Minireview

Lipoprotein lipase, a key role in atherosclerosis?

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Abstract Lipoprotein lipase (LPL) plays a central role in lipid metabolism and transport by catalysing the hydrolysis of triacylglycerol-rich lipoproteins. The importance of LPL expressed by the adipose tissue and muscles in the provision of non-esterified fatty acids and 2-monoacylglycerol for tissue utilisation is well established. However, recent studies on LPL expressed by cells of the vascular wall, particularly macrophages, have identified additional actions of the enzyme that contribute to the promotion of foam cell formation and atherosclerosis. This review deals with the role of LPL in atherosclerosis, and its regulation by mediators that are known to be present in the lesion.

Key words: Lipoprotein lipase; Atherosclerosis; Macrophage; Foam cell; Cytokine

1. Introduction

Atherosclerosis, the underlying cause of heart attacks, strokes and peripheral vascular disease, is directly responsible for over 50% of all deaths in the USA, Europe and some parts of Asia [1]. The disease develops slowly over many years in the intima, the innermost, luminal part of the artery, with the lesions (plaques) characterised by a proliferation of smooth muscle cells, extensive accumulation of connective tissue matrix and lipid deposition. These events eventually result in the occlusion of the artery and, as a consequence, an increase in the likelihood of the clinical complications mentioned above (see [2–4] for reviews).

Initially, the process is hypothesised to be a protective mechanism triggered by damage to the arterial endothelium [2–4]. This may then become dysfunctional and undergo alterations in permeability, adhesive properties and growth stimulatory characteristics. Release of growth regulatory molecules and chemoattractants by the damaged endothelium leads to the attachment of monocytes [5], which enter the subendothelium and mature to macrophages. Macrophages may then transform into so-called foam cells through the accumulation of lipids [2–4], a defining early event in the development of the atherosclerotic lesion. Elucidation of the mechanisms that are responsible for the transformation of macrophages into foam cells has, consequently, been the subject of intense research and has resulted in the identification of novel roles for the enzyme lipoprotein lipase (LPL).

The importance of LPL in the regulation of overall lipid metabolism and transport in humans and other animals is well documented [6–8]. LPL is expressed by the parenchymal cells of several extrahepatic tissues and catalyses the hydrolysis of the triacylglycerol component of chylomicrons and very low density lipoproteins (VLDL), thereby providing non-esterified fatty acids and 2-monoacylglycerols for tissue utilisation [6–8]. Because the circulating lipoproteins are, in general, too large to cross the vascular endothelium intact, the physiological site of LPL action is the luminal surface of the vascular endothelial cells, to which the enzyme is attached via highly charged membrane bound chains of heparan sulphate proteoglycans (HSPG) [6–8]. Although adipose tissue and muscle parenchymal cells are the major source of LPL synthesis [6–8], from where the mature enzyme is secreted and transported to the vascular endothelium, LPL is also expressed and secreted by macrophages. It is this source of LPL that has been implicated to play a major role in the pathogenesis of atherosclerosis and forms the basis of this review. Paradoxically, evidence also exists in support of an anti-atherogenic role for LPL, although this relates mainly to the enzyme expressed by the adipose tissue. Data supporting this involvement will also be presented.

2. The pro-atherogenic action of LPL

The first theory implicating LPL in atherosclerosis was proposed by Zilversmit in 1973 [9]. He postulated that high local concentrations of cholesterol-rich remnants, produced by the action of LPL on VLDL and chylomicrons at the vascular endothelium, would be taken up into the arterial wall and thus lead to the deposition of cholesterol. Supporting this proposition, LPL deficiency in humans, a common genetic cause of chylomicronaemia syndrome, results in very low plasma levels of low density lipoprotein (LDL) cholesterol and is believed to cause resistance to premature atherosclerosis [10]. A great deal of more research has been undertaken recently towards testing Zilversmit's pioneering hypothesis and is presented below.

2.1. LPL is expressed in the atherosclerotic lesion

Although LPL is known to be expressed by both macrophages and smooth muscle cells, detailed immunocytochemical and in situ hybridisation experiments have demonstrated that macrophage-derived foam cells are the primary source of the enzyme within the atherosclerotic lesion [11,12]. In order to investigate the possibility that variations in macrophage LPL synthesis and secretion might constitute a hereditary component of atherosclerosis, Renier and co-workers [13] evaluated LPL gene expression and secretion in macrophages obtained from inbred mouse strains differing in their susceptibility to diet-induced atherosclerosis. Their important find-

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ings were that macrophages isolated from atherosclerosis-susceptible mice showed a two- to three-fold higher basal LPL mass, activity and mRNA levels than those from atherosclerosis-resistant mice, thereby suggesting a contributive role for LPL in the progression of atherosclerosis. Semenkovich et al. [14] have demonstrated that although feeding an atherogenic diet to heterozygous LPL-deficient mice results in a more profound dyslipidaemia due to an increase in non-high density lipoprotein (HDL) lipoproteins, no differences were seen in the atherosclerotic lesion area, thereby indicating that the detrimental effects of dyslipidaemia may be influenced by possibly positive effects of decreased LPL expression in the vascular wall. The significance of these findings becomes more apparent when one considers a very recent and elegant study by Babaev et al. [15] in which mice chimeric for the expression of macrophage LPL were produced by the transplant of $LPL^{-/-}$, $LPL^{-/+}$ or $LPL^{+/+}$ foetal liver cells, the predominant site of haematopoiesis in mammalian embryogenesis, into irradiated female mice. These mice were fed an identical atherosclerotic diet for 19 weeks, killed and their atherosclerotic lesion surface area was measured. The mean lesion area was reduced by 55% in LPL-deficient mice when compared to mice homozygous for macrophage LPL expression, and by 45% when compared with the heterozygous genotype. These data imply that, in the setting of an atherogenic diet, macrophage LPL expression promotes foam cell formation and atherosclerosis in vivo. As foam cells are characterised as lipid-laden macrophages, a pro-atherogenic effect of macrophage LPL is likely to be on the uptake of lipids, and this forms the focus of the next section.

2.2. LPL induces the formation of atherogenic lipoprotein remnants

LPL bound to the arterial surface has been shown to mediate the lipolysis of circulating VLDL and chylomicron particles, thereby leading to both a decrease in their size and an enrichment in their cholesteryl ester content [16]. Studies, in vitro, have shown that such remnants are taken up readily by macrophages [17]. Additionally, the free fatty acids produced by the action of LPL can be re-esterified by macrophages [18]. The overall outcome of these processes is the net accumulation of cholesteryl esters within the macrophage [17–19] and their consequent transformation into foam cells.

LPL-mediated hydrolysis of VLDL also produces LDL, arguably the major contributor to the development of atherosclerotic lesions [20,21]. Frequently, these LDL molecules are oxidised in the intimal space by free radicals which, along with other modifications, increases their rate of uptake into macrophages through the scavenger receptors and thereby promotes further foam cell formation [20,21]. Oxidised LDL also has additional pro-atherogenic properties, including its ability to act as a chemoattractant for monocytes [22] and to mediate endothelial cytotoxicity [23].

This section has demonstrated how the catalytic actions of LPL can modulate the progression of atherosclerosis. The process is further promoted by an additional novel feature of LPL that is independent of its lipolytic action – its ability to act as a pro-atherogenic ligand and this is discussed below.

2.3. LPL acts as an atherogenic ligand

The ability of LPL to facilitate cellular uptake of lipoproteins independent of its catalytic properties was first suggested in 1975 [24] following the observation that LPL molecules remain associated with chylomicrons after hydrolysis and might assist in the hepatic uptake of remnants. Interest in this hypothesis was revived when Beisiegel and co-workers showed that LPL was a ligand for the LDL receptor-related protein (LRP) [25]. Subsequent studies have not only identified other ligands for LPL, but also demonstrated that the enzyme associates with lipoproteins and promotes their binding to HSPG, LRP, the LDL receptor and the VLDL receptor [26–33]. Furthermore, the interaction of LDL with LPL is increased markedly by its oxidation [34–36] and the enzyme has also been shown to act synergistically with sphingomyelinase in the lesion to enhance the association of LDL and the highly atherogenic lipoprotein (a) to the vascular wall [37]. The net result of all these actions is the retention and accumulation of lipoproteins in the arterial subendothelial matrix and their rapid uptake by cells via both receptor- and non-receptor-mediated pathways [30–32,38]. This, along with the cellular uptake of potential lipolytic products, would promote the transformation of macrophages into foam cells [17–19,26,27,38].

In all the examples cited above, LPL appears to act as a molecular bridge because of its ability to bind both lipoproteins and proteoglycans/receptors simultaneously via separate domains (see [26,38]). This bridging function of LPL, which has been supported by numerous tissue culture studies [24–38], has been confirmed in vivo recently by Merkel et al. [39] who showed that transgenic mice expressing catalytically inactive LPL in muscles could still bind to proteoglycans and induce the uptake of VLDL. A further variation on this bridging theme involves cells rather than lipoproteins. For example, LPL has been shown to function as a monocyte adhesion protein probably by forming a 'bridge' between the arterial subendothelial matrix and monocyte surface HSPG [40,41].

3. The anti-atherogenic effects of LPL

As mentioned in Section 1, a paradox exists regarding LPL expression and atherosclerosis. Not only does the enzyme mediate atherogenic events in the vessel wall, it also plays a generalised anti-atherogenic role, as shown by a variety of experimental evidence. Firstly, Benlian et al. [42] have shown recently that several LPL-deficient patients develop relatively advanced atherosclerosis. Additionally, individuals who are heterozygous for LPL mutations that reduce enzymatic activity have been reported to be predisposed to premature atherosclerosis [43–47]. Conversely, a variant of LPL that is associated with increased activity has been shown to confer protection against coronary heart disease [48]. Secondly, the hypertriglyceridaemia that is associated with insulin resistance and type II diabetes and which is implicated in the ensuing acceleration of atherosclerosis is mediated largely via the suppression of adipose tissue LPL expression by cytokines such as tumour necrosis factor-α (TNF-α) and interleukin (IL)-6 [49,50]. Thirdly, efficient lipolysis of triglyceride-rich lipoproteins in adipose tissue, heart and skeletal muscle generally drives the profile of circulating lipoproteins in a non-atherogenic direction [51–56]. For example, overexpression of LPL is highly effective in normalising the atherosclerotic lipoprotein profiles of both apoE-deficient and LDL receptor-deficient mice and protects wild-type mice against diet-induced hyperlipidaemia [51–55]. Additionally, administration of the com-

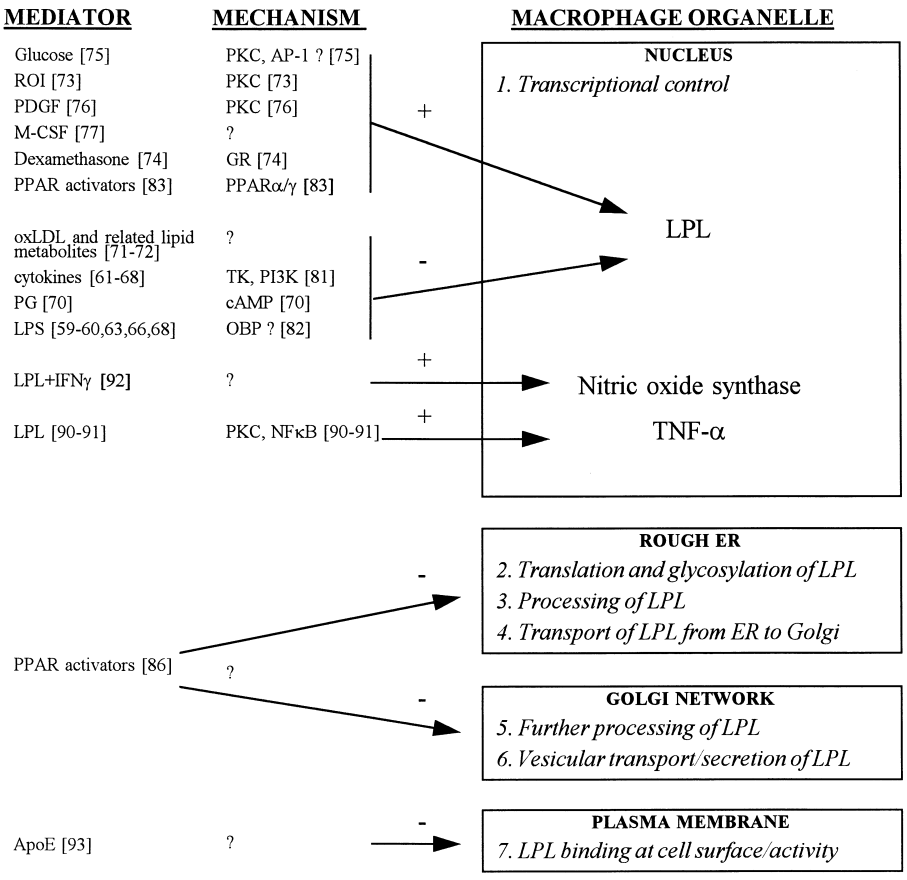

Fig. 1. Possible sites and potential mechanisms for the regulation of macrophage LPL by mediators that are known to be present in the atherosclerotic lesion. The mechanisms by which the mediators activate (+) or inhibit (−) the expression and/or activity of LPL are shown along with the regulation of nitric oxide synthetase and TNF-α by LPL. See text for more details; references are indicated in parentheses. Abbreviations: AP-1, activator protein-1; GR, glucocorticoid receptor; IFN-γ, interferon-gamma; LPS, lipopolysaccharide; M-CSF, macrophage colony-stimulating factor; OBP, octamer binding protein(s); NF-κB, nuclear factor kappa B; OxLDL, oxidised LDL; PDGF, platelet-derived growth factor; PG, prostaglandins; PI3K, phosphatidylinositol 3′-kinase; PKC, protein kinase C; PPAR, peroxisome proliferator-activated receptor; ROI, reactive oxygen intermediates; TK, tyrosine kinase; TNF-α, tumour necrosis factor-α.

pound NO-1886, which increases tissue LPL activity, protects against atherosclerosis due to elevation of HDL [56]. HDL has a dual anti-atherogenic effect: it functions as a removal vehicle for cholesterol, transporting it away from areas of production to the liver where it can be excreted as bile salts and, in addition, it has been shown to prevent the oxidation of LDL by metal ions [57,58]. It is therefore likely that the role of LPL in atherogenesis may depend on the tissue in which it is expressed. In the arterial wall, LPL may be pro-atherogenic whereas in muscle and adipose tissue it may function protectively.

4. Regulation of LPL by agents present in the lesion

As detailed above, the expression of LPL within the vessel wall, especially by macrophages, is likely to be pro-atherogenic. During the development of atherosclerosis, cellular changes in the vascular wall are regulated by many factors, including modified lipoproteins, growth factors, chemotactic factors and cytokines, all of which may be present in the lesion (see [2–4]). The effect of such factors on macrophage LPL expression is, therefore, likely to make a major contribution to the modulation of the atherosclerotic process. Unfortunately, until recently, several studies on the regulation of macrophage LPL expression have produced incomplete and often conflicting results [59–62]. This has been attributed, at least in part, to aspects of experimental design, such as the origin and status of the cells, their culture conditions, the concentration of mediator used and the time course of the observations. We have, however, recently carried out a systematic and detailed analysis of the regulation of macrophage LPL by lipopolysaccharide (LPS) and several cytokines, either singly or in combination, using a range of macrophage cell lines from different species [63–68]. Although LPS, IL-1, IL-11, interferon-γ (IFN-γ) and TNF-α suppressed macrophage LPL activity, mRNA levels and protein content, IL-6 and leukocyte inhibitory factor had no effect. These responses showed several differences to those described previously for adipocytes [7,8,63], thereby suggesting the existence of potential cell-specific mechanisms for the regulation of LPL gene expression by such mediators. Because interactions amongst mediators have been found to be more important in the initiation and progression of diseases, including atherosclerosis, rather than the presence or absence of any given effector [69], we have extended our studies to the use of paired combinations of mediators. Several novel interactions in the regulation of macrophage LPL expression have been identified, of which the most striking was the strong synergism between IFN-γ and TNF-α or LPS [64,68]. Such a synergism was also observed when the cells were exposed sequentially first to IFN-γ and then to

TNF-α or LPS, thereby suggesting a potential priming action of IFN-γ [64,68]. Other agents that have also been shown to suppress macrophage LPL expression include prostaglandins [70], oxidised LDL ([71]; our unpublished observations) and biologically active lipids that are known to form during LDL oxidation, such as lysophosphatidylcholine [71], 7β-hydroxycholesterol [71,72] and 25-hydroxycholesterol [72]. Because cytokines, oxidised LDL and biologically active lipids are generally considered to be pro-atherogenic, the precise significance of their suppressing action on macrophage LPL gene expression (i.e. an anti-atherogenic event) is currently unclear. It is, however, possible that they may limit the transformation of macrophages into foam cells during the initial stages of vascular damage until their actions are over-ridden by other changes in the composition and concentration of effectors, particularly LPL-elevating factors, in the local milieu of mediators as the progression of the disease occurs.

Many effectors have been identified recently that increase macrophage LPL expression, including hydrogen peroxide (oxidant stress/reactive oxygen species), dexamethasone, glucose, platelet-derived growth factor (PDGF) and macrophage colony-stimulating factor [73–77]. Pro-atherogenic actions for these factors have also been identified from other lines of evidence. For example, MCP-1 is found in human atheroma and mice lacking the corresponding gene are less susceptible to atherosclerosis and have fewer monocytes in any vascular lesions that form [78]. Additionally, both glucose and advanced glycation products have been suggested to make a major contribution to the unusually high incidence of atherosclerosis in diabetic patients [79]. Furthermore, elevated production of reactive oxygen intermediates (ROI) in the early atherosclerotic lesion has been implicated in the oxidation of LDL, activation of macrophages and modulation of the action of several mediators that are involved in their cellular proliferation and differentiation [80].

5. Concluding remarks

Given the pivotal role of LPL in the pathogenesis of atherosclerosis, studies aimed at elucidating the molecular mechanisms that are responsible for the regulation of macrophage LPL expression are clearly essential for the identification of potential important targets for therapeutic intervention. Fig. 1 summarises the current state of knowledge on the molecular basis of macrophage LPL expression, and clearly indicates a lack of clarity in our understanding of the mechanisms involved. Thus, with respect to intracellular signalling, protein kinase C has been shown to be involved, at least in part, in the induction of macrophage LPL expression by glucose, PDGF and ROI [73,75,76], cAMP for the suppression by prostaglandins [70] and we have identified that both the tyrosine kinase and the phosphatidylinositol 3′-kinase signal transduction pathways are involved in the LPS and cytokine responses [81]. Although the regulation of LPL expression by cytokines, glucose and ROI is mediated mainly at the transcriptional level [65,73,75], the *cis*-acting regulatory elements and the *trans*-acting factors remain to be identified. A potential role for the activator protein-1 (AP-1) family of transcription factors in the regulation of the glucose response has been implied from the partial inhibition observed when cells were incubated with an antisense oligonucleotide against c-fos, a member of the AP-1 family [75]. Furthermore, the binding of AP-1 to a site present in the murine LPL promoter was increased when extracts from cells exposed to glucose were used [75]. Additionally, exposure of J774 macrophages to LPS induces the binding of proteins to the octamer binding motif present in the LPL promoter, and may be involved in the suppression of gene transcription [82]. However, the most direct evidence of the underlying mechanisms whereby factors involved in the regulation of LPL gene expression operate, in the context of atherosclerosis, relates to studies on the role of the peroxisome proliferator-activated receptors (PPAR) [83]. These receptors belong to the nuclear receptor superfamily of transcription factors that heterodimerise with the retinoid X receptor, and regulate gene expression in response to the binding of ligands such as 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, certain polyunsaturated fatty acids and thiazolidinedione antidiabetic drugs (see [84,85] for reviews). Both PPARα and PPARγ have been shown to induce LPL gene transcription in response to a range of such ligands [83]. PPARα is expressed by monocytes and PPARγ appears only during the differentiation of monocytes into macrophages [86]. Furthermore, PPARγ is expressed at high levels in macrophage-derived foam cells of human atherosclerotic lesions in a pattern that shows a strong positive correlation with the presence of oxidation-derived epitopes and, additionally, its expression is induced by oxidised LDL both in primary macrophage cultures and monocytic cell lines [87,88]. Surprisingly, although the LPL mRNA levels and protein mass in macrophages are induced by a variety of PPAR activators, the LPL activity was found to decrease in all cases [86]. This suggests that PPAR activating agents prevent the formation of active enzyme or its secretion, and could involve either defects in the post-translational processing of the protein [89] or activation of inhibitor(s) of LPL activity. It has been suggested that apoE, which has been shown to inhibit LPL activity in vitro, could represent such an inhibitor that could counteract the pro-atherogenic effect of LPL in the arterial wall [86].

Finally, a further novel role for LPL has been identified, that is as a regulator of macrophage gene expression and protein secretion. Renier and co-workers were the first to show that LPL induces the expression of the TNF-α gene at the level of both gene transcription and mRNA stability [90]. This induction of TNF-α production by LPL is increased during the differentiation of monocytes into macrophages, occurs via a protein kinase C-dependent pathway and is mediated through cell surface proteoglycans [91]. LPL has also been shown to synergise with IFN-γ in the induction of macrophage nitric oxide synthetase mRNA expression at the transcriptional level [92]. More recently, LPL has been identified to reduce the secretion of apoE from macrophages [93]. Given the importance of TNF-α, nitric oxide and apoE in the pathogenesis of atherosclerosis, this novel role of LPL and the corresponding mechanisms need to be investigated further.

In conclusion, substantial experimental evidence indicates a key role for LPL expressed by the arterial wall in the pathogenesis of atherosclerosis, and this involves multiple actions of the enzyme, including lipolysis, bridging and regulation of gene expression. However, the mechanisms that are responsible for the regulation of LPL expression and secretion by cells of the vascular wall, particularly macrophages, during the progression of the disease by factors present in the lesion remain ill defined. We feel that this area should form the focus of intense research, particularly given the existence of multiple

factors that suppress macrophage LPL expression and a good correlation between mediators that induce macrophage LPL expression and their ability to accelerate the atherosclerotic process (e.g. glucose and growth factors). Success in these endeavours should allow the identification of novel targets for therapeutic intervention and prevention.

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