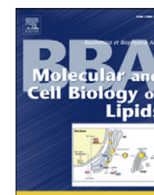
Biochimica et Biophysica Acta 1861 (2016) 1434–1441

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip



Review

Cardiomyocyte-endothelial cell control of lipoprotein lipase☆

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ARTICLE INFO

Article history:
Received 2 February 2016
Received in revised form 14 March 2016
Accepted 15 March 2016
Available online 17 March 2016

Keywords:
Heparanase
GPIHBP1
VEGF
Diabetic cardiomyopathy
STZ diabetes

ABSTRACT

In people with diabetes, inadequate pharmaceutical management predisposes the patient to heart failure, which is the leading cause of diabetes related death. One instigator for this cardiac dysfunction is change in fuel utilization by the heart. Thus, following diabetes, when cardiac glucose utilization is impaired, the heart undergoes metabolic transformation wherein it switches to using fats as an exclusive source of energy. Although this switching is geared to help the heart initially, in the long term, this has detrimental effects on cardiac function. These include the generation of noxious byproducts, which damage the cardiomyocytes, and ultimately result in increased morbidity and mortality. A key perpetrator that may be responsible for organizing this metabolic disequilibrium is lipoprotein lipase (LPL), the enzyme responsible for providing fat to the hearts. Either exaggeration or reduction in its activity following diabetes could lead to heart dysfunction. Given the disturbing news that diabetes is rampant across the globe, gaining more insight into the mechanism(s) by which cardiac LPL is regulated may assist other researchers in devising new therapeutic strategies to restore metabolic equilibrium, to help prevent or delay heart disease seen during diabetes. This article is part of a Special Issue entitled: Heart Lipid Metabolism edited by G.D. Lopaschuk.

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1. Introduction

Fatty acids (*FA*) have numerous biological functions and include the formation of membranes, participation as energy substrates, and initiation of signal transduction. Because of their limited water solubility, long chain FA must undergo esterification with glycerol to form triglycerides (*TG*), which make up a significant portion of circulating lipoprotein TG. It is these particles that deliver the FA to the underlying tissues. This process relies on lipoprotein lipase (*LPL*) [1], an enzyme that hydrolyzes TG-rich lipoproteins (VLDL and chylomicrons) to FA in the vascular lumen, and is termed lipolysis.

The heart is a high-energy organ that has flexibility in utilizing multiple substrates for energy production, including FA, carbohydrates, and ketone bodies, to maintain its function [2]. In the normal heart, nearly 70% of ATP is produced from FA oxidation, with the remainder being provided by glucose and lactate [3]. Although the heart has a high demand for FA, it has a limited capacity to synthesize FA, and thus relies on an exogenous FA source. This includes release from adipose tissue and transport to the heart after complexing with albumin [4], provision through the breakdown of endogenous cardiac TG stores [5], and lipolysis of circulating TG-rich lipoproteins to FA by LPL positioned at the EC surface of the coronary lumen [6]. Given that greater than 90% of plasma FA is contained within lipoprotein-TG and the heart has the most robust expression of LPL, lipolysis of TG-rich lipoproteins mediated by LPL is suggested to be a principal source of FA for cardiomyocyte metabolism [1]. Interestingly, in the heart, LPL is produced in the cardiomyocytes and is transferred to the apical side of the endothelial cell (*EC*), where the enzyme functions [7,8]. In this review, we will discuss the process of LPL synthesis, activation, and its subsequent transfer across the EC to the vascular lumen and how these processes are altered during diabetes.

2. Lipoprotein lipase (LPL)

Although LPL is strategically located at the EC surface of the coronary lumen, ECs have limited LPL expression. This enzyme is predominantly synthesized and processed in the cardiomyocyte [7,9]. In this cell, LPL is synthesized as an inactive monomer that enters the endoplasmic reticulum (*ER*) and undergoes glycosylation [10]. Glycosylation of the Asn residue in the N-terminal domain is necessary for its catalytic activity. It is further processed by calnexin/calreticulin, chaperones that regulate nascent LPL folding into a proper tertiary structure qualified for dimerization [11]. The two inactive monomeric LPL are then non-covalently assembled in a head-to-tail fashion with the help of lipase maturation factor 1 (*LMF1*) into a dimeric enzyme [12–16]. In ER, LPL forms a complex with LMF1 and Sel1L, an essential adaptor protein in the ER-associated degradation. This structure stabilizes LPL and enables it to exit the ER as a dimer [17]. Without LMF1, LPL forms aggregates and is retained in the ER [18,19]. Defects in ER-LPL maturation result in familial hyperchylomicronemia, a form of hypertriglyceridemia that contributes to the development of heart disease and metabolic syndrome in humans [13].

☆ This article is part of a Special Issue entitled: Heart Lipid Metabolism edited by G.D. Lopaschuk.

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http://dx.doi.org/10.1016/j.bbalip.2016.03.016
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After dimeric LPL exits the ER, it is further sorted into secreted vesicles in the Golgi. The exocytosis of the LPL secretory vesicle from Golgi requires protein kinase D [20,21]. In addition to PKD, AMP-activated protein kinase (*AMPK*) is a cellular energy sensor that also regulates LPL [22]. In the heart, AMPK switches on coronary LPL activity in rats undergoing fasting, mostly through a post-translational mechanism. Specifically, by phosphorylating heat shock protein 25 (*Hsp25*), AMPK causes Hsp25 dissociation from actin monomers, leading to actin cytoskeleton polymerization and building of a bridge to transport LPL-containing vesicles from the Golgi to the plasma membrane [23]. In this way, intracellular LPL is moved to the myocyte surface heparan sulfate proteoglycans (*HSPG*).

HSPGs are ubiquitous macromolecules present in every tissue compartment and in particular, the extracellular matrix, cell surface, intracellular granules, and nucleus [24]. They are composed of a core protein to which several linear heparan sulfate (*HS*) side chains are covalently linked, and function, not only as structural proteins but also as anchors [25]. The latter property is implicitly used to bind chemokines, coagulation factors, and enzymes like LPL and growth factors [26]. Attachment of these bioactive proteins is an intelligent arrangement, providing the cell with a rapidly accessible reservoir, precluding the need for de novo synthesis when the requirement for protein is increased. Following detachment from this temporary docking site, LPL translocates across the interstitial space and binds to its transporter glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*), which facilitates LPL relocation from the basolateral to the apical (luminal) side of the EC [8]. Out here, it can also act as a platform to bind lipoproteins [27]. GPIHBP1 allows LPL to actively metabolize the lipoprotein-TG core, thereby liberating FAs that are transported to the cardiomyocytes.

Multiple factors regulate LPL at the vascular lumen, with FA being a key modulator of LPL activity. Specifically, FA may decrease coronary LPL in multiple ways: a) displacing LPL from EC surface binding sites for degradation in the liver [15], b) directly inactivating LPL enzyme activity [28], and c) impairing LPL vesicular trafficking to the myocyte surface through the caspase-3-mediated cleavage of PKD [29]. In addition to FA, angiopoietin-like proteins (Angptl), especially Angptl3 and Angptl4 can also modulate LPL activity [30]. They are composed of a NH2-terminal coiled-coil and a C-terminal fibrinogen-like domain [31]. Angptl3 is mainly expressed in the liver and is considered to promote proprotein convertase that can disassociate dimeric LPL on cell surface [32]. However, in humans, the level of Angptl3 is not related to that of post-heparin plasma lipase activity and plasma triglycerides [33]. Angptl4 is widely expressed in the liver, white adipose tissue, skeletal muscle, and heart [34]. Unlike Angptl3, Angptl4 forms disulfide-linkage oligomers in the NH2-terminal coiled-coil domain that is essential for its stability and LPL's inhibitory effect [35]. The secreted N-terminal oligomers function in circulation, converting dimeric LPL at the vascular lumen into inactive monomers [36]. In response to elevated FA and PPARδ activation, Angptl4 expression is increased in skeletal muscle [37]. Interestingly, when dimeric LPL transfers onto EC and complexes with GPIHBP1, this structure appears to protect it from inactivation by Angptl4. A more recent study reveals that Angptl4 was capable of binding and inactivating LPL even when it is complexed to GPIHBP1 on the surface of endothelial cells [38,39].

LPL synthesis and activity are altered in a tissue-specific manner by physiological conditions like cold exposure [40,41], lactation [42,43], or feeding and fasting [44,45]. In fasting, with ensuing hypoinsulinemia, LPL activity decreases in adipose tissue but increases in the heart. As a result, FA from circulating TG is diverted away from storage to meet metabolic demands of the heart. Hence, LPL fulfills a gate-keeping role by regulating the FA supply to meet metabolic requirements of different tissues. However, when excessive FA uptake exceeds its mitochondrial oxidative capacity, as a result, an increase in FA conversion to potentially toxic FA metabolites, including ceramides, diacylglycerols, and acylcarnitines, paired with increased formation of reactive oxygen species secondary to elevated FA oxidation, can provoke cardiac cell death (lipotoxicity) [46]. Not surprisingly then, cardiac-specific LPL overexpression caused severe myopathy characterized by lipid oversupply and deposition, muscle fiber degeneration, excessive dilatation, and impaired left the ventricular function in the absence of vascular defects, a situation comparable to diabetic cardiomyopathy [47–49]. Interestingly, loss of cardiac LPL also causes cardiomyopathy [50–52]. Hence, although specific knockout of cardiac LPL increased glucose metabolism, neither this effect nor albumin-bound FA could substitute the action of LPL, and cardiac ejection fraction decreased [51]. These experiments in genetically modified mice demonstrate that cardiac LPL is of crucial importance, and disturbing its natural function is sufficient to cause cardiac failure.

3. Heparanase

Following it secretion onto the cardiomyocyte heparan sulfate proteoglycans (*HSPGs*), LPL requires transfer across the interstitial space. Heparanase is an endo-glucuronidase with a unique ability to hydrolyze HSPG into oligosaccharides [24]. In the heart, given its proximity to the cardiomyocyte and the unique position to detect metabolic changes in the circulation, endothelial heparanase is a potential regulator of LPL translocation.

3.1. Active heparanase

Heparanase is initially synthesized as pre-proheparanase (68 kDa) [53], and is processed into latent heparanase (65 kDa), which undergoes cellular secretion and HSPG-facilitated reuptake [54,55]. After latent heparanase undergoes a proteolytic cleavage in the lysosome, an active 50-kDa polypeptide is formed, that can be mobilized by demand and secreted to degrade cell surface heparan sulfate. In cancer cells, extracellular nucleotides, such as adenosine triphosphate (*ATP*), adenosine diphosphate, and adenosine, through a purinergic receptor, G-coupled protein-coupled protein kinase C, and protein kinase A activation signal cascade, are known to be the active agents in stimulating heparanase secretion [56]. Although a role for heparanase in physiology (e.g., embryonic morphogenesis) has been described, it was intensive research focused on cancer progression that hinted towards a unique responsibility in cardiac metabolism. In cancer, degradation of HS chains by the increased expression of heparanase is associated with extracellular matrix and basement membrane disruption to facilitate tumor cell invasion [57,58]. In the heart, active heparanase secretion from the basolateral side of EC can liberate LPL from the cardiomyocyte into the interstitial space for onward progress to the vascular lumen [59].

3.2. Latent heparanase

The human heparanase gene encodes a polypeptide composed of 543 amino acids, and is transcribed into pre-proheparanase (68 kDa) that contains a N-terminal signal peptide, a C-terminal hydrophobic peptide, five cysteine residues, and six N-glycosylation sites [53]. When pre-proheparanase undergoes glycosylation in the endoplasmic reticulum and its signal peptide removed, a 65 kDa latent heparanase is formed. Latent heparanase is secreted following its transport into the Golgi and packaging into vesicles. Although it is ~100-fold less active than 50 kDa active heparanase [60,61], latent heparanase has some remarkable properties, including a greater competence for releasing myocyte surface growth factors [such vascular endothelial growth factor (*VEGF*)] [62], as compared to active heparanase, in addition to LPL. It was the reported liberation of VEGF anchored to heparan sulfate that was most provocative in cancer. VEGF enhances microvessel density [63,64], an angiogenic feature that provides tumor cells with sufficient nutrition and the potential for distant metastasis. In the heart, VEGF-associated angiogenesis would be required for an increased oxygen demand to provide the oxygen necessary for increased LPL-derived FA oxidation [65,66]. Another intriguing non-enzymatic function of latent heparanase is to modulate gene transcription by

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