus, it is now generally thought that saturated fatty acids alter cellular membrane properties to promote TLR activation, rather than acting as TLR ligands. Moreover, in many systems the potentially harmful effects of saturated fatty acids have been neutralized by the addition of oleic acid (a monounsaturated fatty acid), perhaps due to greater esterification of intracellular palmitate to triglyceride [46].

Saturated fatty acids also induce apoptosis in endothelial cells [41*,47]. The effects of saturated fatty acids are counteracted by unsaturated fatty acids [47], and overexpression of stearoyl-CoA desaturase, which results in increased conversion of C16:0 and C18:0 to the monounsaturated C16:1 and C18:1 protects endothelial cells from the apoptotic effects of saturated fatty acids [48]. Saturated fatty acid-induced endothelial cell apoptosis appears to be largely independent of TLR4 [41*].

Whole-body TLR4-deficiency protects against atherosclerosis [49–50]. It is possible that the atherogenic effect of TLR4 is due to at least some extent to endothelial expression of TLR4, because TLR4-deficiency restricted to the hematopoietic cells had only minor effects on atherosclerosis [51]. In support of this concept are findings from mice deficient in MyD88, an adapter protein that mediates some of TLR4 signaling, but also signaling from other TLRs. MyD88-deficienct mice, like whole-body TLR4-deficient mice, exhibit reduced atherosclerosis [49]. Endothelial cells from these *Myd88*$^{-/-}$ mice show reduced binding of leukocytes [49], suggesting that increased monocyte recruitment into lesions due to exacerbated endothelial cell binding of these cells could be an important mechanism for how TLR4 and MyD88 promotes atherosclerosis through endothelial effects. Endothelium-specific TLR4-deficient mice have not yet been reported. It is important to emphasize that TLR4 binds and is activated by a number of ligands, so that an effect of TLR4-deficiency on atherosclerosis is not necessarily due to reduced fatty acid-mediated TLR4 activation.

Another possible inflammatory mechanism of saturated fatty acids is the generation of toxic ceramides. Serine palmitoyltransferase (SPT) is the first enzyme of the *de novo* biosynthetic pathway of sphingomyelin, which combines palmitoyl-CoA and serine to form 3-ketoshinganine and leads to downstream synthesis of ceramide, sphingomyelin, and sphingosine 1 phosphate (S1P). SPT is composed of 2 subunits and a recent study showed that SPT subunit 2 haploinsufficiency in myeloid cells reduced atherosclerosis [52*]. In contrast, despite beneficial effects of SPT deficiency in heart lipid toxicity [53],

cardiomyocyte SPT deletion — which reduces heart ceramide content — leads to heart dysfunction and ER stress as ER phospholipids become palmitate enriched [54]. Whether SPT-deficiency has the same effect in endothelial cells is an important question, which can now be addressed by generating endothelium-specific SPT-deficient mice. In this context, it is interesting that inhibition of SPT protects endothelial cells from the deleterious effects of palmitate on endothelium-dependent vasorelaxation [55]. Reduced levels of SPT may decrease levels of sphingomyelin in lipid rafts and reduce function of lipid raft-associated proteins, including TLR4 [52*]. Thus, SPT-deficient macrophages exhibited reduced cytokine production following stimulation with lipopolysaccharide (LPS) or palmitate, and increased cholesterol efflux through the cholesterol exporters ABCA1 and ABCG1. These studies suggest that the function of lipid rafts has important downstream effects *in vivo*, including stimulation of atherosclerosis.

A recent study revealed another mechanism whereby saturated fatty acids might exert inflammatory effects in endothelial cells. Both saturated fatty acids (C16:0) and LPS (a TLR4 ligand) inhibit insulin-induced phosphorylation of the transcription factor FoxO1, thereby increasing its activity [56]. Deletion of the three genes encoding isoforms of FoxO specifically in endothelial cells protected the endothelial cells from inflammatory activation by LPS, and also protected low-density lipoprotein receptor-deficient ($Ldlr^{-/-}$) mice from atherosclerosis induced by high fat feeding [56]. Thus, FoxO transcription factors might provide an additional important link between saturated fatty acid-induced endothelial cell dysfunction and atherosclerosis.

Whereas a lot of attention has been given to the adverse effects of saturated fatty acids in endothelial cells, unsaturated and polyunsaturated fatty acids also affect these cells. For example, the literature contains a number of examples of *in vitro* effects (usually beneficial) of omega 3 fatty acids [57]. The role(s) of omega 3 fatty acids as anti-atherogenic molecules are in controversy as recent studies have failed to show beneficial effects in clinical outcome studies [58].

Further studies are required to establish whether saturated fatty acids indeed induce endothelial dysfunction *in vivo*, and whether this contributes to atherosclerosis in mice and humans. It is important to consider that cells are never exposed to a single saturated fatty acid *in vivo*, and that combinations of saturated fatty acids and unsaturated fatty acids that mimic those seen in plasma of fat-fed animals or humans do not induce the same inflammatory and apoptotic effects as single saturated fatty acids in isolated endothelial cells [41*].

To what extent are the fatty acid effects mediated through acyl-CoA formation?

As discussed above, a majority of the effects of saturated fatty acids in endothelial cells would be expected to be mediated by processes that require the conversion of free fatty acids into their acyl-CoA derivatives, such as incorporation into membrane phospholipids that might govern the activity of TLR4 in lipid rafts, ceramide synthesis and ER stress. The synthesis of acyl-CoAs from free fatty acids is catalyzed by the ACSL gene family, reviewed in [59]. Endothelial cells express ACSL1, ACSL3, ACSL4, and ACSL5, but not ACSL6 [39,41*]. Early studies took advantage of a pharmacological ACSL inhibitor (triacsin C, a fungal metabolite) to block activity of many of the ACSL isoforms in endothelial cells. These studies suggested that the effect of palmitate on apoptosis (caspase 3 activity) in endothelial cells is dependent on ACSL activity, but that palmitate-induced NF-kB nuclear translocation is not [60]. Recently, several mouse models deficient in specific ACSL isoforms in selected cells types have been generated [61–63], including an endothelium-targeted ACSL1-deficient mouse [41*]. Interestingly, endothelial cells isolated from these mice did not show any protection against pro-inflammatory and pro-apoptotic

effects of saturated fatty acids, nor did these mice demonstrate reduced recruitment of macrophages to adipose tissue during high fat feeding [41*]. These studies suggest that other ACSL isoforms are more important than ACSL1 in mediating detrimental effects of saturated fatty acids in endothelial cells, or perhaps, that some effects of saturated fatty acids are mediated by the free fatty acid rather than an acyl-CoA-dependent lipid mediator, or that saturated fatty acids are not detrimental *in vivo* in the presence of unsaturated fatty acids and other lipids. It will be important to address the role of other ACSL isoforms in endothelial cells.

Does the endothelium regulate HDL and *vice versa*?

Endothelial surfaces are the stage for most intravascular lipoprotein metabolism. This highly regulated process creates atherogenic lipoproteins; chylomicrons are converted to remnants and VLDL to LDL, as discussed above. In addition, catabolism of triglyceride-rich lipoproteins creates HDL and reduces the cholesteryl ester transfer protein (CETP) reaction. The CETP reaction reduces HDL cholesterol due to transfer of cholesteryl ester for triglyceride, lipolysis of HDL by hepatic and endothelial lipases, and greater clearance of small HDL by the kidney. It is unknown whether reduced lipolysis changes HDL composition and allows more rapid HDL removal from the circulation. It is also unknown whether the reduction in HDL cholesterol affects HDL's function, such as its ability to remove cholesterol from macrophages. Together, these observations suggest that the endothelium may contribute to regulation of HDL levels and possibly function.

The role of HDL as a mediator of reverse cholesterol transport is well known, as is the inverse putative relationship between HDL efflux capacity and CVD risk [64**]. In addition, HDL may function as an anti-inflammatory molecule, as recently shown in a study of cytokine production by adipocytes [65]. HDL has been reported to exert protective effects in endothelial cells. Thus, S1P associated with HDL promotes endothelial barrier function [66], ApoA-I, the structural protein in HDL, protects endothelial cells from palmitate-induced TLR4 recruitment into lipid rafts [45], and HDL protects eNOS activity in cholesterol-loaded endothelial cells [67]. Thus, HDL modulates endothelial cell function.

Although HDL cholesterol levels are often reduced in patients with metabolic syndrome and T2DM, they are sometimes strikingly increased in well-insulinized patients with T1DM [68]. There might be issues both of HDL quantity and function that differ between T1DM and T2DM. HDL from patients with diabetes has been shown to contain more oxidation products and to be less able to reduce endothelial cell adhesion molecule expression, as compared with HDL from non-diabetic controls [69]. It is interesting to speculate that diabetes might render HDL less able to suppress inflammatory processes in endothelial cells.

How is the endothelium affected by diabetes and the metabolic syndrome?

A number of cardiovascular risk factors are altered by diabetes and the metabolic syndrome, each of which might negatively impact the endothelium. Three different factors might affect endothelial biology in the setting of diabetes: hyperglycemia, reduced (or increased) insulin actions, and exposure to lipids or other circulating factors such as advanced glycation endproducts (AGEs). Brownlee has suggested that a characteristic of endothelial cells is their failure to reduce glucose uptake in the presence of increased glucose exposure [70]. While most cells obtain glucose via insulin-regulated transporters, such as GLUT4, endothelial cell glucose uptake appears to be via non-insulin regulated processes such as via GLUT1 [71]. Support for a role of hyperglycemia in a type 1 diabetes mouse model was recently illustrated in a study showing that glucose reduction via inhibition of the sodium glucose co-transporter 2 (SGLT2) improves regression of aortic lesions in diabetic mice [6].

What atherogenic processes are altered in diabetic endothelium? Diabetic mice exhibit increased monocyte adhesion to endothelial cells through mechanisms that are intrinsic to the endothelial cells themselves. It has been suggested that endothelial cells exposed to a diabetic environment become "primed" to bind monocytes [72]. The increased endothelial cell ability to bind monocytes under conditions of hyperglycemia and diabetes has been explained by several different mechanisms, which are not mutually exclusive. These mechanisms, which will be mentioned only briefly, include increased levels of AGEs associated with diabetes [73], increased production of reactive oxygen species through mitochondria [74] and NADPH oxidase 1 [75], aldose reductase activity [4,7], activation of protein kinase C by hyperglycemia [76], and lack of proper insulin signaling [77–78]. Creation of a double heterozygous knockout of insulin receptors and IRS1 on the apoE-deficient background increased atherosclerosis, an effect associated with defective endothelial cell function [78]. Insulin receptor deficiency specifically in endothelial cells accelerates atherosclerosis in *Apoe*$^{-/-}$ mice [77], suggesting that insulin has beneficial effects in endothelial cells. In contrast, endothelial cell deletion of the three FoxO transcription factors, which act downstream of Akt, resulted in reduced atherosclerosis [56]. Loss of FoxOs improved NO production and reduced ROS and adhesion molecule expression; these protective effects occurred in the setting of reduced IRS phosphorylation and Akt phosphorylation. Thus, the relationship between vascular disease and insulin signaling in endothelial cells is multifactorial.

Diabetes also results in impaired vasodilation, mediated, at least in part, through a reduced ability of eNOS to generate normal levels of the vasodilator NO. This might be due to ROS generation secondary to greater uptake of glucose [79] and fatty acids [24]. Thus, acetylcholine-mediated endothelium-dependent vasorelaxation is impaired in mouse models of diabetes [80–81]. Part of the detrimental effect of diabetes on vasodilatation may also be mediated by a reduced expression of stromal interaction molecule 1 (STIM1) and sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase 3 (SERCA3), which leads to an impaired ability to mobilize Ca^{2+} from the ER [82]. It is unclear if reduced vasodilatation leads to increased atherosclerosis, although it is well established that hypertension is a risk factor for cardiovascular disease.

Thus, so far much of the research on effects of diabetes on the endothelium has focused on glucose-mediated adverse effects. With the development of an increasing number of mouse models with endothelial-targeted deletion or overexpression of molecules involved in lipid metabolism, the next few years are likely to see an increase in studies on diabetes-mediated changes in lipids in endothelial cells, and the relationship to atherosclerosis.

Translational relevance and conclusions

More studies are needed to evaluate to what extent the studies based on isolated endothelial cells hold true *in vivo*. Although numbers of *in vitro* studies have shown toxic effects of various lipids on endothelial cells, *in vivo* models to modulate lipolysis along the artery are missing. Even identification of the putative toxic lipids is tenuous as lipid metabolic pathways are very interconnected and addition of a single species to cultured cells is likely to lead to changes in many intracellular species. The interactions between changes in circulating triglyceride and other lipoproteins, especially HDL levels and function, are still uncertain. Basic mechanisms of lipid uptake and transport by the endothelium are not understood. Similarly, very few studies have investigated the roles of fatty acid-handling proteins specifically in endothelial cells in relation to atherosclerosis. Even more importantly, human studies are needed before we know if these mechanisms are of relevance in humans and to what extent they might contribute to cardiovascular events.

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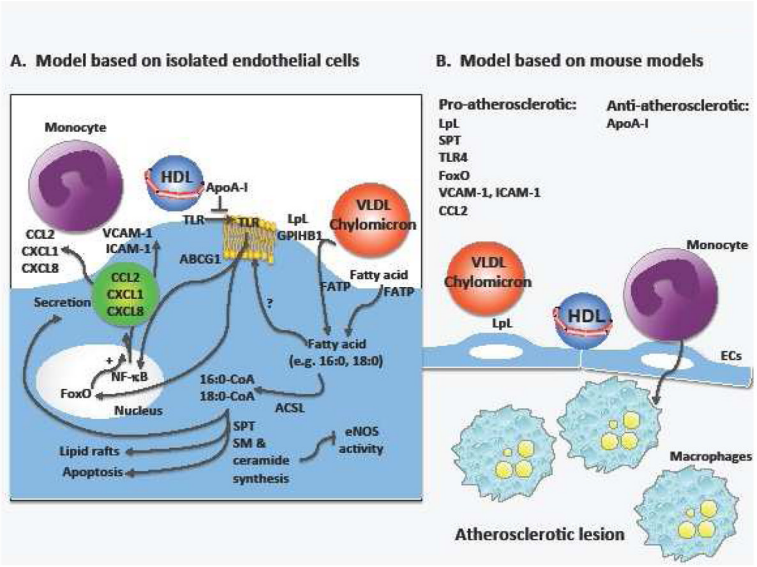

Figure 1. Effects of lipoprotein lipolysis and fatty acids in endothelial cells in relation to atherosclerosis

Fatty acids are liberated from triglyceride-rich lipoproteins, such as VLDL or remnants, by the action of lipoprotein lipase (LpL) tethered to the luminal endothelial surface by proteoglycans and a specific LpL binding protein, glycosyl inositol HDL binding protein 1 (GPIHBP1). Fatty acids also circulate in blood bound to albumin. The fatty acids are taken up by endothelial cells through transport proteins, including the fatty acid transport proteins (FATP) FATP3 and FATP4. Some uptake is believed to occur through diffusion through the plasma membrane and through the scavenger receptor CD36. Once fatty acids enter the cell, they are bound to intracellular fatty acid binding proteins or are converted into hydrophilic acyl-CoAs by a group of enzymes with acyl-CoA synthetase activity. All members of the long-chain acyl-CoA synthetase (ACSL) family are expressed in endothelial cells, with the exception of ACSL6. The acyl-CoAs are used by the cell for membrane phospholipid synthesis and re-acylation, ceramide synthesis, beta-oxidation, protein modification, and several other processes. An unanswered question is whether saturated fatty acids have to be converted to acyl-CoAs in order to promote TLR4 movement to lipid rafts, whereas the pro-apoptotic effects of saturated fatty acids are dependent on ceramide synthesis and acyl-CoA formation. Ceramides have also been implicated in eNOS inhibition. Saturated fatty acid-mediated activation of TLR4 results in NF-kB activation and production of pro-atherosclerotic cytokines and chemokines, as well as adhesion molecules, which increase monocyte binding and recruitment into the artery wall. Finally, ApoA-I and recombinant HDL have the ability to inhibit palmitate-induced TLR4 translocation into lipid rafts in endothelial cells. Although much of this model is based on studies on cultured endothelial cells and addition of single fatty acids to these cells (A), mouse models of atherosclerosis are starting to provide a picture of important roles of several of the enzymes and proteins involved in fatty acid handling in atherosclerosis (B).