The pivotal role of lipoprotein lipase in atherosclerosis

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1. Introduction

Atherosclerosis, the underlying cause of heart attacks, stroke and peripheral vascular disease, is responsible for over 50% of all deaths in developed countries. The disease can generally be viewed as a form of chronic inflammation that is induced and perturbed by lipid accumulation and involves a number of components, including the damaged endothelium, monocytes/macrophages, T cells, smooth muscle cells and a regulatory network of growth factors and cytokines (see Refs. [1,2] for reviews). The process is believed to be triggered by damage to the arterial endothelial cells leading to dramatic changes in their properties and increased expression of both chemokines and adhesion molecules [1,2]. This causes an infiltration of both T lymphocytes and monocytes to the site of damage. The monocytes then differentiate into macrophages, internalise lipoproteins, and transform into lipid-loaded foam cells to form the fatty streak seen in early lesions [1,2]. This transformation of macrophages into foam cells represents a critical initial event in the pathogenesis of atherosclerosis. It is, therefore, not surprising that a major focus in cardiovascular research has been devoted to understanding the molecular basis of foam cell formation and has resulted in the identification of a key, but complex, role of the enzyme lipoprotein lipase (LPL; EC 3.1.1.34) in the process.

LPL is a central enzyme in overall lipid metabolism and transport, being responsible for catalysing the hydrolysis of triglycerides transported in the bloodstream by chylomicrons and VLDL, thereby providing non-esterified fatty acids and 2-monooacylglycerols for tissue utilization [3,4]. Due to the large size of its substrates, the physiological site of LPL action is at the luminal surface of blood vessels, to which the enzyme is attached via highly charged heparan sulphate proteoglycans (HSPG) [3,4]. Mature LPL is secreted to the vascular endothelium from the parenchymal cells of the adipose and muscle tissues, its major sites of synthesis, and a variety of other tissues which have also been implicated as lesser, but significant, sources of the enzyme [3,4]. Of these alternative sources, studies on LPL expressed by cell types found in the locus of the vascular wall, particularly by monocyte-derived macrophages, have identified additional, pathophysiological actions of the enzyme that promote foam cell formation and, ultimately, atherosclerosis. In direct contrast to this, LPL produced by adipose tissue and muscle has a protective effect with respect to atherosclerosis. As a result of these observations, LPL has been identified as a potential therapeutic target in the enzyme that promote foam cell formation and, ultimately, atherosclerosis. In direct contrast to this, LPL produced by adipose tissue and muscle has a protective effect with respect to atherosclerosis. As a result of these observations, LPL has been identified as a potential therapeutic target.

2. Pro-atherogenic actions of LPL

The importance of LPL in the atherosclerotic process was first proposed in 1973 by Donald Zilversmit [5]. He postulated that the action of LPL on circulating VLDL and chylomicrons would lead to high, localized concentrations of cholesterol-rich remnants, which would subsequently be taken up into the arterial wall and propagate lesion formation. Since this hypothesis was formulated, it has
been shown to be true but, as this article will discuss, is far more complex than originally anticipated.

3. Importance of LPL expression in the atherosclerotic lesion

Of the cell types present in the atherosclerotic lesion, LPL is known to be expressed by both monocyte-derived macrophages and smooth muscle cells [3,4]. The differentiation of monocytes to macrophages is accompanied by a substantial increase in LPL mRNA, protein and activity levels [6] and has also recently been shown to lead to an increase in the level of apolipoprotein C-II [7], a known activator of LPL [3]. These macrophages transform into foam cells through the accumulation of lipids [1,2]. Detailed immunocytochemical and in situ hybridization experiments have shown that it is the macrophage-derived foam cells, and not smooth muscle cells, that are the primary source of LPL in the lesion [8]. In addition, the expression of LPL mRNA, protein and enzymatic activity have all been found to increase in response to damage sustained by the arterial wall [9,10]. Vascular injury has long been known to be a precursor of clinical conditions associated with atherosclerosis and is, indeed, how the well-established ‘response to injury’ hypothesis for atherogenesis was derived [1,2].

The possibility that variations in macrophage LPL synthesis and secretion might constitute a hereditary component of atherosclerosis was investigated by Renier and colleagues [11] who evaluated LPL levels in macrophages from inbred mouse strains differing in their susceptibility to diet-induced atherosclerosis. It was observed that macrophages isolated from mice susceptible to atherosclerosis showed a 2- to 3-fold higher basal LPL mass, activity and mRNA levels than those from mice resistant to it, thereby inferring a contributive role for LPL in the progression of the disease. More recently, Semenkovitch et al. [12] have shown that feeding an atherogenic diet to heterozygous LPL deficient mice results in profound dyslipidaemia, due to an increase in non-HDL lipoproteins, no differences were seen in atherosclerotic lesion area when compared to normal mice fed the same diet. It therefore appears that the decreased presence of LPL in the vascular wall might have conferred a protective effect against the highly atherogenic lipoprotein profile [12]. The LPL mRNA, mass and activity levels have also been found to be substantially higher in monocyte-derived macrophages from diabetic patients when compared to those from normal subjects, and such an increase can be conferred to normal macrophages by culturing them in serum obtained from diabetic patients [13]. Given that atherosclerosis is a major complication of diabetes, this observation provides further evidence for an association of LPL with atherogenesis.

The most compelling data concerning the relationship between macrophage LPL and atherosclerosis has come from several recent transplantation studies in which the expression of LPL in macrophages was modulated [14–16]. Such transplantation approaches were necessary because homozygous LPL deficient mice die soon after birth due to the accumulation of chylomicrons, a particular problem in the lungs where they prevent the contact of erythrocytes with the endothelium [17]. Babaev et al. [14] initially transplanted irradiated female mice with foetal liver cells, the predominant site of hematopoiesis in mammalian embryogenesis, from mice with LPL−/−, LPL+/− and LPL+/+ genotypes whereas Van Eck et al. [15] carried out bone marrow transplantation from LPL−/− and LPL+/+ mice. In both cases, the mice were fed an identical atherogenic diet for several weeks and their atherosclerotic lesion areas were measured. Similar reductions, of around 50%, were seen in both studies in mice that are deficient for macrophage LPL, thereby indicating that this source of enzyme directly leads to atherosclerosis in the setting of a pro-atherogenic diet. It is also interesting to note that Van Eck and co-workers [15] observed a 2-fold reduction in apolipoprotein E (apoE) levels in macrophage LPL−/− mice. Macrophage-derived apoE has been shown to have a preventative effect upon atherosclerosis by promoting cholesterol efflux from the cells [18]. That macrophage LPL knockout still has such a significantly protective effect upon atherosclerosis in the pro-atherogenic environment induced by reduction of apoE expression provides further indication of the central role played by the enzyme in the promotion of atherosclerosis.

Both of the studies identified above [15,16] were carried out in C57BL/6 mice, a strain that has previously been shown to have limitations as a model for human atherosclerosis [19]. When fed a pro-atherogenic diet, these mice develop only relatively mild fatty streak lesions, which are exclusively located in the proximal aorta [19]. However, C57BL/6 mice that are homozygous negative for LDL receptor (LDLR−/−) display an enhanced susceptibility to diet-induced atherosclerosis throughout the length of the aorta [20]. In addition, the extent of atherosclerosis in these mice can be modulated by altering the duration of the high fat diet used to generate the disease process, thus providing the framework for studies at different stages of lesion formation [20]. Using this improved system, Babaev and co-workers used their same experimental approach, as previously described [14], to create macrophage LPL chimeras [16]. They found that LDLR−/− mice reconstituted with LPL+/− mice reconstituted with LPL−/− mice developed significantly less atherosclerosis when challenged with an atherogenic diet for either 8 weeks (early stage atherosclerosis) or 19 weeks (later stage atherosclerosis) compared to those mice with LPL+/+ or LPL+/− macrophages, as determined by en face analysis of pinned-out distal aortae. However, when cross-sectional analysis of the proximal aorta, the region most susceptible to atherosclerosis, was carried out (as used in their earlier study) [14], similar
results to those obtained using the en face procedure were seen at 8 weeks but no differences between genotypes were observed at 19 weeks, a time point when the lesions are extremely complex in this region. It was therefore concluded that although macrophage LPL expression undoubtedly promotes foam cell formation and atherosclerosis in vivo, its impact is limited to the macrophage-rich early lesions as opposed to more complex, advanced lesions.

More recently, Clee et al. [21] have carried out studies to distinguish between the effects of plasma LPL (i.e., enzyme bound to the endothelial cells and derived predominantly from the adipose tissue and muscle) and/or vessel wall LPL (i.e., enzyme derived mainly from macrophages) on atherosclerosis susceptibility in apoE-deficient mice. They showed that decreased LPL expression from both sources (LPL+/−E−/−) was associated with a reduction in atherosclerotic lesion area compared to the LPL+/+E−/− mice despite a pro-atherogenic lipid profile. Thus, the loss of the macrophage-derived LPL protein in the vessel wall had a dominant effect on limiting atherogenesis because a reduction was seen even in the presence of an atherogenic lipid profile caused by low plasma LPL activity.

Overall, therefore, the use of the modern transgenic technologies, detailed above, have given greater credence to several previous in vitro studies (reviewed in Refs. [22,23]), and firmly indicate that, within the setting of an atherogenic diet, macrophage LPL expression promotes foam cell formation. However, the involvement of the enzyme in the latter stages of the disease, characterised by complex lesions, needs to be resolved.

In addition to the analysis of the relationship between elevated LPL expression and atherosclerosis, the precise mechanisms through which the enzyme causes macrophage lipid uptake and foam cell formation has also been the subject of intense research in the last few years. The findings from these studies form the focus of the next section.

4. The catalytic action of LPL induces the formation of atherogenic lipoprotein remnants

LPL bound to the luminal surface of the vascular endothelium is responsible for mediating the lipolysis of circulating VLDL and chylomicron particles, thereby leading to both a decrease in their size and enrichment in their cholesteryl ester content [24]. Studies in vitro have shown that such remnants are readily taken up by macrophages [25]. In addition to this, the free fatty acids produced by the action of LPL can be re-esterified by macrophages [26]. The net outcome of these processes is the accumulation of cholesteryl esters within macrophages and, as a consequence, their transformation into foam cells [25,26].

LPL-mediated hydrolysis of VLDL also leads to the production of LDL, arguably the major contributor to the development of atherosclerotic lesions [1,2]. Frequently, these LDL molecules are oxidized 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 [1,2].

In vitro studies carried out in the last few years have also indicated the possibility that the enzymatic action of LPL may affect other cell types present in the atherosclerotic lesion, namely endothelial and smooth muscle cells. For example, Hennig and co-workers [27] have demonstrated that selected fatty acids and LPL-derived remnants of lipoproteins isolated from hypertriglyceridaemic subjects can activate vascular endothelial cells and disrupt endothelial integrity. As mentioned earlier, vascular injury is thought to be a principal cause of the initial recruitment of macrophages to the arterial wall and is, therefore, a probable initiating event in atherosclerosis. In addition, LPL enzyme activity has also been shown to lead to the proliferation of vascular smooth muscle cells [28]. Such cells are known to secrete extracellular matrix proteins that promote the formation of fibrous plaques, a prominent characteristic of the later stages of atherogenesis [1].

All of the observations presented above illustrate how the catalytic actions of LPL affect the progression of atherosclerosis. An additional feature of LPL is its ability to act as a pro-atherogenic ligand independent of its catalytic activity, a phenomenon that is discussed below.

5. LPL acts as an atherogenic ligand

The ability of LPL to facilitate cellular uptake of lipoproteins independently of its catalytic properties was initially proposed in 1975 following the observation that LPL molecules remain associated with chylomicrons after hydrolysis and, therefore, might assist in their hepatic uptake [29]. Interest in this hypothesis was not revived until 1991 when Beisiegel and colleagues showed that LPL was a ligand for the LDL receptor-related protein (LRP) [30]. Further studies have not only identified other ligands for LPL, but have also demonstrated that the enzyme associates with various lipoproteins and promotes their binding to LRP, HSPG, LDL receptor, VLDL receptor, gp330 and apoE receptor 2 (see Refs. [22,23,31,32] for reviews).

The net result of all the interactions between lipoproteins and LPL or cell surface receptors is the retention and accumulation of lipoproteins in the arterial subendothelial matrix and their rapid uptake by cells. There are three potential pathways by which LPL may enhance cellular uptake of lipoproteins. The first is receptor mediated uptake of lipoproteins bound to the cell surface via LPL [33,34]. Secondly, LPL may act directly as a ligand for
receptors [31] and, finally, the entire HSPG–LPL–lipoprotein complex may be internalised by a receptor-independent pathway [35,36]. All of these, along with the uptake of potential lipolytic products of LPL, would promote the transformation of macrophages into foam cells. Various other aspects of the involvement of LPL, in a non-enzymatic capacity, in the atherosclerotic process have also been investigated in the last few years and are discussed below.

LPL has been found to substantially enhance the binding, uptake and degradation of another modified lipoprotein, glycated LDL, in fibroblasts, endothelial cells and macrophages [37]. Glycation of LDL is a naturally occurring chemical modification of its apolipoprotein B residues by glucose and is, therefore, more prevalent in diabetic patients [37]. Given that diabetic patients have macrophages that express higher levels of LPL [13] and that they are more likely to produce glycated LDL, it can be proposed that higher levels of this potentially atherogenic lipoprotein may accumulate in their arteries than those from normal subjects, and may therefore go some way towards explaining the increased incidence of atherosclerosis in diabetic patients.

In addition to mediating the binding of lipoproteins to HSPG on cell surfaces, LPL can also perform the same function with extracellular vascular proteoglycans [22]. In atherosclerotic lesions, two predominant proteoglycans are versican, present primarily in areas rich in smooth muscle cells, and biglycan, which is abundant in the extracellular matrix adjacent to the sites of macrophage infiltration [38]. Olin et al. [39] have recently demonstrated that the binding of both oxidized and native LDL to versican and biglycan is promoted by the presence of LPL. Similarly, glycosaminoglycan filaments extending from collagen fibres in the subendothelial matrix have been found to accumulate LDL [40]. Modelling this environment using decorin-coated collagen, Pentikainen and co-workers [41] have shown that LPL increases the binding of both native and oxidized LDL. Due to the fact that there are large quantities of collagen in the arterial intima and that proteoglycans substantially accumulate during the course of the atherosclerotic process, there is great potential for LPL to mediate a significant accumulation of LDL and oxidized LDL on these surfaces [41]. These observations become particularly striking when the recent work of Kaplan and Aviram [42] is considered. They have shown that macrophage uptake of oxidized LDL bound to macrophage-derived extracellular matrix is entirely dependent upon the presence of LPL. Taken together these studies indicate that LPL is not only responsible for the accumulation of atherogenic lipoproteins, but is a crucial factor in their uptake by macrophages as well.

Calcium is known to be present in atherosclerotic lesions and has the ability to enhance the binding of native and oxidized LDL to the extracellular matrix [43] and VLDL to the subendothelial matrix [44]. Latterly, Wang et al. [45] have shown that in mouse peritoneal macrophages, Ca$^{2+}$ and LPL can synergistically increase the binding and uptake of native and oxidized LDL, and the deposition of esterified cholesterol derived from it. Possible reasons for this synergy include the ability of Ca$^{2+}$ to increase the binding of native and oxidized LDL to LPL and to enhance the structural stability of LPL [45,46].

It is well established that heparin competes with HSPG and receptors for the binding of LPL [22,31]. It therefore follows that when heparin is present in the blood, cell surface LPL–lipoprotein complexes should be reduced and, as a consequence, there should be less lipoprotein accumulation in macrophages. Indeed, an in vivo study in rats has shown that heparin treatment prolongs the clearance of oxidized LDL [47]. This hypothesis was further tested recently using a heparin-mimicking compound, RG-13577, currently under consideration for clinical use in the prevention of atherosclerosis. Neuger and co-workers [48] found that, as expected, the compound released LPL into rat blood. In addition, their in vitro work showed that RG-13577 released LPL bound to extracellular matrix produced by both endothelial cells and the monocyte-derived THP-1 macrophages. The binding of LDL to LPL and its subsequent cellular uptake was also prevented by this drug, thereby indicating that targeting of the bridging action of LPL could represent a potential strategy for an anti-atherogenic treatment.

All of the evidence cited above illustrates how LPL acts as a molecular bridge due to its ability to bind simultaneously to lipoproteins and proteoglycans/receptors via separate domains. The proposed bridging function of LPL has been supported by numerous tissue culture studies (see Refs. cited above and [22,23]) and has also been confirmed in vivo [49]. A further variation on the bridging theme involves cells rather than lipoproteins as LPL has been shown to function as a monocyte adhesion protein by forming a ‘bridge’ between the arterial subendothelial matrix and monocyte surface HSPG [50,51].

6. Anti-atherogenic nature of LPL

As mentioned earlier, a paradox exists with respect to LPL expression and atherosclerosis. As well as being responsible for atherogenic events in the arterial wall, it has also been shown to play a generalised anti-atherogenic role, as proven by a variety of experimental evidence. For instance, decreased adipose tissue LPL activity has been implicated to be responsible, at least in part, for the hypertriglyceridaemia that is associated with insulin resistance and type II diabetes, which then makes a major contribution to the ensuing atherosclerosis in these individuals [23,52]. The suppression of LPL expression in these clinical conditions is believed to be mediated by cytokines that are present at high levels, such as...
interleukin-6 and tumour necrosis factor-α (TNF-α) [23,52]. In addition, studies on patients participating in the Regression Growth Evaluation Statin Study (REGRESS) have identified a strong link between post-heparin LPL activity and severity of angina [53]. Of the patients in the lowest LPL activity quartile, 47% reported signs of severe angina. However, this figure was significantly lower (29%) in the highest LPL activity quartile. Furthermore, a recent clinical study in Japan [54] has also shown considerably lower levels of pre-heparin serum LPL mass in patients with coronary atherosclerosis compared to those in healthy individuals. Moreover, several homozygous LPL-deficient patients have been found to develop relatively advanced atherosclerosis [55]. Finally, a number of heterozygous LPL genetic variants have been identified that are associated with a pro-atherogenic lipid profile and an increased risk for cardiovascular disease (see Refs. [32,56] for recent reviews). This includes the Asp9Asn and Asn291Ser mutations that occur at carrier frequencies of up to 5% and are characterised by a reduction in LPL enzymatic activity [32,56]. Similarly, the T-93G promoter variant, which reduces LPL promoter activity by inhibiting the binding of the transcription factors Sp1 and Sp3, has been found to be associated among patients with mild elevation in plasma triglyceride levels and ischemic heart disease [57]. Conversely, a serine 447-stop variant, which is characterised by increased LPL activity and has a carrier frequency of approximately 20%, is associated with an anti-atherogenic lipid profile and a reduced risk of coronary heart disease [32,56,58,59].

It is well-established that efficient lipolysis of triglyceride-rich lipoproteins in heart, skeletal muscle and adipose tissue generally drives the circulating lipoprotein profile in a non-atherogenic direction [60–62]. Thus, in contrast to macrophage LPL, the endothelium-bound enzyme derived from the parenchymal cells of adipose tissue and muscle plays an antiatherogenic role. Indeed, Clee et al. [21] have recently shown that transgenic mice with increased plasma LPL but with no changes in the expression of the enzyme in macrophages, and thus the vessel wall, have reduced atherogenesis. Overexpression of LPL is highly effective in normalizing the atherosclerotic lipoprotein profiles of both apoE-deficient and LDL receptor-deficient mice and protects wild-type mice against diet-induced hyperlipidaemia [21,60–62]. Of particular importance are the levels of HDL, which functions as a removal vehicle for cholesterol, transporting it away from areas of production to the liver for excretion into the bile (reverse cholesterol transport) [63]. In addition, HDL has been shown to prevent the oxidation of LDL by metal ions [64]. Furthermore, genetic syndromes characterised by high HDL levels are usually associated with decreased atherosclerosis [65]. Post-heparin plasma LPL activity has also been linked directly to HDL levels in humans [66] with a heterozygous LPL genotype associated with reduced HDL-cholesterol levels [67]. Equally, administration of the compound NO-1886, which increases tissue LPL activity, protects against atherosclerosis via elevation of HDL levels [68].

Another class of hypolipidaemic agents, the statins, have recently been tested in several large clinical trials and found to cause an approximate 30–40% reduction in coronary events [69,70]. This was also accompanied by a significant reduction in both the total cholesterol:HDL-cholesterol and LDL-cholesterol:HDL-cholesterol ratios [71]. Interestingly, statins have been shown to enhance LPL activity in adipose tissue and heart as well as decreasing plasma levels of apolipoprotein C-III, an LPL inhibitor [72]. Similar effects upon LPL have also been exhibited by a third class of drugs, the fibrates, which have again proven effective in reducing coronary atherosclerosis [73]. The increased hydrolysis of triglycerides in such cases may result in the transfer of lipids and apolipoproteins to HDL [74], and thereby facilitate their excretion.

7. Regulation of LPL by factors implicated in atherogenesis

The regulation of macrophage LPL by factors that have been implicated in atherosclerosis is likely to make a major contribution to the initiation and the progression of the disease. It is therefore not surprising that this aspect has been the subject of intense research in several laboratories, including our own [23,75–90]. Similarly, the regulation of LPL expression in the muscle and the adipose tissue has been investigated in the light of the anti-atherogenic potential of LPL produced by these tissues [4,91,92]. With respect to macrophage LPL, an excellent correlation has been found in several cases between the role of the regulating factor in atherogenesis and its action on LPL expression. For example, glucose, hydrogen peroxide (source of oxidant stress/reactive oxygen intermediates), many free fatty acids (e.g. linoleic acid, palmitic acid, stearic acid), homocysteine, platelet-derived growth factor and macrophage colony stimulating factor (M-CSF) all increase macrophage LPL expression [23,75–81]. The pro-atherogenic role of all these factors is well documented. For example, peripheral factors dysregulated in diabetes, including glucose and free fatty acids, are known to contribute to the high incidence of atherosclerosis in diabetic patients [13,75,76,78]. Similarly, hyper-homocysteinemia represents an independent risk factor for atherosclerosis [79]. Reactive oxygen intermediates are also present at high levels in the atherosclerotic lesion and have been implicated in the oxidation of LDL and the production of several other pro-atherogenic factors [77]. M-CSF has also been found to be present in the lesion and mice lacking the corresponding gene are less susceptible to atherosclerosis [23,81]. In contrast, consistent with the complex aetiology of atherosclerosis, a more complicated story emerges for several other factors. For instance,
Macrophage LPL expression is suppressed by bacterial lipopolysaccharide, a range of cytokines, prostaglandins, and oxidized LDL and metabolites that are known to be produced during LDL oxidation, including lysophosphatidylcholine, 7β-hydroxycholesterol and 25-hydroxycholesterol [82–90]. As oxidized LDL, bioactive lipids and certain cytokines are considered to be pro-atherogenic, the precise significance of their LPL suppressing, anti-atherogenic action currently remains unclear. However, as atherosclerosis is initially a protective mechanism [1], it is possible that these factors may limit the transformation of macrophages into foam cells during the early stages of vascular damage until their actions are over-ridden by changes in the composition and concentration of LPL activating agents in the local milieu of mediators during the progression of the disease.

The expression of LPL in the muscle and the adipose tissue is regulated by nutritional status and a plethora of factors, including hormones, growth factors and lipid metabolite products [4,91,92]. Again, a good correlation exists in several cases between the atherogenic potential of the factor and its action on LPL expression. For example, the hypolipidemic fibrates and the antidiabetic thiazolidinediones, which display potent triglyceride-lowering activities and limit atherogenesis, induce the expression of the LPL gene through peroxisome proliferator activated receptors [91,92].

8. Concluding remarks

The evidence presented in this review clearly indicates a key pro-atherogenic role of macrophage-derived LPL whereas the enzyme expressed by the muscle and the adipose tissue acts in an anti-atherogenic manner by improving the circulating lipoprotein profile. Future therapeutic approaches should therefore seek to decrease macrophage LPL expression whilst increasing its action in adipose tissue and muscle. Gene therapy [61] represents a potential avenue to achieve such specificity and it is essential that more research on this aspect is urgently carried out. It is, however, interesting to note that studies on the modulation of LPL expression have identified several examples of tissue/cell-specific regulation. For example, LPS directly suppresses LPL gene expression in macrophages but not adipocytes [82]. In addition, fibrates selectively induce LPL mRNA levels in the liver but not the adipose tissue whereas thiazolidinediones have no effect in the liver but act primarily on the adipose tissue [91,92]. Such selectivity is likely to extend to other tissues/cell-types because individuals taking such drugs have reduced atherosclerosis whereas global elevation of LPL expression by these agents would be expected to increase the risk through their action on the enzyme expressed by macrophages. Furthermore, treatment of diabetic rats with rexinoids (retinoid X receptor-selective retinoids) has been shown to suppress LPL activity in skeletal- and cardiac-muscles but not in adipose tissue [93]. More recently, mice that have been fed diets containing high cholesterol or oxysterol liver X receptor-selective agonists have been found to exhibit a significant increase in LPL expression in the liver and macrophages but not in other tissues (e.g. adipose and muscle) [94]. It is therefore possible that through more research on the regulation of LPL expression, particularly the signal transduction pathways and the transcription factors that are involved in the process, pharmacological agents could be developed that differentially regulate LPL expressed by adipose tissue/muscle and macrophages.

Several recent studies have also identified additional, novel roles for LPL. For example, as discussed previously, LPL has been found to stimulate the proliferation of smooth muscle cells [28], a potentially atherogenic event. In addition, LPL induces the expression of the TNF-α gene in macrophages via a pathway that is mediated through cell surface proteoglycans and requires protein kinase C [95–97]. LPL also reduces the secretion of apoE in macrophages and synergizes with IFN-γ in the induction of macrophage nitric oxide synthetase expression [98,99]. Given the importance of TNF-α, apoE and nitric oxide in atherogenesis, it is essential that more research is carried out in order to elucidate the relevance of such a novel role of LPL and the corresponding mechanisms of action.

In conclusion, the exciting findings from research carried out in the last few years have not only emphasized the key role of LPL in atherogenesis but clarified the potential contribution of the enzyme expressed by macrophages and adipose tissue/muscle in the disease. Thus, the enzyme expressed by the adipose tissue and muscle is generally regarded as anti-atherogenic whereas that produced by macrophages is considered to be pro-atherogenic. In addition, an excellent correlation has been found on the action of several factors on LPL gene expression and their role in atherosclerosis (e.g. glucose and growth factors). Future studies should seek to obtain a detailed understanding of the regulation of LPL expression and develop strategies that could be used to modulate its action in a tissue/cell-specific manner.

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