

# Lipoproteins: A Source of Cardiac Lipids

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**Abstract** Lipids are the major substrate for cardiac ATP production and they are derived from adipose tissue or lipoprotein triglycerides. Lipoproteins are synthesized in the liver and they obtain their mature form following interaction with enzymes that are present in the circulation. Lipoprotein-derived fatty acids are released by lipoprotein lipase and are then taken up by cardiomyocytes either passively or via fatty acid receptors, such as CD36. Uptake of remnant lipoproteins via cardiomyocyte lipoprotein receptors is also possible. Besides fatty acids, other hydrophobic molecules such as cholesteryl esters, retinyl esters and vitamins are delivered by lipoproteins to the heart. While lipids are important for normal cardiac function, excessive lipid uptake, also known as lipotoxicity, may lead to cardiac abnormalities. This chapter focuses on the role of lipoproteins in providing fatty acids and other essential lipids to the heart in healthy conditions as well as in cardiac disease.

**Keywords** Lipoprotein triglyceride • Lipoprotein lipase • Fatty acid receptors • Fatty acid uptake • Cardiomyocytes • Cardiac lipoprotein receptors

## 1 Introduction

The heart can obtain energy from several sources including lipids, glucose, ketones and lactate. 70 % of cardiac ATP is thought to be produced via fatty acid (FA) oxidation [1]. Triglycerides (TGs) are the primary source of FAs in circulation and

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constitute, not surprisingly, the primary lipid source used for cardiac energy production [2]. Over 90 % of plasma FAs are esterified within either TG or phospholipids. Lipoprotein-associated FAs are derived from dietary fat, as well as from endogenous hepatic de novo FA synthesis. The heart primarily obtains FAs after their release from TG-rich lipoproteins by the enzyme lipoprotein lipase (LpL). Some cardiac FAs as well as hydrophobic lipids such as cholesteryl esters and retinyl esters are dissociated from lipoproteins or they are obtained via internalization of whole lipoprotein particles by lipoprotein receptors. Cardiac FA uptake occurs either via passive non-receptor transport, also known as “flip-flop” [3], or via cell membrane receptors, such as cluster of differentiation (CD) 36 [4, 5] and fatty acid transport protein (FATP) [6, 7]. The exuberant use of lipids by the heart makes it an ideal organ to gain insights into the routes of uptake of lipid from liver, gut, and circulation. This chapter will focus on reviewing the role of lipoproteins in providing FAs and other essential lipids to the heart.

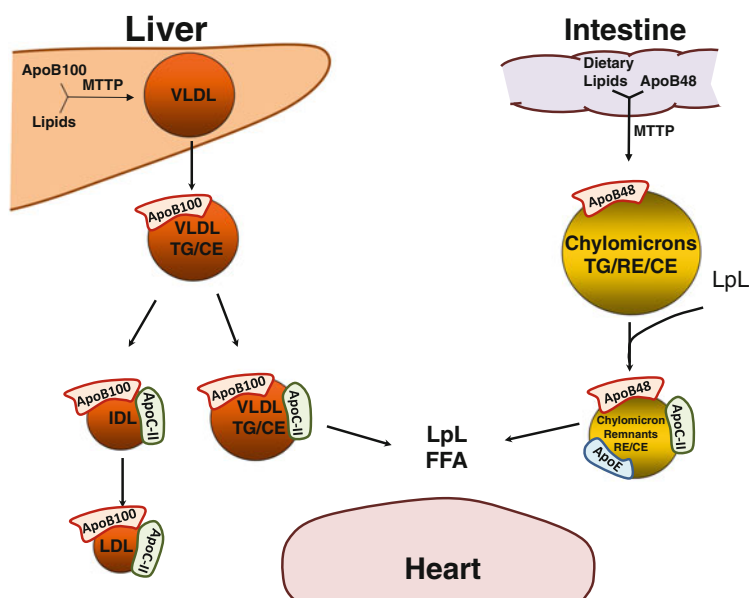
## 2 General Structure and Physiologic Role of Lipoproteins

Lipoproteins are water-soluble macromolecules that transfer lipids amongst different tissues. They consist of a polar surface of phospholipids, free cholesterol and apolipoproteins (Apos) and a non-polar lipid core that contains primarily cholesteryl ester and TGs as well as fat soluble vitamins. There are two major classes of TG-rich lipoproteins: chylomicrons, which are produced from dietary fat, and very low density lipoproteins (VLDL) that have hepatic origin and are carriers of endogenously produced FAs (Fig. 1). The major cholesterol-containing lipoproteins are low density lipoproteins (LDL) and high density lipoproteins (HDL).

Lipoproteins were originally differentiated by their floatation in the ultracentrifuge as salt was added to the serum, hence their names. Lipoproteins can also be separated based on their size using gel filtration, and by charge using electrophoresis. They can also be distinguished by NMR. The largest and most buoyant lipoproteins contain the greatest amount of lipid, which is predominantly TG. The smaller more dense lipoproteins have cholesteryl ester as the major non-polar lipid. The lipids that each lipoprotein class carries reflect its major physiologic role: delivery of dietary or hepatic produced TG or cholesterol.

## 3 Chylomicrons

Dietary TGs are packaged in chylomicrons. In most cases FAs not esterified to glycerol, free FAs (FFAs), but not TGs cross cell membranes. Dietary TG is converted into FFAs by intestinal lipases and then re-esterified within the enterocyte. TG and the ester forms of other lipids such as cholesterol and retinol are packaged into particles via the actions of microsomal TG transfer protein (MTTP). The major structural protein of chylomicrons is ApoB48, which is an edited version of the longer hepatic ApoB100 (Fig. 1).



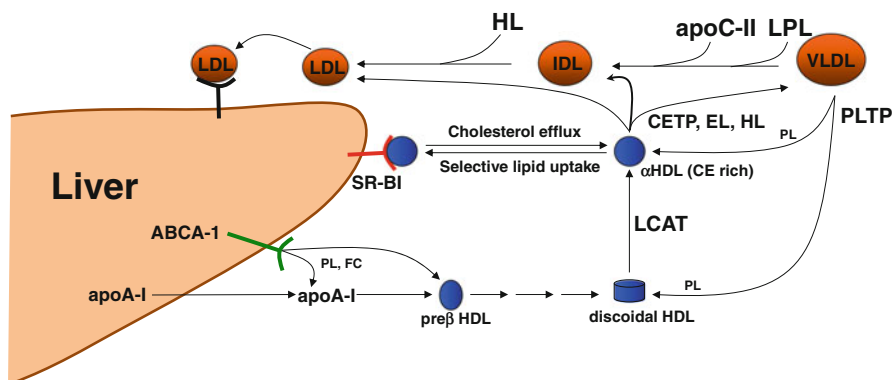
**Fig. 1** Biosynthesis of VLDL and chylomicrons—VLDL production in the liver requires and transport ApoB and microsomal triglyceride transfer protein (MTTP). VLDL are carriers of triglycerides (TG) and cholesteryl ester (CE). Gradual lipoprotein lipase (LpL)-mediated hydrolysis of TG leads to conversion of VLDL to IDL and LDL. Chylomicrons are produced in the intestine and transfer TG, CE and retinyl esters. Following hydrolysis of TG by LpL chylomicron remnants are formed. Lipolysis accounts for most FA uptake by the heart

Chylomicrons are not secreted directly into the circulation, but arrive into the superior vena cava via the lymphatic system. Thus, they reach the heart prior to their exposure to the liver or peripheral tissues such as skeletal muscle and adipose tissue. Once in the bloodstream, chylomicron surface proteins, such as ApoC-II, the LpL activator, are exchanged with other lipoprotein proteins. Chylomicrons deliver cholesterol and FAs to the heart as shown by studies *in vivo* [8–10] and in isolated hearts of rats that were perfused with chylomicrons enriched in radiolabelled cholesterol and/or FAs [8–10].

FFAs obtained by the heart can serve as fuel or components of structural lipids and lipid droplets. While the vast majority of albumin-bound FFAs are used for oxidation, chylomicron-derived cardiac FAs are used evenly for oxidation and storage [10].

## 4 VLDL

Hepatic TGs are secreted as a component of VLDL, TG-rich lipoproteins that are smaller and less buoyant than chylomicrons (Fig. 1). VLDL-associated TGs are from three sources, which differ under physiologic and pathologic conditions. Some



**Fig. 2** Lipoprotein metabolism – HDL and VLDL are produced in the liver. HDL biosynthesis begins with gradual addition of phospholipids (PL) and free cholesterol (FC) on ApoA-I that leads to formation of discoidal HDL particles. Discoidal HDL are converted to spherical HDL via contribution of lecithin cholesterol acyl-transferase (LCAT) and addition of PL by phospholipid transfer protein (PLTP). Transfer of cholesteryl ester (CE) to VLDL is mediated by CE transfer protein (CETP). Gradual hydrolysis of TG by LpL, which is activated by ApoC-II, and hepatic lipase (HL), liberates lipids and apolipoproteins that transfer to HDL. SR-BI mediates HDL uptake and will obtain some HDL lipids without ApoA-I; this is known as selective uptake

TGs are produced via *de novo* synthesis that converts glucose or amino acids to FAs. Other FAs are products of lipolysis in the periphery or are derived from TG returned to the liver via uptake of partially digested TG-rich lipoproteins, termed remnants. The third source of hepatic FAs are those liberated from intracellular lipolysis of TG stored in adipocytes; adipocytes TG lipolysis is mediated by adipose TG lipase (ATGL) and hormone sensitive lipase (HSL). These enzymes are inhibited by insulin and activated by catecholamines and thyroid hormone.

The packaging of liver TGs with ApoB100 is regulated by insulin, FFAs, and liver inflammation [11–13]. After secretion, VLDL undergoes gradual TG hydrolysis first by LpL and then by hepatic lipase (HL) leading to conversion of VLDL to IDL and LDL (Fig. 2).

## 5 LDL

Although LDLs are the major cholesterol carrier in human blood, HDLs are the greater carriers of circulating cholesterol in wild type rodents. Mice with defects in the LDL receptor or ApoE, both of which should reduce cholesterol uptake by the liver, do not have a cardiac phenotype. In part this might be because the heart is one of the least important sites of LDL uptake [14]. In addition heart synthesizes very little cholesterol [15]. Perhaps, as shown in isolated perfused hearts [9], the robust metabolism of TG-rich lipoproteins, as they circulate through the heart, is sufficient to provide cholesterol for the myocardium.

## 6 HDL

HDL biosynthesis takes place in the liver and small intestine. ApoA-I is secreted by the liver and interacts with hepatic ABCA1 transporter (Fig. 2). ApoA-I is then lipidated with phospholipids and cholesterol and forms discoidal HDL particles. Discoidal HDL is converted to spherical HDL following the action of the enzyme lecithin cholesterol acyl transferase (LCAT). LCAT esterifies cholesterol with FA to form cholesteryl ester, which is forced to the inner core of HDL. Loss of either LCAT [16] or ABCA1 [17, 18] prevents formation of mature HDL and leads to lower HDL cholesterol levels.

HDL is removed from the circulation via cell surface receptors, following the action of two lipases: HL [19] and endothelial lipase (EL) [20]. Most HDL lipid is returned to the liver via scavenger receptor receptor-B-I (SR-BI) [21]. However, HDL proteins are degraded in both the liver and kidney; the latter is most important in removal of smaller relatively lipid-poor HDL [22].

## 7 Apolipoproteins

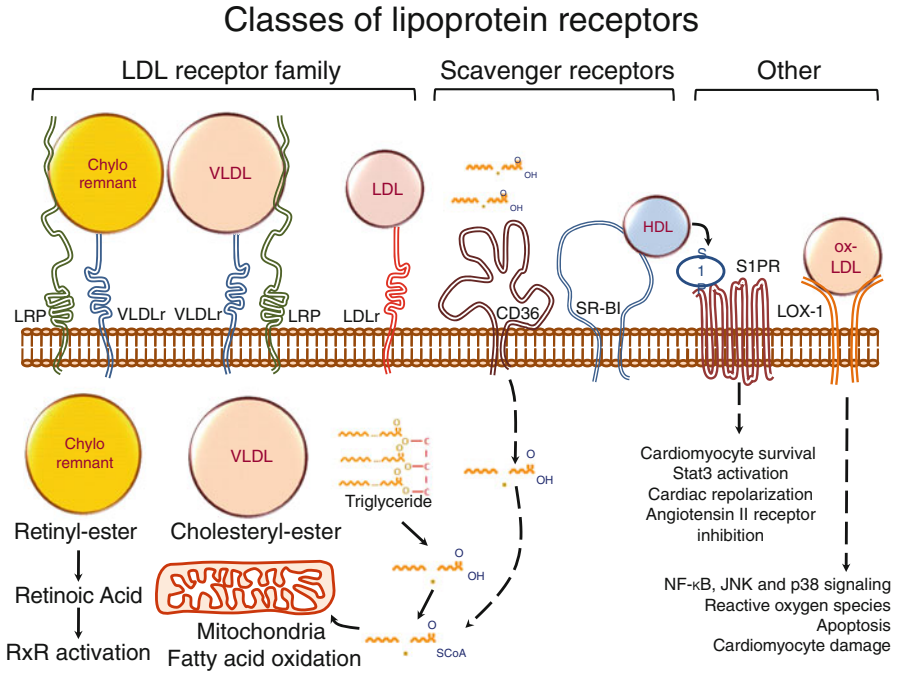
These lipid-binding proteins are amphipathic, thus able to interact with aqueous and non-aqueous media. Apolipoproteins allow interaction of lipoproteins with cell surface receptors and metabolic enzymes.

### 7.1 ApoB

ApoB is the main structural protein of chylomicrons and VLDL and remains attached to these lipoproteins throughout their formation and catabolism. Two ApoB species have been described: hepatic ApoB100 and intestinal ApoB48, which corresponds to the N-terminal 48 % of ApoB100. Following gradual TG hydrolysis by LpL and conversion of VLDL to IDL and subsequently LDL, ApoB100 is recognized by the LDL receptor, which mediates LDL uptake by the liver. The heart expresses both ApoB and MTTP [23], but is generally believed to secrete only small amounts of lipoproteins. However, it has been proposed that secretion of cardiac TG-enriched ApoB-containing lipoproteins may occur as a defensive mechanism to protect from cardiac lipotoxicity in obesity [24], diabetes [25] and heart failure [25].

### 7.2 ApoE

ApoE is present in chylomicrons, VLDL, IDL, LDL and HDL and is recognized by lipoprotein receptors, such as LDL receptor (LDLr) [26], LDL receptor related protein (LRP)-1 [27], VLDL receptor (VLDLr) [28], ApoE receptor 2 [29], SR-BI [30],



**Fig. 3** Classes of cardiac lipoprotein receptors

[31] and ABCA-1 [32] (Fig. 3). ApoE is primarily expressed in the liver [33], but also in peripheral tissues, including the intestine and the heart [34]. Among the three human ApoE isoforms, ApoE2 and ApoE3 show a preference for binding on HDL, while ApoE4 has higher affinity for VLDL and LDL [35]. As cardiomyocytes express VLDLr [36] and LRP1 [37, 38] and low levels of LDLr [36] and SR-BI [39], ApoE may be a component of the lipoprotein-derived cardiac lipid uptake process.

### 7.3 *ApoCs*

ApoCs are short polypeptides that are associated with chylomicrons, VLDL and HDL [40]. ApoC-I activates LCAT and increases cholesterol and TG levels, perhaps because it inhibits uptake of remnant lipoproteins [40]. LpL is also regulated by ApoCs. Specifically, ApoC-II activates LpL [41], while ApoC-III is inhibitory and promotes hypertriglyceridemia [42]. Loss of ApoC-III prevents hypertriglyceridemia in some situations, such as rodent diabetes [43]. ApoC-III is also thought to regulate lipoprotein uptake by receptors.

## 8 Enzymes that Modulate Lipoproteins

Following secretion in the circulation, chylomicrons and VLDLs interact with a number of enzymes that modulate their size and affect their interaction with lipoprotein receptors that mediate lipoprotein catabolism (Fig. 2), such as lipases, phospholipid transfer protein (PLTP) and cholesteryl ester transfer protein (CETP). Lipoprotein-associated TGs are hydrolyzed by LpL within the circulation, allowing cardiomyocytes to take up released FFAs for  $\beta$ -oxidation or activation of transcriptional factors, such as PPAR $\alpha$  [44, 45]. Although cardiac LpL is produced primarily by cardiomyocytes [46], it is thought to be most active when associated with endothelial cells [47, 48]. At least in the mouse, heart LpL accounts for a significant portion of circulating TG catabolism. Mice that express LpL in cardiomyocytes but not in adipose tissue and skeletal muscle have normal plasma TG levels [49]. Also deletion of LpL only in cardiomyocytes leads to hypertriglyceridemia [50].

Endothelial cell-associated LpL is likely bound to both glycosyl phosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) [47, 51] and heparin sulfate proteoglycans (HSPGs) [52, 53]. A variety of proteins have been identified as either activators of LpL-mediated TG hydrolysis, such as Apo-CII [54] and Apo-AV [55, 56], or inhibitors, such as Apo-CIII [57, 58], ApoA-II [59], angiopoietin-like protein (ANGPTL) 3 [60], ANGPTL4 [61] and ANGPTL8 [62]. ANGPTL4, which is the predominant isoform in the heart and adipose tissue, exerts its inhibitory function by converting catalytically active LpL dimers to inactive monomers [63].

HL and EL also mediate intravascular TG hydrolysis [64]. HL hydrolyzes chylomicron remnant-, IDL- and HDL-associated TGs [65], while endothelial lipase catalyzes hydrolysis of HDL phospholipids [66]. Neither lipase has been associated with cardiac lipid uptake under normal conditions. However, a recent study showed increased endothelial lipase and reduced LpL levels in a pressure overload-induced cardiac hypertrophy animal model [67]. Despite downregulation of LpL, endothelial lipase-expressing hearts had increased ATP levels and improved function as compared to endothelial lipase deficient hearts [67]. This observation indicates a potential role for endothelial lipase and HDL in providing FAs to the heart when LpL-mediated lipolysis is compromised during cardiac hypertrophy. More details on lipolysis and its regulation are included in another chapter.

PLTP facilitates transfer of phospholipids from VLDL to HDL, which affects the size of HDL [68]. Hepatic PLTP also modulates VLDL secretion [69]. CETP mediates exchange of cholesteryl ester within HDL and LDL for TG in VLDL and chylomicrons [70].

## 9 Cardiac Lipoprotein Receptors

Some lipid-loaded lipoproteins or lipoprotein remnants likely enter cardiomyocytes via lipoprotein receptors (Fig. 3), but the physiologic importance of these receptors is unclear. Many receptors that primarily bind to ApoB100 or ApoE are expressed

in the heart. These include the LDLr [36], VLDLr [36] and LRP1 [37, 38], as well as the HDL receptor SR-BI [39]. Furthermore, failing hearts express lectin-like oxidized-LDL receptor-1 (LOX-1) [71]. However, genetic deletion of each of these receptors in isolation leads to no obvious cardiac phenotype.

VLDLr is a member of the LDLr superfamily that binds ApoE-TG-rich lipoproteins such as VLDL [72] and chylomicrons [73]. VLDLr is expressed in heart [36] and particularly in cardiomyocytes [74, 75], as well as in endothelial cells [76]. Besides and contributes to lipid uptake. Besides remnant lipoprotein uptake, VLDLr are important for transportation of LpL to the luminal surface of vascular endothelial cells [77], as well as for enhancing cardiac LpL activity [78]. However, *Vldlr*<sup>-/-</sup> mice do not have lower cardiac TG levels; neither do they develop cardiac dysfunction [74].

LRP1 was initially described as the back-up receptor that allowed chylomicron remnant uptake by the liver in LDLr deficient mice [79–81]. However, there are no data indicating a role for LRP1 in cardiac lipid metabolism under normal conditions. Treatment of isolated cardiomyocytes with increasing doses of LDL and VLDL in normoxic conditions led to increased levels of VLDLr and LRP1 expression, while LDLr expression did not change [82]. When LRP1 was knocked down in isolated cardiomyocytes that were treated with LDL, cholesteryl ester uptake continued although at a significantly slower rate [82].

Although cardiomyocytes express receptors for HDL, these receptors do not seem to have a role in cardiac function under normal conditions. The receptor for HDL, SR-BI [39], is expressed in cardiomyocytes although this lipoprotein class does not seem to have a role in acquisition of lipids and cardiac energy production. HDLs provide sphingosine-1-phosphate to cardiomyocytes via the S1P receptor [83], which seems to be protective during cardiac stress [84]. Thus, cardiac SR-BI may serve as a “docking station” for HDL to allow lipolysis and release of S1P. SR-BI may contribute in cardiomyocyte cholesterol efflux to HDL, although this process has been shown to be predominantly mediated by cardiac ABCA1 and ABCG1 [85]. It is likely that much of the lipid needed for cardiac metabolism is supplied during lipolysis of TG-rich lipoproteins.

## 10 Role of Lipoprotein-Carried Vitamins in Cardiac Metabolism and Function

Lipoproteins also serve as carriers of vitamins that are important for cardiac energetics and function such as  $\beta$ -carotene [86], a precursor of vitamin A, vitamin A [87], vitamin D [88],  $\alpha$ -tocopherol (vitamin E) [89] and vitamin K1 [90]. The importance of these vitamins for maintaining normal cardiac function has been demonstrated in several studies. Tissue accumulation of vitamin A is via uptake of retinol or retinyl ester. Dietary vitamin A is absorbed as retinyl esters within chylomicrons [91, 92]. Following LpL-mediated hydrolysis of retinyl esters [93, 94] retinol is released and enters tissues. In cardiomyocytes some retinyl esters are also taken up by lipoprotein receptors [8] without being cleaved [94]. LpL-mediated



conversion of chylomicrons to chylomicron remnants is necessary as shown by compromised cardiac uptake of retinyl esters in LpL-deficient hearts [8]. Retinol can also be obtained from its major circulating pool that is associated with retinol binding protein.

Fat soluble vitamins affect a number of basic cardiac metabolic pathways. Retinol is converted to retinoic acid that activates RxR, the transcriptional partner of PPAR $\alpha$ , which is a major regulator of cardiac fatty acid oxidation [95]. Vitamin K1 is also important for cardiac energetics as it provides derivatives that serve electron transportation between mitochondrial electron-donating and electron-accepting enzyme complexes that facilitate ATP production in cardiomyocytes [96]. Vitamin E with its anti-oxidant properties is important for alleviating the effects of cardiac oxidative stress [97, 98] by inhibiting lipid peroxidation [99, 100], stress signaling pathways [101] and apoptosis [102, 98, 101]. Regarding vitamin D, although there is not much information about its role in cardiac fatty acid oxidation, it has been associated with increased fatty acid oxidation in other organs such as liver [103] and bone cartilage [104]. Thus, vitamin D may have a positive effect on cardiac fatty acid oxidation.

## 11 Cardiac Lipoprotein Metabolism in Disease

### 11.1 Cardiac Hypertrophy

Cardiometabolic diseases compromise several components of the lipoprotein metabolism pathways. Pressure overload-induced left ventricular hypertrophy switches the metabolic pattern of the heart to a fetal profile characterized by reduced FA oxidation and increased glucose catabolism [105]. Although this is not associated with marked reduction in circulating lipoproteins, the uptake of lipids into the heart should be reduced due to downregulation of LpL and CD36 expression that has been observed in human [106] and mouse [67, 107] hearts. Reduced PPAR $\alpha$  activation may be a major event that accounts for the changes in LpL and CD36 [108]. Similarly, reduced LpL and VLDLr levels and increased glucose utilization were observed in hearts of spontaneously hypertensive rats-stroke prone, an animal model for hypertension-induced cardiac hypertrophy [109, 75].

Oxidized-LDL and their receptor, (Lox-1) may play a role in heart failure. Cardiomyocyte LOX-1 expression is increased by endothelin and norepinephrine [71] and it seems to aggravate heart failure. Activation of LOX-1 by oxidized LDL leads to increased release of reactive oxygen species [110], apoptosis [71], cardiomyocyte damage [111] and elevation of heart failure biomarkers, such as brain natriuretic peptide and monocyte chemoattractant protein-1 [112]. LOX-1 expression is induced by angiotensin-mediated hypertrophy [113, 114] and is inhibited by curcumin and rosuvastatin, which also inhibits cardiomyocyte growth [113, 114]. The cause and effect relationship of these effects is uncertain.

Although HDL does not seem to have a role in providing FAs for cardiac energy production, an exception may occur during pressure overload-induced cardiac hypertrophy, when downregulation of LpL is compensated by EL upregulation that mediates HDL lipolysis and provides phospholipids [67]. Induction of pressure overload-mediated cardiac hypertrophy in EL<sup>-/-</sup> mice resulted in a more severe systolic dysfunction accompanied by lower levels of cardiac fatty acid oxidation-related gene expression and ATP levels as compared to wild-type mice [67].

## 11.2 Ischemia

Hypoxic hearts show reduced cardiac TG utilization in rats [115] and increased TG accumulation in dogs [116] and mice [74]. This may involve the VLDLr [74], although changes in cardiac lipid uptake and accumulation during ischemia might be model specific. In one report, myocardial infarction in mice led to a marked increase in expression of VLDLr and accumulation of intracellular lipids; this was prevented by with VLDLr deficiency [74]. Increased VLDLr expression levels due to ischemia may be driven by hypoxia-inducible factor (HIF)-1 $\alpha$ , which is elevated in ischemic hearts [82] and is a positive regulator of VLDLr expression [74, 117]. However, in rat models of low-flow ischemia cardiac FA uptake and TG content were reduced [118].

VLDLr-mediated lipoprotein uptake in hypoxic cardiomyocytes is facilitated by LRP1 [37]. Increased LRP-1 expression occurs in ischemic cardiomyopathy patients [82] who have increased cardiac TG and cholesterol, as well as in isolated cardiomyocytes during hypoxia [37]. siRNA-mediated knock-down of LRP1 prevented hypoxia-induced VLDL-cholesteryl ester uptake in isolated neonatal rat ventricular myocytes and a mouse cardiomyocyte cell line [37]. LRP1 protein expression levels increase in patients with ischemic cardiomyopathy [82].

LOX-1 is upregulated by ischemia-reperfusion [119, 120]. Abrogation of LOX-1 in an animal model of chronic ischemia reduced infarct size, improved cardiac hemodynamics, prevented cardiac remodeling and fibrosis and improved survival [121]. Besides chronic ischemia, LOX1 may also be detrimental for cardiac damage that occurs in ischemia-reperfusion. Specifically, LOX-1 increased in rat cardiomyocytes following ischemia-reperfusion, while administration of anti-LOX-1 antibody reduced myocardial infarction size [120] and LOX-1 genetic deletion reduced ischemia-driven collagen accumulation [121]. Therefore, LOX-1 appears to be involved in ischemic heart failure as it activates stress signaling kinases, such as JNK and ERK [112]. Accordingly, treatment of mouse cardiomyocytes with JNK or ERK inhibitors prevented ox-LDL-induced increase of BNP [112]. The beneficial effect of LOX-1 inhibition in ischemia has been attributed to reduced myocardial oxidative stress and inhibition of pathological NF- $\kappa$ B, JNK and p38 MAPK signaling pathways [121].

HDL interact with the sphingosine-1-phosphate (S1P) receptor to provide S1P to cardiomyocytes [83]. S1P improves cardiomyocyte survival during hypoxia [122],

protects against doxorubicin toxicity [123], promotes phosphorylation of connexin 43 [124] and activates Stat3, a transcription factor with an important role in adaptation of myocardium to stress [125, 126].

The increased expression profile of lipoprotein and FA receptors in ischemia may seem contradictory to the observed reduction in TG and FFA in hearts of patients with advanced heart failure [127]. This discrepancy suggests that increased uptake of lipoprotein-carried FAs, cholesteryl ester and vitamins may be an acute compensatory response of the myocardium to ischemia, which is attenuated as of the myocardium fails. Thus, ischemic cardiomyopathy is associated with increased lipoprotein catabolism, at least during the early stages of the disease. This may reflect increased need of the ischemic heart for provision of fuel and nutrients that may be important for healing processes in the damaged myocardium.

### ***11.3 Cardiomyopathy in Both Type I and II Diabetes***

Both type 1 and type II diabetes have been associated with abnormal lipoprotein metabolism and increased cardiac lipid uptake and accumulation [128, 129]. The increased lipid uptake might result from greater circulating levels of FFA and TG and induction of FA uptake pathways. Diabetic hearts consume primarily VLDL and chylomicron remnants [130]. Cardiac utilization of VLDL was shown to increase in isolated-perfused hearts of diabetic mice [131]; this was associated with increased cardiac LpL secretion [132] and activity [133], as well as enhanced CD36 expression levels [134, 135]. There is no evidence that the increased heart TG in the setting of diabetes is due to upregulation of lipoprotein receptors. In fact, diabetic hyperlipidemia reduces heart VLDLr protein [136] due to post-translational regulation. This change may represent a compensatory response that occurs in advanced stages of diabetes aiming to counterbalance cardiac lipid uptake and lipotoxicity that occur in diabetic hearts [137].

### ***11.4 Sepsis***

Sepsis is a systemic inflammatory disease that begins with bacterial infection and is associated with altered lipoprotein metabolism characterized by elevated plasma TG and FFA [138–141] and suppression of energy production in several organs, including the heart [138, 142, 143]. Increased plasma TG levels are due to compromised intravascular lipolysis [144, 145] and not defective hepatic lipoprotein production [146]. Sepsis also increases cardiac lipid accumulation but this is primarily due to reduced expression levels of PPAR nuclear receptors [138, 147] and suppression of FA oxidation [138, 142]. Cardiac LpL activity is reduced due to lower LpL and increased Angptl4 gene expression levels [138, 148]. Cardiac VLDLr and CD36 expression levels are also reduced in sepsis. These changes would be expected

to compromise lipid uptake and cardiac function [149]. Genetic and pharmacologic interventions that increase cardiac FA oxidation during sepsis, such as PPAR $\gamma$  or PGC-1 $\beta$  activation and JNK inhibition, prevent heart dysfunction [143, 142, 138] and improve survival [138].

Efficient lipoprotein clearance from circulation during sepsis can contribute to the removal of bacterial endotoxins, as the latter stick on lipoproteins [150], particularly chylomicrons [151]. Thus, the observed reduced expression of lipoprotein receptors during sepsis may be a defense to prevent cardiac lipid overload as FA oxidation is reduced. In addition, since lipopolysaccharide is carried on lipoproteins, the delivery of these toxins to the heart may be inhibited via downregulation of the lipoprotein receptors.

## 12 Conclusions

Although the heart avidly utilizes other sources of energy, such as glucose, FFA, lactate, and ketones, the bulk of circulating energy substrates are within lipoproteins. Gain and loss of function studies of LpL confirm that lipoprotein metabolism within the heart is required for its normal acquisition of FA as well as esterified lipids such as cholesteryl esters and retinyl esters. The heart expresses several lipoprotein metabolic pathways and a number of lipoprotein receptors. While a single receptor does not appear to be essential for normal heart function, lipoprotein receptors may contribute to development of cardiac abnormalities with ischemia, hypertrophy, diabetes and sepsis.

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