Multiple miRNA Regulation of Lipoprotein Lipase

46

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Contents

Introduction 886
miRNAs Involved in LPL Regulation 887
miR-29 Family 887
miR-27 Family 888
LPL Regulation by miRNAs in Macrophages 889
miRNA Interactions with LPL Genetic Variants 890
miRNA Regulation of LPL Cofactors 891
APOA5 892
APOC3 892
ANGPTL3 and 4 893
Conclusion 893
Key Facts of miRNA Regulation of LPL 894
Summary Points 894
References 894

Abstract

Lipoprotein lipase (LPL) is the key enzyme involved in the intravascular lipolysis of triglyceride (TG)-rich lipoproteins. The regulation of LPL expression and activity is complexed, tightly regulated by hormonal, nutritional, and genetic mechanisms, which remain partially unknown. LPL is highly regulated at a posttranscriptional level that could involve miRNA. miR-27 and miR-29 families are the most studied miRNAs responsible for a decreased LPL expression, mainly in adipose tissue but also in hepatocytes. These miRNAs and several others, miR-467 and miR-590, have been shown to directly target LPL in macrophages and

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prevent atherosclerosis in animal models. Moreover, a LPL haplotype associated with lower TG was shown to disrupt several miRNA-binding sites. LPL activity can also indirectly be regulated by miRNA which regulates the expression of its cofactors such as APOA5 and ANGPTL3/4.

Keywords

Adipose tissue · Angtpl3 · Angtl4 · Apolipoprotein A5 · Apolipoprotein C3 · Lipoprotein lipase · Macrophages · miR-27 · miR-29 · miRNA · Triglycerides

List of Abbreviations

Angptl	Angiopoietin-like protein
Apo	Apolipoprotein
FA	Fatty acids
GPIHBP1	Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1
HTG	Hypertriglyceridemia
LPL	Lipoprotein lipase
miRNA	MicroRNA
SNP	Single-nucleotide polymorphism
TG	Triglycerides
TGRL	Triglyceride-rich lipoproteins
UTR	Untranslated region

Introduction

Lipoprotein lipase (LPL) is the key enzyme involved in the intravascular catabolism of triglyceride (TG)-rich lipoproteins and a major player in the regulation of plasma TG concentration. It is submitted to a complex transcriptional and posttranscriptional regulation, both direct and indirect, via its cofactors. MicroRNA (miRNA) provide a new layer of regulation to optimize the continuous adjustment of LPL activity, between fasting and post-prandial state.

LPL is mainly expressed in adipose tissue and muscles. After a complex maturation in the endoplasmic reticulum involving lipase maturation factor 1, LPL is transported to the luminal side of the capillary endothelium by glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1). LPL is active as dimers bound to GPIHBP1 and hydrolyzes the TG into fatty acids (Fig. 1). Additionally, LPL is expressed in macrophages, mammary gland cells, and fetal hepatocytes (Kersten 2014).

The major role of LPL in plasma TG metabolism is illustrated by the severe hypertriglyceridemia (HTG) in patients carrying homozygous or compound heterozygous mutations. Many LPL polymorphisms are associated with either lowered or increased plasma TG concentrations (Hegele et al. 2014).

The regulation of LPL is complexed, tightly regulated at both transcriptional and posttranscriptional levels involving hormonal, nutritional, and genetic mechanisms

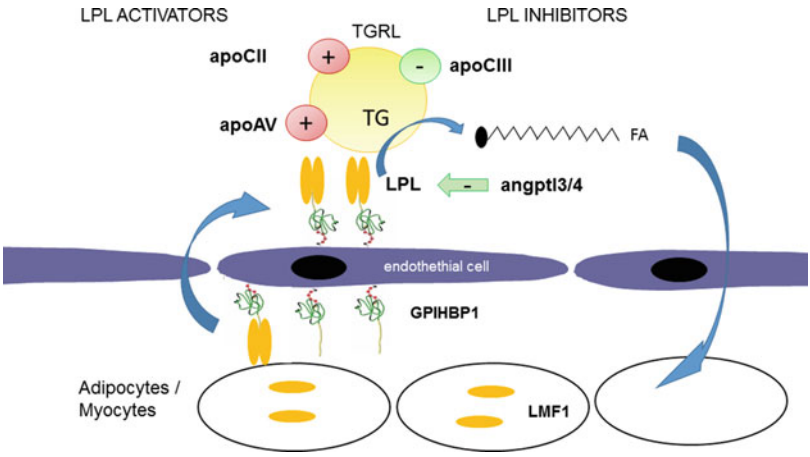

Fig. 1 LPL and its main regulator genes or cofactors. *Angptl* angiopoietin-like protein, *apo* apolipoprotein, *FA* fatty acids, *GPIHBP1* glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1, *LMF1* lipase maturation factor 1, *LPL* lipoprotein lipase, *TG* triglycerides, *TGRL* triglyceride-rich lipoproteins

which remain partially unknown (Li et al. 2014). Several arguments are in favor of a posttranscriptional regulation of LPL. First, the LPL 3′untranslated region (UTR) is particularly long. This region was suggested to play an important role in the downregulation of LPL translation, as deletion of the 3′UTR increases LPL mass and activity without affecting LPL transcription, both in vivo and in vitro (Ranganathan et al. 2000; Hensley et al. 2003). miRNAs are evolutionally conserved 19–22 nucleotides of noncoding RNA that posttranscriptionally downregulate gene expression by binding target mRNAs. This process leads to mRNA degradation or translation repression. Recent data have suggested that miRNAs predominantly decrease mRNA stability through base pairing with the 3′UTR of target mRNAs (Bartel 2009; Fabian and Sonenberg 2012). Therefore, the discovery of miRNAs, which have emerged as major posttranscriptional regulators of most mammalian mRNAs, had offered new keys to improve the knowledge of the complex regulation of LPL and TG metabolism.

miRNAs Involved in LPL Regulation

miR-29 Family

The most studied miRNAs in LPL regulation belong to the miR-29 family which includes in humans miR-29a, miR-29b1/b2, and miR-29c. miR-29b1 and miR-29b2 have identical mature sequences and are together called miR-29b. miR-29's mature sequences are highly conserved between species, with large overlap of their sequence and an identical seed region, critical for the recognition of target gene

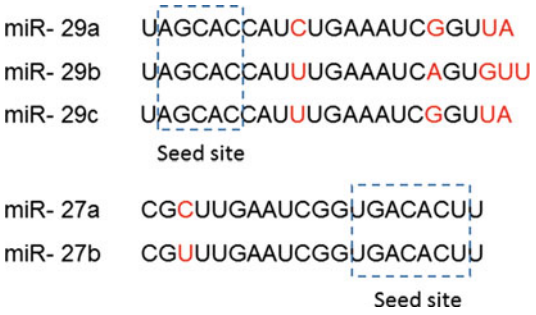

Fig. 2 Mature sequences of the miR-27 and miR-29 families' members share identical seed sites. Nucleotides that differ among the families' members are shown in *red* (Adapted from Kriegel et al. and Zhang et al. (Kriegel et al. 2012; Zhang et al. 2014))

sequences (Fig. 2). The miR-29 family plays a major role in anti-fibrotic and proapoptotic processes in several organ diseases such as cardiac, pulmonary, hepatic, or renal fibrosis (Kriegel et al. 2012; Deng et al. 2017).

Chen et al. were the first to report a role of miR-29a in LPL posttranscriptional regulation. They showed that the inhibition of miR-29a expression in dendritic cells increased LPL mRNA levels, whereas enhancing miR-29a expression decreased LPL mRNA expression (Chen et al. 2011). LPL is mainly expressed in adipose tissue and muscles. miR-29a repression on LPL mRNA was shown during 3T3-L1 adipocyte differentiation (Bouvy-Liivrand et al. 2014) and recently in human subcutaneous adipose tissue biopsies with a significant inverse correlation between LPL mRNA levels and miR-29a expression (Kristensen et al. 2017).

LPL expression is repressed in adult hepatocytes. In a mice model, Mattis et al. identified miR-29a as the miRNA responsible for repressing LPL in hepatocytes. Interestingly, in this model of fatty liver disease, the inhibition of miR-29a is responsible for both a decreased hepatic LPL expression and an increased hepatic lipid accumulation (Mattis et al. 2015). These findings suggest that the loss of hepatic miR-29a expression could be involved in the pathogenesis of fatty liver diseases. In agreement, previous studies have shown that miR-29a levels were decreased in livers of animals or humans with fatty liver diseases (Jin et al. 2009; Roderburg et al. 2011; He et al. 2016) and that LPL levels were increased in biopsies of human fatty livers (Pardina et al. 2009).

miR-27 Family

The miR-27 family is composed of two homologous isoforms, miR-27a and miR-27b, sharing 20 out of 21 nucleotides and highly conserved during evolution (Fig. 2). Several studies suggested that miR-27 family plays an important role in angiogenesis, adipogenesis, lipid metabolism, inflammation, oxidative stress, insulin resistance, and type 2 diabetes (Chen et al. 2012).

Both miR-27a and miR-27b were also shown to be abundantly expressed in mouse and human adipocytes. They were shown to be downregulated during adipogenesis and to target both PPAR gamma and LPL gene (Karbiener et al. 2009; Kim et al. 2010; Bouvy-Liivrand et al. 2014).

Karbiener et al. have identified miR-27b as the first negative miRNA regulator on adipogenesis in human. They found a decreased expression of miR-27b during adipogenesis in a cell model of human adipogenesis (human multipotent adipose-derived stem cells). They also showed that overexpression of miR-27b was responsible for an impaired TG accumulation in adipose cells and for the repression of several adipogenic marker genes including PPAR gamma and LPL, decreasing their mRNA expression (Karbiener et al. 2009). In addition, miR-27b could indirectly decrease LPL activity by repressing ANGPTL3 mRNA expression in the liver, decreasing angptl3 plasma circulating concentration (see further) (Vickers et al. 2013). Interestingly, circulating miR-27 levels were found to be elevated in obese children and to be associated with elevated TG (Can et al. 2016).

Kim et al. also showed that miR-27a was a negative regulator of adipogenesis in 3T3-L1 cells and repressed PPAR gamma and LPL (Kim et al. 2010). Bouvy-Liivrand et al. demonstrated that miR-27a is inversely correlated with the mRNA level of LPL. They showed that both miR-27a and miR-29a acted in a combinatorial manner to increase their repressive effect on LPL expression. miR-27a was also shown to inhibit the translation of PPAR gamma, the key transcriptional regulator of LPL. Therefore, the authors suggested that these miRNA's and transcription factor's actions might form a feedforward loop to enhance the repressive effect on LPL expression (Bouvy-Liivrand et al. 2014; Li et al. 2014). Interestingly, both miR-27a and miR-29a were shown to be upregulated in adipocytes of diabetic rats (He et al. 2007; Herrera et al. 2010), suggesting that they could play a role in the decrease of LPL which contribute to the hypertriglyceridemia observed in diabetes. In addition, miR-27a/b could also play an important role in the adipogenesis and the pathophysiology of obesity.

LPL Regulation by miRNAs in Macrophages

Apart from its role in intravascular lipolysis, LPL is also expressed in macrophages. It stimulates lipid accumulation in macrophages by increasing the uptake of lipoproteins, such as LDL and oxidized LDL, and thus might promote atherosclerosis (Li et al. 2014).

Several miRNAs, previously identified to have protective effects on cardiovascular diseases, have been involved in macrophage LPL downregulation. miR-27a/b (Zhang et al. 2014; Xi 2016), miR-29a (Chen et al. 2011), miR-467b (Tian et al. 2012; Tian et al. 2014), and miR-590 (He et al. 2014; He et al. 2015) have been shown to inhibit both lipid uptake and pro-inflammatory cytokine secretion in macrophages or dendritic cells, by directly targeting the 3′UTR LPL in macrophages. These mechanisms were involved in atherosclerosis prevention by miR-27 and miR-467b and miR-590 in APOE KO mice model (Tian et al. 2014; He et al. 2015; Xie et al. 2016).

Conversely, miR-134 was shown to exert pro-atherogenic properties, promoting LPL-mediated lipid accumulation and inflammatory response by targeting ANGPTL4 in THP-1 macrophages (Lan et al. 2016).

Therefore, targeting miRNA could offer novel strategies to prevent atherosclerotic cardiovascular diseases. Nevertheless, as miRNAS target multiples genes, to date, it is not possible to have a specific effect on a single gene, inhibiting one miRNA.

miRNA Interactions with LPL Genetic Variants

The recognition of target mRNA by miRNA involves a small complementary sequence from two to seven nucleotides long. Sequence alteration by single-nucleotide polymorphisms can either generate or suppress miRNA-binding sites in mRNAs (Gong et al. 2012). For example, such a finding was previously reported for obesity-associated c.*2270A>G (rs8887) which creates an illegitimate miR-522-binding site in the 3′UTR of perilipin 4 (PLIN4) and promotes its downregulation in adipose tissue (Richardson et al. 2011) (Fig. 3).

Richarson et al. were the first to investigate the potential regulation by miRNA of LPL variants associated with TG. They showed that the rs13702 minor C allele, strongly associated with both lower TG and greater HDLc in large populations, disrupts a miRNA recognition element seed site and abolished the response of a functional miR-410 site in the LPL 3UTR (Richardson et al. 2013) (Fig. 4).

Interestingly, Corella et al. report in the PREDIMED study that the rs13702 C allele carriers had both lower TG and stroke risk; these associations were reenforced by a high-unsaturated fat MedDiet intervention (Corella et al. 2014).

This rs13702 belongs to a specific LPL haplotype harboring the rare alleles of several polymorphisms including the four single nucleotide polymorphisms (SNPs) rs328, rs13702, rs1059611, and rs10645926. This haplotype (Hap4) associates with lower TG levels in large population studies. Caussy et al. went further into deciphering the miRNA regulation of this specific haplotype associated with lower TG. They first identified several putative miRNA-binding sites on the wild-type LPL haplotype, lost on Hap4. Then, they evidenced in cell models the presence of functional binding sites for the miR-410 and also miR-29a, miR-29b, and miR-1277 on the human LPL transcripts harboring the wild-type Hap1 haplotype, disrupted by the minor alleles of the Hap4 haplotype SNPs (Fig. 5). This loss of

Fig. 3 Creation of a novel miR-522-binding site in the PLIN4 3′UTR by the rs8887 minor A allele. The rs8887 variants are in bold (Adapted from Richardson et al (2011))

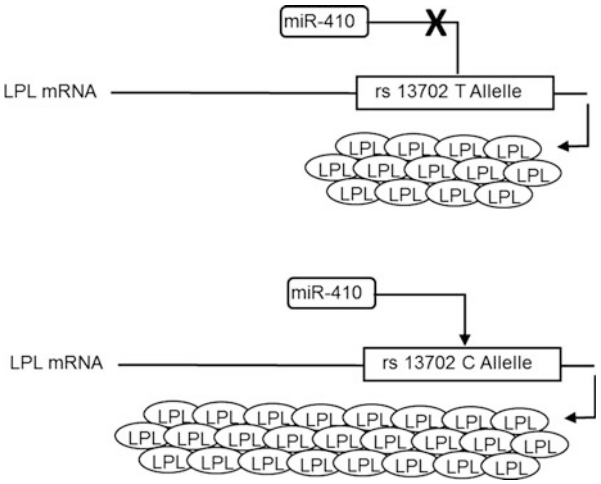

Fig. 4 rs13702 allele-specific consequences on miR-410 binding and LPL expression The rs13702 T allele in the LPL 3′UTR creates a binding site for miR-410, which leads to lower LPL concentrations, whereas in the presence of the rs13702 C allele, LPL expression is not affected by miR-410 (Adapted from Richardson et al. (2013))

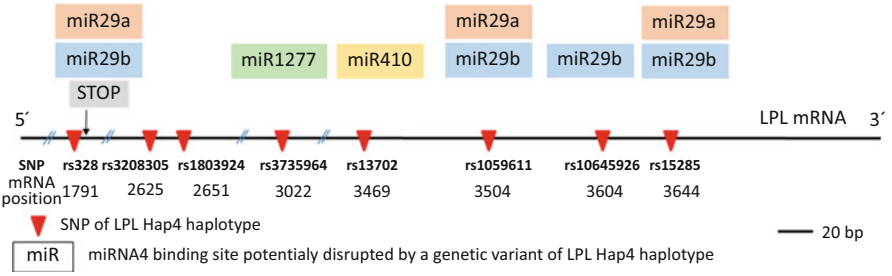

Fig. 5 miRNA-binding sites lost in the presence of rare variants of LPL Hap4 haplotype (Adapted from Caussy et al. (2016))

specific miRNA-binding site in the presence of Hap4 was independent of the allelic variation of p.Ser474Ter (rs328) (Caussy et al. 2016).

Thus, Caussy et al. highlighted a new concept of a multiple miRNA regulation of a specific LPL TG-lowering haplotype. They also suggested that the well-known coding rare variant rs328 (p.Ser474Ter), associated with lower TG concentration, whose functionality is not clearly explained in literature, could be at least partially explained by its strong linkage disequilibrium with these functional 3′UTR SNPs (Caussy et al. 2016).

miRNA Regulation of LPL Cofactors

LPL activity could also be indirectly regulated by a miRNA regulation of its cofactors or regulatory genes (Fig. 1).

APOA5

ApoA5, encoded by APOA5 gene, is a liver-expressed 366 amino acid apolipoprotein that binds to very-low-density lipoprotein, high-density lipoprotein, and chylomicrons in plasma. Its involvement in TG metabolism was first demonstrated in mouse models: Apoa5 KO mice showed a fourfold increase in plasma TG concentrations, whereas Apoa5 overexpression in mice significantly reduced TG levels (Pennacchio et al. 2001).

In mice, apoA5 lowers plasma TG levels by increasing LPL activity, as confirmed by in vitro and in vivo studies (Grosskopf et al. 2005; Merkel et al. 2005). However, the underlying mechanism is still not completely understood. In humans, APOA5 plays a critical role in HTG physiopathology. Deleterious APOA5 mutations were found to be involved in familial hyperchylomicronemia by inducing a LPL activity defect (Marçais et al. 2005). Moreover, two common APOA5 variant haplotypes tightly modulate triglyceridemia either in mild or severe HTG (Pennacchio et al. 2002; Charriere et al. 2008; Charrière et al. 2009). One of these APOA5 haplotypes (APOA5*2) includes the C rare allele of the c.*158C>T SNP (rs2266788), which is located in the APOA5 3′UTR, and is in strong linkage disequilibrium with three additional SNPs: g.4430C>T (rs662799), c.-3A>G (rs651821), and c.162-43A>G (rs2072560). This haplotype is strongly associated with plasma TG concentrations in general population in genome-wide association studies (Willer et al. 2008).

Several studies in literature have suggested that APOA5*2 might modulate APOA5 expression at the posttranscriptional level. Caussy et al. demonstrated that the rare c.*158C APOA5 allele creates a functional target site for liver-expressed miR-485-5p, which could account for the hypertriglyceridemic effect of APOA5*2 (Caussy et al. 2014).

APOC3

ApoC3 is also a major regulator of plasma triglyceride (TG) metabolism by promoting liver VLDL assembly and secretion, inhibiting hydrolysis of TG-rich lipoproteins by lipoprotein lipase and decreasing the uptake of TG-rich remnant lipoproteins by the liver. Several APOC3 3′UTR noncoding variants are strongly associated with TG, but their functionality is not clearly established (Hoffer et al. 1998; Groenendijk et al. 2001).

The S2 rare allele of SStI 3′UTR variant (c.*40G>C, rs5128) was shown to be associated with both moderate and severe HTG (Marçais et al. 2000). Dancer et al. investigated if this APOC3 variant could be responsible for the loss of a miRNA-binding site, could increase APOC3 mRNA expression, and could consequently raise plasma TG concentration. In silico studies predicted a potential loss in the binding of five miRNAs induced by the SStI S2 rare variant. However in vitro, the S2 variant did not modulate the APOC3 3′UTR reporter gene expression in several hepatic and intestinal human cell lines. Thus, the hypothesis of a direct regulation of the APOC3 SstI variant by hepatic or intestinal miRNAs was not confirmed. (Dancer et al. 2016).

Another APOC3 3′UTR common variant BbvI (c.*71 G>T, rs4225) was studied for miR regulation by Hu et al., although this variant is inconstantly associated with TG in literature. They reported, in a large Chinese Han population, that the rare allele T of rs4225 was significantly associated with decreased triglyceride levels and reduced CHD risk. T allele carriers (GT and TT groups) had also lower apoC3 levels compared to GG group. They demonstrated that, in vitro, the T allele of BbvI APOC3 variant created a functional miR-4271-binding site, which could be responsible for a decreased APOC3 expression and the hypertriglyceridemic effect of this 3′UTR variant (Hu et al. 2016).

ANGPTL3 and 4

ANGPTL3 and ANGPTL4 are both potent LPL inhibitors, decreasing LPL activity. ANGPTL3 is specifically expressed in the liver and secreted in the circulation. Loss of function mutations or SNPs of ANGPTL3/4 are responsible in humans of low TG concentration and decreased LPL activity (Musunuru et al. 2010; Dewey et al. 2016). ANGPTL4, expressed mainly in adipocytes, downregulates LPL activity during fasting and exercise. ANGPTL4 irreversibly inhibits LPL activity by disrupting its dimerization, converting the enzyme into inactive monomers, and reduces LPL affinity for GPIHBP1 (Dijk and Kersten 2016). Both ANGPTL3 and ANGPTL4 were shown to be regulated by miRNAs.

Vickers et al. showed that miR-27b regulated the mRNA expression of several lipid metabolism genes including ANGPTL3 in a human hepatocyte cell line (HuH7). Moreover, they found that in APOE KO mice under high-fat diet, TG were decreased by about two/three, miR-27b was upregulated by about 1.5-fold in the liver, and miRNA levels of ANGPTL3 were reduced by 30% (Vickers et al. 2013).

ANGPTL4 was shown to be regulated by miR-134 in THP-1 macrophages (Lan et al. 2016). Nevertheless, to date, no data about a potential regulation of ANGPTL4 in adipocytes by miR-134 or other miRNAs is available in literature.

Conclusion

In this review, we have described several miRNAs involved into the direct regulation of LPL expression or the indirect regulation of its activity by LPL cofactors targeting mechanisms likely to modulate plasma TG concentration. miRNAs are also new keys to understand the functionality of 3′UTR variants. Collective consideration of these data reveals that miRNAs must be integrated in the multilayer system that regulates LPL activity and TG metabolism. Many work remains to decipher the relative contribution of each miRNA, their potential regulation by nutrition, and their correlation with dyslipidemia, in order to identify miRNAs as new therapeutic targets in the treatment of HTG and cardiometabolic disorders.

Key Facts of miRNA Regulation of LPL

- The complex regulation of LPL involves direct or indirect regulation of LPL expression or activity by miRNAs.
- miR-27 and miR-29 families are involved in the downregulation of LPL expression in adipocytes.
- The LPL of macrophages, which control lipid accumulation and promotes atherosclerosis, is also regulated by miRNA such as miR-27, miR-29, miR-467, and miR-590.
- Polymorphisms of LPL and its cofactor APOA5 could modulate miRNA regulation, disrupting or creating miRNA-binding sites.

Summary Points

- Lipoprotein lipase is the key enzyme of the catabolism of triglyceride-rich lipoproteins.
- The regulation of LPL is complex, involving a posttranscriptional level.
- miRNAs are major posttranscriptional regulators of mRNAs and offer new keys to improve the knowledge of the complex regulation of LPL and TG metabolism.
- miR-27 and miR-29 families are the most studied miRNAs in LPL regulation. They are involved in LPL decrease during adipogenesis and hepatocytes maturation. The dysregulation of miRNAs regulating LPL could be involved in the pathophysiology of metabolic disease.
- miR-27, miR-29, miR-467, and miR-590 target LPL in macrophages and prevent atherosclerosis in animal models.
- A LPL haplotype associated with lower TG was shown to disrupt several miRNA-binding sites.
- The regulation of LPL cofactors such as APOA5 or ANGTL3/4 by miRNAs can also indirectly regulate LPL activity.

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