Regulation of Plasma Lipid Homeostasis by Hepatic Lipoprotein Lipase in Adult Mice

Gan Liu¹,²*, Jun-Nan Xu¹*, Dong Liu³,¹, Qingli Ding¹, Meng-Na Liu³,¹, Rong Chen²,⁴, Mengdi Fan¹,⁵, Ye Zhang¹,², Chao Zheng⁵, Da-Jin Zou²,⁴, Jianxin Lyu³, Weiping J. Zhang¹,²

¹Department of Pathophysiology, ²Obesity and Diabetes Research Center, Second Military Medical University, Shanghai 200433, China
³The Key Laboratory of Laboratory Medicine, Ministry of Education of China, Wenchou Medical University School of Laboratory Medicine and Life Sciences, Wenchou, Zhejiang 325035, China
⁴Department of Endocrinology, Changhai Hospital, Shanghai 200433, China
⁵Department of Endocrinology, the Second Affiliated Hospital, Wenchou Medical University, Wenchou, Zhejiang 325000, China

* They contributed equally to the work.

Running title: Hepatic LPL regulates plasma lipid homeostasis

Corresponding author:
Weiping J. Zhang, Department of Pathophysiology, Second Military Medical University, 800 Xiangyin Road, Shanghai 200433, China, Tel/Fax: +86-21-8187 1018, Email: wzhang@smmu.edu.cn.

Jianxin Lyu, Wenchou Medical University School of Laboratory Medicine and Life Sciences, Wenchou, Zhejiang 325035, China. Email: jxlu313@163.com
Abstract

Lipoprotein lipase (LPL) is a pivotal rate-limiting enzyme to catalyze the hydrolysis of triglyceride in circulation, and plays a critical role in regulating lipid metabolism. However, little attention has been paid to LPL in the adult liver due to its relatively low expression. Here we show that endogenous hepatic LPL plays an important physiological role in plasma lipid homeostasis in adult mice. We generated a mouse model with Lpl gene specifically ablated in hepatocytes with the Cre/LoxP approach, and found that specific deletion of hepatic Lpl resulted in a significant decrease in plasma LPL contents and activity. As a result, the postprandial triglyceride clearance was markedly impaired, and plasma triglyceride and cholesterol levels were significantly elevated. However, deficiency of hepatic Lpl did not change the liver triglyceride and cholesterol contents or glucose homeostasis. Taken together, our study reveals that hepatic LPL is involved in the regulation of plasma LPL activity and lipid homeostasis.

Key words: LPL, lipoprotein, lipid metabolism, liver, hypertriglyceridemia, knockout mice
**Introduction**

Lipoprotein lipase (LPL) is a multifunctional protein and plays a major role in the metabolism and transport of lipids (1). As a rate-limiting enzyme, it catalyzes the hydrolysis of core triglyceride (TG) in circulating chylomicrons (CM) and very low-density lipoproteins (VLDLs). As a result, the released free fatty acids and monoacylglycerol are in part taken up by local tissues for energy storage or utilization (2). LPL is principally synthesized and secreted by the parenchymal cells of tissues including heart, adipose, skeletal muscle, and brain, as well as macrophages, and then translocated to the luminal surface of vascular endothelial cells, where lipolytic processing occurs (3). Whole-body deficiency of LPL results in severe hypertriglyceridemia, and neonatal death in mice (4). Tissue-specific overexpression or deletion of LPL in mouse models suggests that LPL controls entry of fatty acids into the tissues such as skeletal muscle, adipose, heart, and neurons (5-7). Moreover, manipulation of LPL expression in a given tissue causes imbalances in the partitioning of fatty acids among peripheral tissues, which consequently have major effects on glucose and lipid metabolism. For example, the mice with specific overexpression of LPL in skeletal muscle are insulin resistant, with a marked increase in muscle TG content and blood glucose levels (5); the mice lacking Lpl gene specifically in neurons are hyperphagic and obese, with the elevations in the hypothalamic orexigenic neuropeptides such as AgRP and NPY (7). Thus LPL functions as a key regulator of lipid metabolism and gatekeeper of energy partitioning.
However, the biological significance of LPL in adult liver is not well appreciated due to its relatively low expression level (8). LPL expression is developmentally regulated in the liver, with a distinct pattern relative to extrahepatic tissues. In rodents, LPL activity rapidly declines during the first few weeks after birth. As a result, in adult liver, LPL expression was reported to be only detected in some scattered cells by immunohistochemistry, which were most likely Kupffer cells (8). Therefore, liver LPL is putatively regarded to be mainly expressed at embryonic and postnatal stages, when it shunts circulating TG to the liver to provide more energy for the production of VLDL and ketone body at times of metabolic stress (9). Of note, LPL expression is positively regulated by the nuclear receptor LXR in liver (10). Moreover, liver-specific overexpression of LPL leads to a 2-fold increase in liver TG content and insulin resistance in mice (5). These raise an interesting subject that liver LPL may have a physiologically or pathophysiologically significant role in lipid metabolism at adulthood. To test this hypothesis, we generated hepatocyte-specific Lpl knockout mice. Our findings suggest that liver LPL is physiologically active at adulthood and critically involved in the regulation of lipid metabolism.
Results

Expression of LPL in adult liver

To characterize the expression pattern of LPL in postnatal liver, we first performed quantitative RT-PCR analysis. Lpl mRNA levels were maintained at relatively high levels in the liver during the first three weeks after birth, and declined rapidly afterwards (Fig. 1A). Interestingly, Lpl mRNA levels still showed a steady tendency of downregulation in adult liver between two to six months of age. As a result, Lpl mRNA was expressed at quite low levels in adult liver compared with heart (~200-fold lower), skeletal muscle (~20-fold lower), kidney, lung, and brain (~4-fold lower). Nevertheless, liver Lpl mRNA levels were still significantly higher than that in small intestine (~6-fold higher) (Fig. 1B).

Generation of hepatocyte-specific Lpl knockout mice

To evaluate the potential role of LPL in adult liver, we generated hepatocyte-specific Lpl knockout mice (hereafter LPL△hep) by crossing LplFlox/Flox mice with the Alb-Cre driver line, which expresses the Cre recombinase under the albumin promoter (11). Genotyping was performed by PCR analysis of tail genomic DNA, which distinguished the floxed Lpl allele from wildtype (Fig. 2A). RT-PCR analysis showed that liver Lpl mRNA levels were reduced by 90% in adult mutant mice compared to control group (Fig. 2B), suggesting that the hepatocytes rather than endothelial or resident Kupffer cells are the main cellular sources of liver LPL in adult wild-type mice. However, liver LPL protein wasn’t detected by immunoblot analysis even in adult control mice, which was most likely due to its low expression levels. Importantly,
hepatocyte-specific deletion of Lpl did not significantly alter Lpl mRNA levels in other peripheral tissues such as heart, skeletal muscle, and white adipose. These results indicated that liver Lpl was efficiently and specifically deleted in Lpl^△hep mice.

**Deletion of liver LPL decreases plasma LPL activity**

LPL is rapidly transported and anchored onto the luminal surface of vascular endothelial cells after secretion, which can be released into circulation by heparin (12-14). To determine whether deletion of liver Lpl affects plasma LPL activity, we first measured plasma LPL levels in heparinized mice by ELISA. Surprisingly, Lpl^△hep mice displayed 28.7% decrease in plasma LPL levels compared to control (Fig. 3A). In addition, Western blot also showed a significant decrease of LPL protein in the plasma from mutant mice (Fig. 3B). Consistently, LPL activity measures revealed that plasma LPL activity was reduced by 27.2% in the mutant mice (Fig. 3C). Furthermore, deletion of liver LPL did not lead to significant changes of mRNA expression levels of Lipc in the liver (Supplementary Fig. S1), which encodes hepatic lipase (HL) and plays an critical role in lipid homeostasis mainly by hydrolyzing TG in plasma lipoprotein(15). These data suggested that liver plays an important role in the regulation of plasma LPL mass and activity under normal physiological condition, albeit its quite low expression.

**Disturbed lipid metabolism in the absence of liver LPL**

Mice with homozygous deletion of Lpl in liver survived into adulthood without gross abnormalities on the normal chow diet. Both male and female adult LPL^△hep mice grew similarly as the sex-matched littermate controls (Fig. 4A). The liver from adult
LplΔhep mice was in normal appearance and size, and had similar contents of TG and total cholesterol (TC) as control group (Fig. 4B). Interestingly, both male and female LplΔhep mice exhibited a mild and significant increase in serum TG and TC levels compared with their control counterparts under fasting condition (Fig. 4C and Supplementary Fig. S2), whereas their serum free fatty acid (FAA) levels were significantly decreased. FPLC analysis demonstrated that TG contents were significantly increased in VLDL fractions of plasma lipoprotein from mutant mice compared to control (Supplementary Fig. S3). These results suggested that liver LPL is involved in the regulation of plasma lipid metabolism in adult mice.

**Impaired TG clearance in the absence of liver LPL**

To understand the mechanisms by which liver LPL regulates plasma lipid homeostasis, we first assessed plasma TG clearance by postprandial TG test. Compared to control group, LPLΔhep mice displayed a substantial increase in plasma TG levels at 2 and 4 hours after the gavage of corn oil, suggesting that TG clearance was greatly impaired in the absence of liver LPL (Fig. 5A). To determine whether hepatic TG secretion was altered in the absence of liver LPL, we further conducted P407 test, in which hepatic TG secretion is largely reflected by plasma TG accumulation due to the blockage of TG hydrolysis by LPL inhibitor P407. LPLΔhep mice showed a similar response of plasma TG accumulation as control after P407 injection (Fig. 5B), indicative of their normal hepatic TG secretion. Taken together, these data suggested that liver LPL regulates plasma TG metabolism mainly through modulating TG clearance of plasma lipoproteins.
Considering the possibility that Alb-Cre-mediated deletion of LPL in neonatal mice might affect liver development or the expression of LPL-related genes, which could influence TG and cholesterol metabolism, we took another approach to conditional ablation of hepatic Lpl gene in adult mice. Cre recombinase was specifically delivered to the hepatocytes of adult Lp1\textsuperscript{flox/flox} mice by infusion of Cre-expressing recombinant adenoviruses (Ad-Cre). Two weeks after adenovirus delivery, the mice were subject to phenotypic analysis. Compared to Ad-GFP control, Ad-Cre administration in Lp1\textsuperscript{flox/flox} mice reduced Lpl mRNA levels by 80.7% in liver, without significant changes of expression in other tissues, e.g. heart, skeletal muscle, and WAT (Fig.6A). As a result, plasma LPL mass was decreased by 20.2% in the heparinized mice lacking Lpl in adult liver (Fig.6B), with significant elevation in plasma TG and TC levels (Fig.6C), and TG clearance was significantly impaired at 2 hours after corn oil gavage compared to control (Fig.6D). These suggest that hepatic LPL has a role in plasma lipid homeostasis at adulthood.

**Liver LPL ameliorates hyperlipidemia in high-fat diet-induced obese mice**

To further determine the potential role of liver LPL in obesity, we fed male Lpl\textsuperscript{△hep} and control mice with a high fat diet (HFD) for 16 weeks. Lpl\textsuperscript{△hep} and control mice showed comparable body weight gain (Fig. 7A). Compared with the chow diet, HFD feeding substantially increased the liver contents of TG and TC, however, neither of which was significantly different between control and mutant groups (Fig. 7B). Of note, HFD-fed mutant mice displayed a mild and significant elevation in fasting plasma TG and TC levels compared with control group, whereas their plasma FFA
levels showed a tendency of decrease without reaching statistical significance (Fig. 7C). Together, these data suggested that liver LPL facilitates to ameliorate hyperlipidemia in HFD-induced obese mice with no significant effects on tissue adiposity.

**Liver LPL does not contribute to glucose homeostasis**

To explore whether liver LPL contributes to glucose homeostasis, we characterized glucose metabolism in the mutant mice. When fed the normal chow diet, both male and female LPL$^{△\text{hep}}$ mice did not display significant difference in blood glucose levels, fasting serum insulin levels or HOMA-IR compared with controls (Supplementary Fig. S4A,B). In addition, glucose tolerance and insulin tolerance tests revealed LPL$^{△\text{hep}}$ mice had normal glucose metabolism (Supplementary Fig. S4C). When fed on HFD, both control and LPL$^{△\text{hep}}$ mice had comparable blood glucose levels (Supplementary Fig. S4A), and exhibited severe glucose intolerance and insulin resistance, with no significant difference between the two genotypes (Supplementary Fig. S4C). These results suggest that liver Lpl is dispensable for glucose homeostasis under physiological condition and HFD-induced obesity.
Discussion

LPL functions as a key regulator for lipid metabolism and energy partitioning. In the past decades, most interest in LPL is focused on the extrahepatic tissues such as heart, muscle, adipose tissue, brain, as well as macrophages (1, 7). In contrast, little attention has been paid to LPL in adult liver due to its relatively low expression. In the present study, we for the first time provide compelling evidence that liver LPL is critically involved in the regulation of lipid metabolism at adulthood.

Our findings establish that liver significantly contributes to plasma LPL contents and activity in adult mice. Consistent with the previous reports, we show that LPL mRNA levels in adult liver are much lower than heart, adipose tissues, and skeletal muscle. Furthermore, specific deletion of \textit{Lpl} in hepatocytes leads to about 90% reduction in \textit{Lpl} mRNA levels in liver, which strongly supports that liver LPL is mainly derived from hepatocytes rather than Kupffer cells or vascular endothelial cells under physiological condition. Unexpectedly, deletion of liver LPL results in 27~29% decrease in heparin-released plasma LPL levels and activity. Obviously, this remarkable contribution of liver to plasma LPL levels is not proportional to its low expression levels of LPL even if the tissue mass is considered. The discrepancy could be explained by the possibility that not all LPL protein expressed by parenchymal cells is accessible and released by heparin. Typically, after secretion, LPL is rapidly transported by GPIHBP1 and anchored onto the luminal surface of vascular endothelial cells, which can be released into circulation by heparin (12-14, 16). Noteworthy, it was reported that the majority of LPL protein in heart was detected in
myocytes (78%) rather than in capillary endothelium (17). Although the intracellular and extracellular distribution pattern of LPL has not been determined in other tissues, such as skeletal muscle, adipose tissue, or liver, this raised the possibility that cellular localization of LPL may be a highly regulated event and could be tissue-dependent. In addition, the release efficiency of LPL into circulation by heparin could vary in different tissue, which may be regulated by local microenvironment, such as blood flow, nutrients, metabolites, etc. This possibility is partly supported by the previous report that LPL binding to vascular endothelium in the heart is regulated by nutritional status (18). Another possibility is that the LPL turn-over in liver may be quite high. The number of LPL receptors on liver endothelial cells may be low, thereby favoring LPL secretion in the absence of heparin. A high concentration of LPL in the environment of liver cells would enhance LPL binding to lipoproteins and uptake of lipoproteins by liver receptors. Alternatively, it is also possible that liver LPL may regulate the LPL localization pattern in extrahepatic tissues through unidentified mechanisms. The exact mechanism by which liver LPL contributes to plasma LPL contents and activity needs further investigation.

Our findings also establish that liver LPL is involved in the regulation of plasma lipid homeostasis at adulthood, which is consistent with its contribution to plasma LPL. Deletion of liver Lpl results in a remarkable elevation in plasma TG levels and reduction in plasma FFA, which is largely due to impaired TG clearance of lipoproteins. In addition, plasma cholesterol levels were also increased in the mutant mice either on the normal chow or HFD, which could be secondary to plasma TG
metabolism. Considering the fact that liver TG or TC contents were not significantly affected by the loss of liver Lpl, we reason that the free fatty acids produced by liver LPL-mediated TG hydrolysis are most likely taken up by the extrahepatic tissues, which needs to be examined in the future.

Our study indicates that liver LPL has no significant role in glucose metabolism. It was previously reported that liver-specific transgenic overexpression of Lpl increases liver TG content and is associated with insulin resistance (5). Our results indicate that liver LPL has no physiological or pathophysiological effects on liver TG content and insulin resistance. This discrepancy implies that the effects of liver LPL may be dose-dependent. Taken together, this study establishes a critical role of liver LPL in plasma TG metabolism, providing a better understanding of the cellular and molecular mechanisms about plasma lipid homeostasis.
Materials and Methods

Animals. Liver-specific *Lpl* knockout mice were generated by crossing *Lpl* flox/flox (Jackson Laboratory, #6503) mice (6) with albumin-Cre transgenic mice (11, 19). The mice were genotyped by PCR analysis of tail genomic DNA with primers producing a 515-bp band for the floxed allele and a 465-bp band for the wild-type band (6). To delete *Lpl* gene in adult liver, *Lpl* flox/flox mice were i.p. injected with adenoviruses Ad-Cre or Ad-GFP as control (0.2 O.D. per mouse), and maintained on chow fed for another 2 weeks before experiments. The primers for Cre PCR amplification were described as previously (19). All mice were maintained on autoclaved chow diet in filter-topped cages in SPF animal room. In all animal experiment, littermates carrying the loxP-flanked alleles but lacking Cre recombinase were used as wild-type controls. For diet-induced obesity, mice were fed a high-fat diet (HFD) (20.1% carbohydrate, 59.9% fat, 20.0% protein) for 16 weeks at 4 weeks of age. All animal experiments were done following institutional guidelines.

Plasma metabolite measurements. Blood was collected from the retro-orbital plexus into heparinized tubes after 6-hr fast. The tubes were place on ice and centrifuge at 4°C, and stored at -80°C. Plasma and tissue TG concentrations were determined using the serum triglyceride determination kit TR0100 (Sigma, St. Louis, MO, USA). Plasma free fatty acids were determined using a kit (Cat. #294-63601) from WAKO Chemicals (Sopachem, OCHTEN, NZL). For lipoprotein separation, plasma samples pooled from five mice per genotype were resolved by fast performance liquid chromatography (FPLC) on a gel filtration column Superose 6 (Bio-Rad), with the
eluates collected in 0.5ml fractions at a flow rate of 0.5 ml/min, and TG levels were measured with the triglycerides quantification colorimetric/fluorometric kit (Biovision).

**Liver TG secretion and postprandial TG Test.** Liver TG was extracted with acetone for colorimetric assays. Liver TG production test was performed by intraperitoneal injection of poloxamer 407 (1 mg/g, Sigma, St. Louis, MO, USA) into 16-h fasted mice, and plasma TG was measured at 0, 1, 2, 6, 24 h after injection (20). Postprandial TG test was performed on 16-h fasted mice by gavage of corn oil (10 μl/g, Sigma, St. Louis, MO, USA), and plasma TG was measured at 0, 2, 4, 6, 8 h after gavage.

**Glucose and insulin tolerance test.** GTT and ITT were performed as described previously (21). Following the overnight fast (6h), glucose and insulin tolerance tests were by bolus intraperitoneal injection of glucose (2 g/kg, Sigma, St. Louis, MO, USA) or insulin (0.5 U/kg, Sigma, St. Louis, MO, USA), respectively. Blood glucose was measured using glucose glucometer by tail bleeding at 0, 15, 30, 60, 120 min after injection.

**Quantitative RT-PCR.** Total RNA was isolated from liver samples by Trizol (Invitrogen, Carlsbad, CA, USA) reagent and cDNA was synthesized by using reverse transcription reagent (Promega, Madison, WI, USA). Quantitative real-time PCR (qRT-PCR) was performed using a standard SYBR green PCR kit (Promega, Madison, WI, USA), and PCR-specific amplification was conducted in the Eppendorf real-time PCR machine (19). The expression of gene was calculated with the $2^{(\Delta\Delta C_t)}$ method.
Primer sequence for Lpl: forward: CAGAGTTTGACCGCCTTCC, reverse: AATTTGCTTTTGATGTCTGAGAA.

**LPL protein and activity assays.** For post-heparin plasma LPL levels, blood was collected at 10min after tail vein injection of heparin (0.1 U/g body weight) diluted in PBS. Plasma LPL levels were measured using specific ELISA kits (Cat#SEA386Mu, Cloud-Clone Corp, Houston, USA) following the manufacturer's instructions. For Western blot analysis, 10 ul of plasma was loaded on SDS-PAGE gel to resolve before probing with anti-LPL antibody (Santa Cruz Biotechnology). Plasma LPL activity was determined with $^3$H-triolein as substrate tracer (22). Briefly, 10 µl samples were mixed with the anhydrous emulsion containing 0.01% $^3$H-triolein in the presence of heparin and heat-inactivated fast rat serum. After reaction at 37°C for 60 min, the mixture was extracted with an organic solvent (21% methanol, 44% chloroform, 35% heptane), and 1 ml of the upper aqueous phase were removed to mix with 4 ml of scintillator liquid for counting in a spectrometer (Beckman LS 6500). To abolish LPL activity, samples were pre-treated with 1M NaCl, and LPL activities were obtained by total enzyme activities subtracted NaCl-treated enzyme activities.

**Statistics.** Data are presented as mean ± standard error of the mean (SEM). Statistical significance between two experimental groups was assessed using a Student’s t test. Significance was accepted at the level of p<0.05(*).
Declaration of interest

All the authors declare that there is no conflict of interest of this work.
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References


Author contributions

W.Z. designed the experiments, G.L., J.X., D.L., Q.D., M.L., R.C., M.F., and Y.Z. performed the experiments, G.L., C.Z., D.Z., J.L., and W.Z. analyzed the data, and W. Z. wrote the paper.
Figure Legends

Fig.1. Characterization of liver *Lpl* mRNA expression in adult mice. *Lpl* mRNA expression was detected by real-time RT-PCR in the tissues from normal C57BL/6 mice. (A) *Lpl* mRNA expression in the liver at the indicated ages. (B) *Lpl* mRNA expression in the indicated tissues from adult mice at the age of 3~4 months. *Lpl* mRNA levels were normalized by internal control 36B4. n=4~6.

Fig.2. Generation of hepatocyte-specific *Lpl* knockout mice. (A) PCR analysis of tail genomic DNA distinguishing the *Lpl*^flox^ allele and WT allele. PCR products in the size of 515-bp and 465-bp correspond to the floxed and wild-type (WT) alleles, respectively. Genotypes are indicated above each lane. F, floxed allele. (B) The adult LPL^△hep^ mice displayed a substantial and tissue-specific reduction in *Lpl* mRNA levels in the liver. n=4~6 per group.

Fig.3. Deletion of hepatic *Lpl* gene decreases plasma LPL contents and activity. The control and mutant adult mice were pre-treated with heparin, then their plasma were harvested for measuring LPL contents and activity. (A-B) Plasma LPL contents were determined by ELISA (A) and Western blot (B). 15 µl of plasma from paired mice was resolved by SDS-FAGE gel before probing with anti-LPL antibody. (C) Plasma LPL activity was decreased by the deletion of hepatic *Lpl*. Results represent mean ± SEM. *, p<0.05 vs.control; n=4-5 for each group.

Fig.4. Disruption of liver LPL altered plasma lipid metabolism. The control
and \( Lpl^{\Delta_{hep}} \) male mice at the age of 2~6 months were fed normal chow diet. (A) Body weight was not affected at the age of 2~6 months. (B) The TG and TC contents in the liver were not affected by the deletion of hepatic \( Lpl \). (C) LPL\(^{\Delta_{hep}} \) mice showed an increase in fasting plasma TG and TC levels and a decrease in plasma FFA levels. The mice were fasted for 6h. Results represent the mean ± SEM. *, p<0.05 vs. control, n=6-10 for each group.

**Fig.5. Disruption of liver LPL impaired postprandial TG clearance.** (A) Postprandial TG clearance test. Four-month old male mice were administered corn oil by gavage following a 16-hour fasting, and plasma TG levels were determined at indicated time points. Area under curve (AUC) was plotted with the indicated values. (B) VLDL secretion test. Male mice at the age of 3~4 months were i.p. injected with LPL inhibitor P407, and plasma TG levels were determined at indicated time points. Results represent the mean ± SEM. *, p<0.05 vs. control; n=4~5 for each group.

**Fig.6. Effects of adenovirus-mediated deletion of liver LPL on plasma lipid metabolism in adult mice.** Adult \( Lpl^{\text{flox/flox}} \) mice (2~3 months of age, male) were i.v. injected with Ad-Cre or Ad-GFP, and fed normal chow for 2 weeks before sacrifice. (A) \( Lpl \) mRNA levels in the liver and other tissues as indicated. (B) Plasma LPL contents measured in heparinized mice by ELISA. (C) Plasma lipid levels. (D) Postprandial TG clearance test. Results represent the mean ± SEM. *, p<0.05 vs. Ad-GFP control; n=4~6 for each group.

**Fig.7. Liver LPL regulated plasma lipid metabolism in HFD-induced...**
obese mice. Male control and Lpl$^{\Delta\text{hep}}$ mice were fed high-fat diet for 3 months starting from 3 weeks of age. (A) Body weight was not affected in Lpl$^{\Delta\text{hep}}$ mice after 2~6 months of HFD feeding. (B) The TG and TC contents in the liver were not affected in obese mice by the deletion of hepatic Lpl. (C) Fasting plasma lipid levels after 3 months of HFD feeding. Results represent the mean ± SEM. *, p<0.05 vs. control; n=6~8 for each group.
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