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ORIGINAL ARTICLE

Heterozygous lipoprotein lipase knockout mice exhibit impaired hematopoietic stem/progenitor cell compartment

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Abstract

Background: Hematopoietic stem cells (HSC) maintain the hematopoietic system homeostasis through self-renewal and multilineage differentiation potential. HSC are regulated by the microenvironment, cytokine signaling, and transcription factors. Recent results have shown that lipid pathways play a key role in the regulation of HSC quiescence, proliferation, and division. However, the mechanism by which lipid metabolism regulates HSC proliferation and differentiation remains to be clarified. Lipoprotein lipase (LPL) is an essential enzyme in the anabolism and catabolism of very low-density lipoprotein, chylomicrons, and triglyceride-rich lipoproteins.

Methods: The percentage of hematopoietic stem/progenitor cells and immune cells were determined by fluorescence-activated cell sorting (FACS). The function and the mechanism of HSCs were analyzed by cell colony forming assay and qPCR analysis. The changes in $LPL^{+/-}$ HSC microenvironment were detected by transplantation assays using red fluorescent protein (RFP) transgenic mice.

Results: To explore the function of LPL in HSC regulation, heterozygous LPL-knockout mice ($LPL^{+/-}$) were established and analyzed by FACS. $LPL^{+/-}$ mice displayed decreased hematopoietic stem/progenitor cell compartments. In vitro single-cell clonogenic assays and cell-cycle assays using FACS promoted the cell cycle and increased proliferation ability. qPCR analysis showed the expression of $p57^{KIP2}$ and $p21^{WAF1/CIP1}$ in $LPL^{+/-}$ mice was upregulated.

Conclusions: $LPL^{+/-}$ mice exhibited HSC compartment impairment due to promotion of HSC proliferation, without any effects on the bone marrow (BM) microenvironment.

KEYWORDS
cell cycle, HSCs, LPL

1 | INTRODUCTION

All mature immune cells develop from hematopoietic stem cells (HSC), which have properties of self-renewal and multipotent differentiation potential.[1–3] HSCs are regulated by cell-intrinsic transcriptional programs, and cell-extrinsic factors from the microenvironment and/or niche.[4] Many recent papers have shown that regulation of lipid metabolism plays a critical role in HSC differentiation and proliferation.[5,6] In mice, inactivation of cholesterol efflux transporters or high cholesterol levels promotes HSC mobilization into the blood, and increases HSC proliferation and differentiation to monocytes and neutrophils.[7–9] However, the mechanism by which lipid metabolism regulates HSC remains to be clarified.

The enzyme lipoprotein lipase (LPL) plays a crucial role in lipid metabolism. LPL dysfunction is related to many pathophysiological conditions, including hypertension, Alzheimer's disease, type II diabetes, and obesity. LPL is a prognostic marker in B cell chronic lymphocytic leukemia (B-CLL) and expression of LPL mRNA is upregulated in chronic lymphocytic leukemia (CLL).[10–12] LPL induces a dose-dependent increase in natural killer (NK) cells' proliferation and cytotoxic activity.[13] Genome-wide expression profiles of HSC generated by microarray analysis showed that LPL expression is 1.7-fold higher in old mice than in young mice.[14] These results suggest that LPL plays a key role in the regulation of HSC function.

Mice completely lacking LPL died within 18 h after birth and exhibited massive plasma hypertriglyceridemia, with severe reductions in lipid droplets in many organs. Furthermore, adipose tissue was virtually absent.[15] In this study, we established heterozygous LPL-knockout ($LPL^{+/-}$) mice to explore the mechanism of LPL in the regulation of HSCs. Here, we show that heterozygous LPL-knockout in the bone marrow (BM) led to impaired B lymphocyte development, alteration in the HSC/hematopoietic progenitor cells (HPC) compartment, and affected the cell-cycle regulation of BM lineage$^-$ (Lin^-) Sca-1^+ c-Kit^{High} population (LSKs), but had no effect on the HSC microenvironment.

2 | MATERIALS AND METHODS

2.1 | Animals

All mice were maintained in a C57BL/6J background and provided with a standard diet and water in a pathogen-free environment. All experimental animals were cared for in accordance with the Animal Care and Use Committees of the Institute of Laboratory Animal Science of Peking Union Medical College.

In the transplantation assays, BM cells (2×10^6) from red fluorescent protein (RFP) transgenic mice were transplanted into $LPL^{+/+}$ and $LPL^{+/-}$ lethally irradiated host mice. Four months post-transplantation, the donor derived chimerisms in peripheral blood (PB) and BM were detected by fluorescence-activated cell sorting (FACS).

2.2 | Antibodies and flow cytometry

Cells were harvested from 2-month-old $LPL^{+/-}$ and $LPL^{+/+}$ mice. After euthanization, the thymus and spleen were excised, washed, and weighed. Thymus and spleen were homogenized with glass slides, and then the cells were suspended in phosphate-buffered saline (PBS). PB cells were treated with lysing buffer (BD Biosciences, USA), according to the product instruction. BM cells were stained using biotin-conjugated anti-mouse B220 (RA3-6B2), CD4 (RM4-5), CD8a (53–6.7), CD11b (M1/70), Gr1 (RB6-8C5), and TER119 (TER-119). Staining was followed by APC-eFluor 780-conjugated Streptavidin antibody. Lineage markers were surface stained with the following antibodies: PE-Cy7 B220 (1:100, RA3-6B2), FITC IgD (1:100, 11–26), APC IgM (1:100, II/41), FITC B220 (1:100, RA3-6B2), PerCP-Cy5.5 CD3e (1:100, 145-2C11), APC-eFluor 780 CD11b, PE-Cy7 Sca-1 (1:100, D7), FITC CD34 (1:100, RAM34), PE CD16/CD32, PE Flt3 (1:100, A2F10), and PerCP-Cy5.5 CD127 (1:100, A7R34) (93). The cells were stained with antibody for 30 min at 4°C. All antibodies were from Thermo Fisher Scientific (San Diego, USA). All FACS was performed using a FACS Aria II (BD, USA). The data were processed using FlowJo software (Three Star, Ashland, USA).

2.3 | Quantitative reverse transcriptase-polymerase chain reaction

Total RNA was isolated from LSK cells using TRIzol reagent (Thermo Fisher Scientific, USA) and reversed transcribed to cDNA using M-MLV (Promega, USA). PCR primers and conditions were as follows: *LPL* (5′-GACCCCAAGCATCTCAACGAC-3′ and 5′-GGATCGCAGAAGGTATGGACG-3′, 61°C, 27 cycles); $p18^{INK4C}$ (5′-GGGACCTAGAGCAACTTACT-3′ and 5′-TGACAGCA AAACCAGTTCCA-3′, 62°C, 30 cycles); $p21^{WAF1/CIP1}$ (5′-TCCAGA CATTCAGAGCCACA-3′ and 5′-CGAAGAGACAACGGCACACT-3′, 61°C, 30 cycles); $p57^{kip2}$ (5′-AGGAGCAGGACGAGAATCAA-3′ and 5′-TTCTCCTGCGCAGTTCTCTT-3′, 60°C, 30 cycles); *Bmi1* (5′-AGC AGCAATGACTGTGATGCACTTGAG-3′ and 5′-GCTCTCCAGCATT CGTCAGTCCATCCC-3′, 57°C, 35 cycles), *Notch1* (5′-CAGCCACAG GAACTTACCACTCCAG-3′ and 5′-TAAATGCCTCTGGAATGTGGGT GAT-3′, 57°C, 34 cycles); *c-myc* (5′-CTGGATTTCCTTTGGGCGTT-3′ and 5′-AATAGGGCTGTACGGAGTCG-3′, 60°C, 29 cycles); *GAPDH* (5′-GAGCGAGACCCCACTAACAT-3′ and 5′-TTCACACC CATCACAAACAT-3′, 61°C, 26 cycles). qPCR was conducted using SYBR Premix Ex Taq™ II reagent kits (TaKaRa Shuzo, Japan) on the ABI StepOne system (Applied Biosystems, USA).

2.4 | Cell colony-forming assay

Cells were plated in 96-well cell culture plate (5/well) in a methylcellulose-base medium (R&D) for 2 weeks at 37°C. The colonies were manually counted under a light microscope. Colonies were

defined for three classes: small colonies, <1000 cells; medium colonies, 1000–10 000 cells; large colonies, >10 000 cells.

2.5 | Statistical analysis

All data were presented as mean and standard deviation (SD) and analysed using Student's *t*-test using GraphPad Prism software. $p < .05$ was considered statistically significant.

3 | RESULTS

3.1 | LPL$^{+/-}$ mice exhibited changes in mature immune cell populations

To investigate the function of LPL gene in HSC and HPC, we first analyzed LPL expression in the BM of LPL$^{+/+}$ and LPL$^{+/-}$ mice by real-time PCR. LPL transcript expression decreased in BM, spleen, and thymus in LPL$^{+/-}$ mice compared with levels detected in LPL$^{+/+}$ mice (Figure 1A). FACS analysis revealed changes in the mature immune cell populations in LPL$^{+/-}$ mice compared with LPL$^{+/+}$ mice. The frequency of T cells (CD3$^+$) increased in the PB (Figure 1B), the frequency of B cells (B220$^+$) increased in PB, BM, and spleen (Figure 1C), and the frequency of myeloid cells (CD11B$^+$) decreased in PB (Figure 1D) of LPL$^{+/-}$ mice compared with LPL$^{+/+}$ mice. These changes may be due to intrinsic cellular alterations or changes in the microenvironment.

3.2 | LPL$^{+/-}$ mice exhibited lymphocyte defects

Since the frequency of T and B cells was altered in LPL$^{+/-}$ mice, we next investigated the CD4$^+$ and CD8$^+$ populations in LPL$^{+/+}$and LPL$^{+/-}$ mice. Compared with LPL$^{+/+}$ mice, the frequency of CD4$^+$ cells increased in both thymus and spleen in LPL$^{+/-}$ mice (Figure 2A), and the frequency of CD8$^+$ cells increased in spleen, while there was no obvious change in thymus (Figure 2B). To detect the role of LPL in B lymphocytes development, we used FACS to measure the frequency of mature B (IgD$^+$IgM), immature B (IgD$^-$IgM$^+$), and pre-B (IgD$^-$IgM$^-$) in the BM[16] (Figure 2C). The frequency of immature B cells clearly decreased, and the frequency of mature B cells increased in LPL$^{+/-}$ mice compared with LPL$^{+/+}$ mice (Figure 2D). These data indicate the existence of lymphocyte defects in LPL$^{+/-}$ mice.

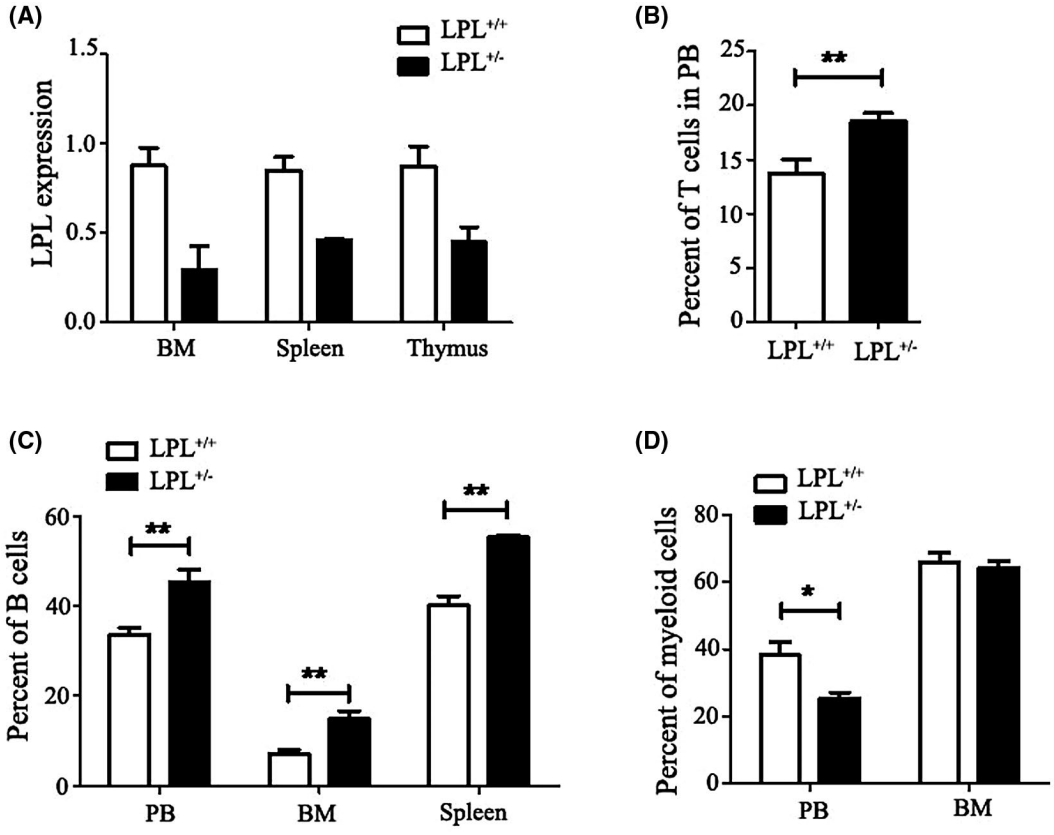


FIGURE 1 The frequency of T and B cells from PB, BM, and spleen were increased in LPL$^{+/-}$ mice ($n = 5$ mice/group). (A) Expression level of LPL mRNA detected by qPCR in the BM, spleen, and thymus. (B) Frequency of T cells in BM, PB, and spleen analyzed by flow cytometry. (C) Frequency of B cells in BM and PB analyzed by flow cytometry. (D) Frequency of myeloid cells in PB analyzed by the flow cytometry. Results represent the mean ± SD ($n = 3$). $^{**}p < .01$, $^{*}p < .05$. *GAPDH* was used for normalization

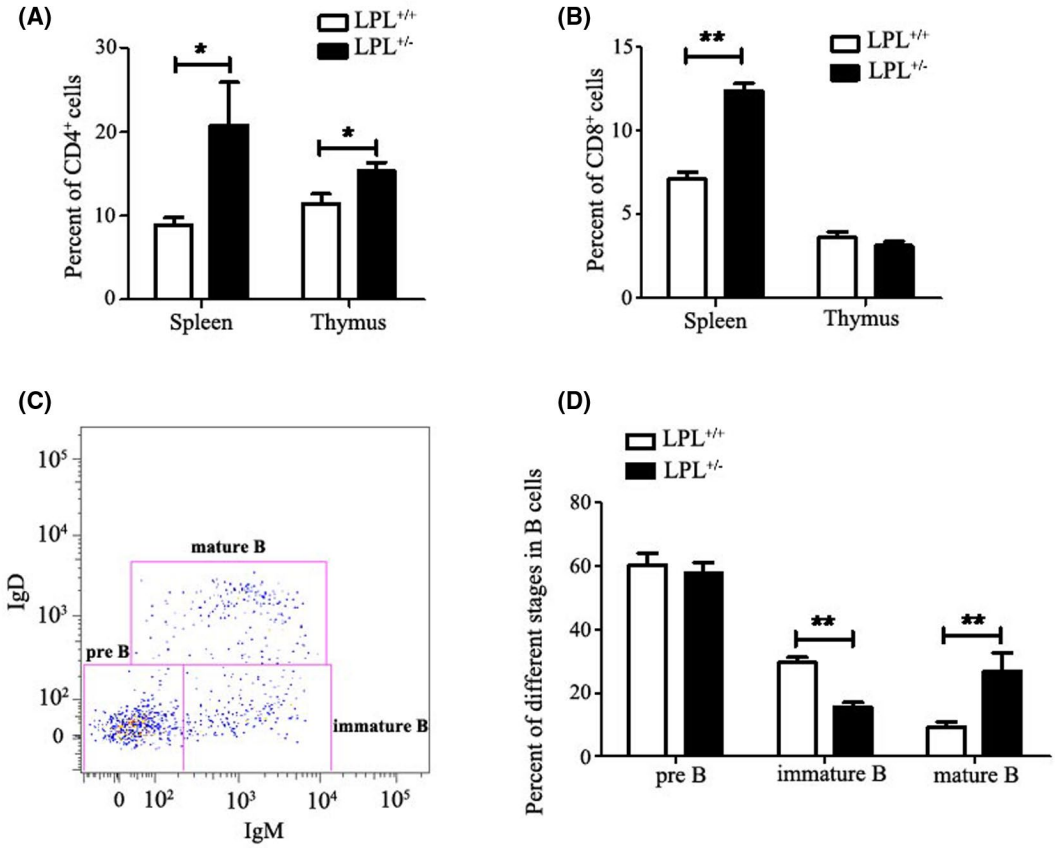


FIGURE 2 $LPL^{+/-}$ mice displayed impaired B cell development. (A) Frequency of $CD4^+$ cells in the thymus and spleen analyzed by flow cytometry. (B) Frequency of $CD8^+$ cells in the thymus and spleen analyzed by flow cytometry. (C) FACS profiles of B cell development in the BM. (D) Frequency of cells in (C) from $LPL^{+/+}$ and $LPL^{+/-}$ mice ($n = 5$/group). Data represent the mean ± SD ($n = 3$). $^{**}p < .01$, $^{*}p < .05$ [Colour figure can be viewed at wileyonlinelibrary.com]

3.3 | $LPL^{+/-}$ mice displayed alterations in the HSC/HPC compartments

The change in the frequency of mature cells in $LPL^{+/-}$ mice might be affected by the HSC and HPC compartments. Therefore, we analyzed the HSC/HPC compartments in $LPL^{+/+}$ and $LPL^{+/-}$ mice by flow cytometry (Figure 3A).[17] Compared with $LPL^{+/+}$ mice, $LPL^{+/-}$ mice had lower frequencies of LSK among the total BM cells (Figure 3B). LSK can be separated into multipotent progenitors ($Flt\text{-}3^+$), short-term hematopoietic stem cells (ST-HSC; $CD34^+Flt\text{-}3^-$), and long-term hematopoietic stem cells (LT-HSCs; $CD34^-Flt\text{-}3^-$) according to the expression of CD34 and Flt-3 (Figure 3A). Compared with $LPL^{+/+}$ mice, BM LSKs from $LPL^{+/-}$ mice contained decreased frequencies of multipotent progenitors (MPP), LT-HSC, and ST-HSC cells (Figure 3C).

Further differentiation of HSC produces common lymphoid progenitors (CLP, $Lin^-c\text{-}Kit^{low}Sca\text{-}1^{low}CD127^+$) and myeloid progenitors (MP, $Lin^-c\text{-}Kit^+Sca\text{-}1^-$) in the BM. MPP can be divided based on the expression of CD16/CD32 and CD34 into common myeloid progenitors (CMP; $CD16/CD32^-CD34^+$), granulocyte–macrophage progenitors (GMP; $CD16/CD32^+CD34^+$), and megakaryocyte–erythroid progenitors (MEP; $CD16/CD32^-CD34^-$)[17] (Figure 3A). BM from $LPL^{+/-}$ mice had lower frequencies of CMP than $LPL^{+/+}$ mice, but no obvious changes in MEP and GMP (Figure 3D). Compared with $LPL^{+/+}$ mice, $LPL^{+/-}$ mice showed a large reduction in the frequency of CLP in the BM cells (Figure 3E).

Collectively, these data demonstrated that the HSC/HPC compartment is decreased in the BM from $LPL^{+/-}$ mice compared with that in $LPL^{+/+}$ mice.

3.4 | $LPL^{+/-}$ mice exhibited altered LSK cell-cycle regulation

The decrease in the HSC/HPC compartment was associated with proliferation of HSC. Therefore, we analyzed the single-cell clonogenic capacity of LT-HSCs sorted from $LPL^{+/+}$ and $LPL^{+/-}$ mice. After incubation for 2 weeks, we found that LT-HSCs colonies from $LPL^{+/-}$ mice were larger than those generated from $LPL^{+/+}$ mice (Figure 4A,B).

We also analyzed LSK cell proliferation and cell-cycle progression using the cell proliferation markers Ki-67 and 7-AAD, used as markers of DNA content. Cell-cycle analysis exhibited that the frequency of cells in G2/M phase was increased in $LPL^{+/-}$ mice (Figure 4C), indicating that LPL deficiency ($LPL^{+/-}$) promotes the proliferation of LT-HSC.

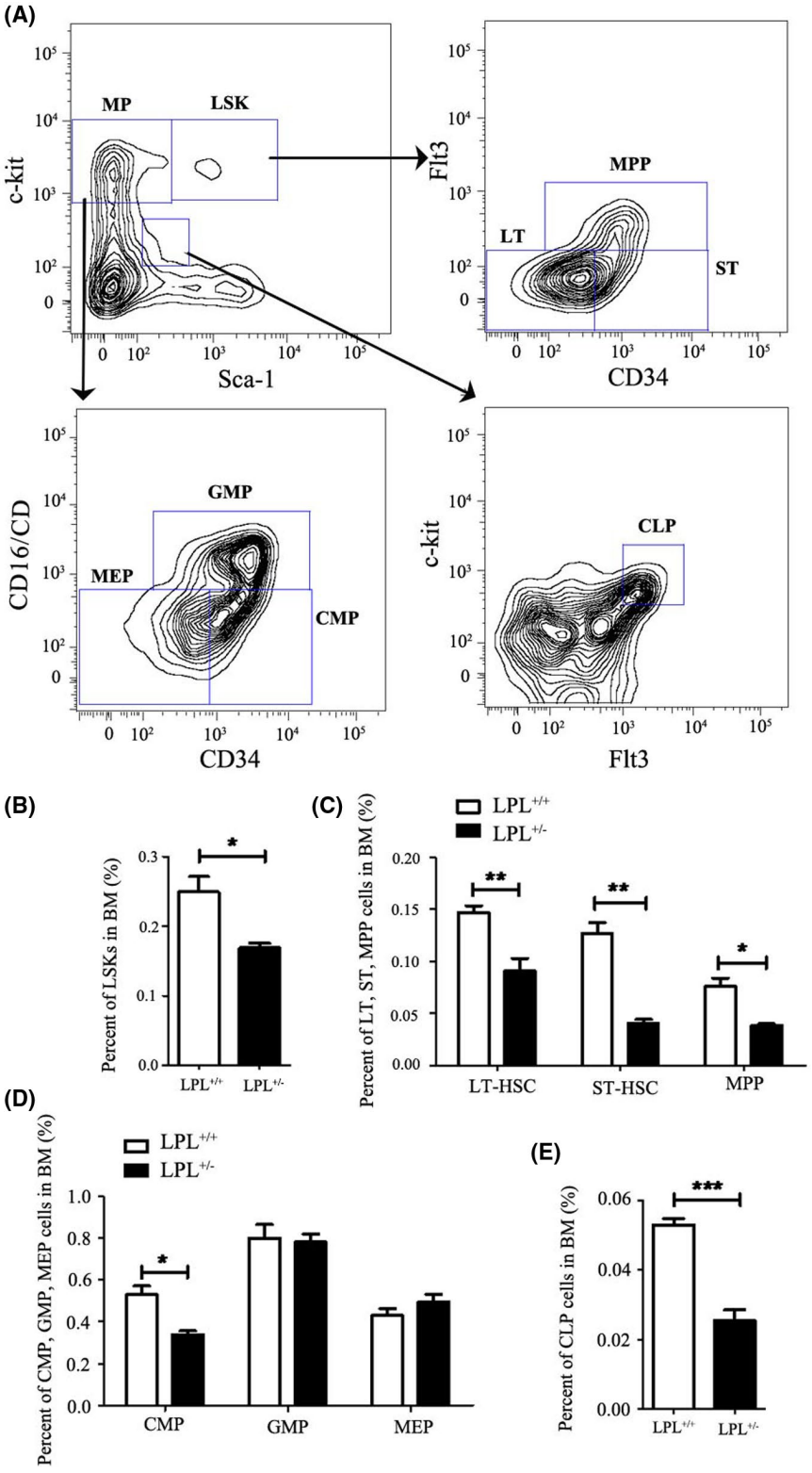


FIGURE 3 Frequency of HSC and HPC defects in LPL$^{+/-}$ mice. (A) Representative profiles for BM HSC and HPC. (B) Frequency of LSK, MPP, ST, and LT cells (C) from LPL$^{+/+}$ and LPL$^{+/-}$ mice analyzed by flow cytometry. (D) Frequency of CMP, GMP, and MEP cells in BM from LPL$^{+/+}$ and LPL$^{+/-}$ mice analyzed by flow cytometry. (E) Frequency of CLP in BM from LPL$^{+/+}$ and LPL$^{+/-}$ mice ($n = 5$ mice/group) analyzed by flow cytometry. Data represent the mean ± SD ($n = 3$). $^{***}p < .005$, $^{**}p < .01$, $^{*}p < .05$ [Colour figure can be viewed at wileyonlinelibrary.com]

3.5 | Genes involved in the regulation of LSKs

We hypothesized that alterations in LSK proliferation associated with LPL deficiency leads to changes in the expression levels of signal pathway regulator genes. LSK from LPL$^{+/+}$ and LPL$^{+/-}$ mice was sorted using FACS, and the expression of genes involved in HSC regulation and the cell cycle was detected by qPCR. No remarkable changes were found in the cell-cycle regulators p18^{INK4C}, Notch 1 pathway, or Bmi-1 pathway, while the proteins p21$^{WAF1/CIP1}$ and p57^{KIP2} were upregulated (Figure 5).

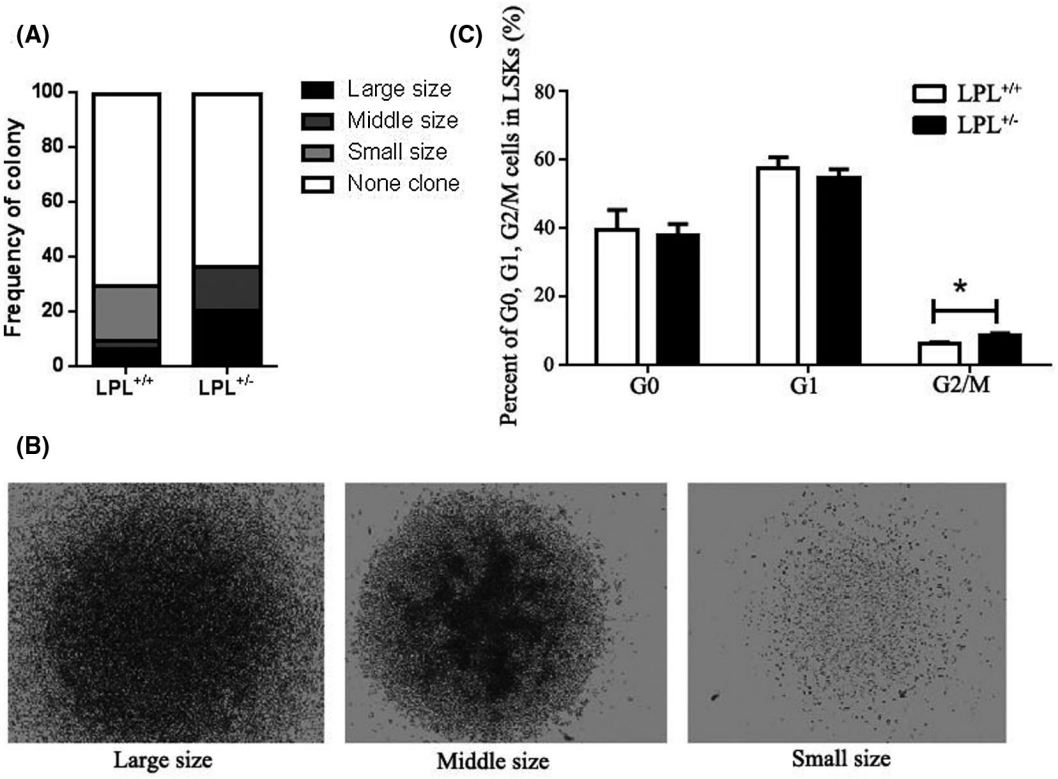
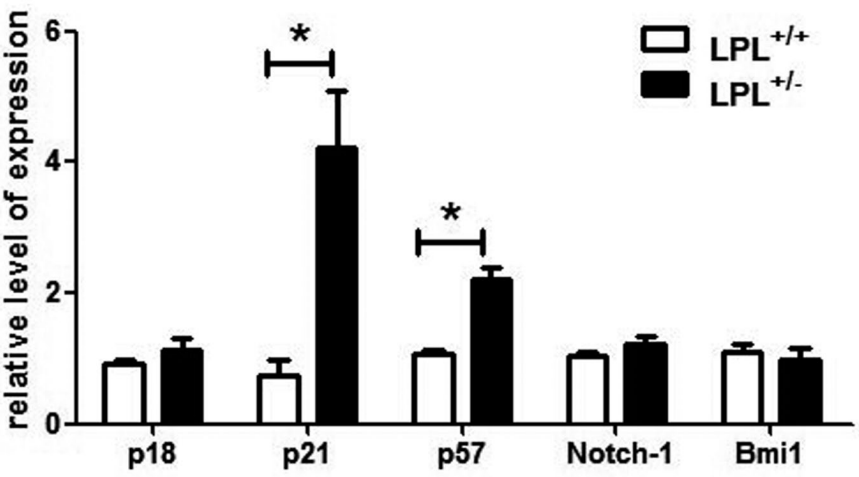


FIGURE 4 LPL defect promotes clonogenic ability and accelerates cell-cycle progression of LSKs. (A) In vitro signal-cell clonogenic potential of LT-HSC from $LPL^{+/+}$ and $LPL^{+/-}$ mice ($n = 3$). (B) The size of large, medium, and small colonies of LT-HSCs. (C) The frequency of LSK cells at every phase of the cell cycle from $LPL^{+/+}$ and $LPL^{+/-}$ mice

FIGURE 5 Gene expression levels in LSK cells from $LPL^{+/+}$ or $LPL^{+/-}$ mice. *GAPDH* was used as internal standard for normalization. Data represent the mean ± SD ($n = 3$). *$p < .05$



3.6 | LPL has no effect on the HSC microenvironment

Stem cell function is regulated by internal and external cytokines. To investigate the ability of LPL to alter the HSC environment, we transplanted RFP transgenic mice BM cells (aged 2 months) into cohorts of irradiated $LPL^{+/+}$ and $LPL^{+/-}$ littermates. Four months post-transplantation, data showed no significant differences in the frequencies of RFP-derived T, B, and M cells in PB (Figure 6A), BM (Figure 6B), or spleen (Figure 6C) between the $LPL^{+/+}$ and $LPL^{+/-}$ transplanted mice. These data show that deletion of LPL has no effect of the HSC environment.

4 | DISCUSSION

In this paper, we established heterozygous LPL-knockout ($LPL^{+/-}$) mice to investigate the role of LPL in the regulation of HSC. Compared with $LPL^{+/+}$ mice, heterozygous LPL-knockout mice exhibited decreased numbers of HSC/HPC, but HSC proliferation

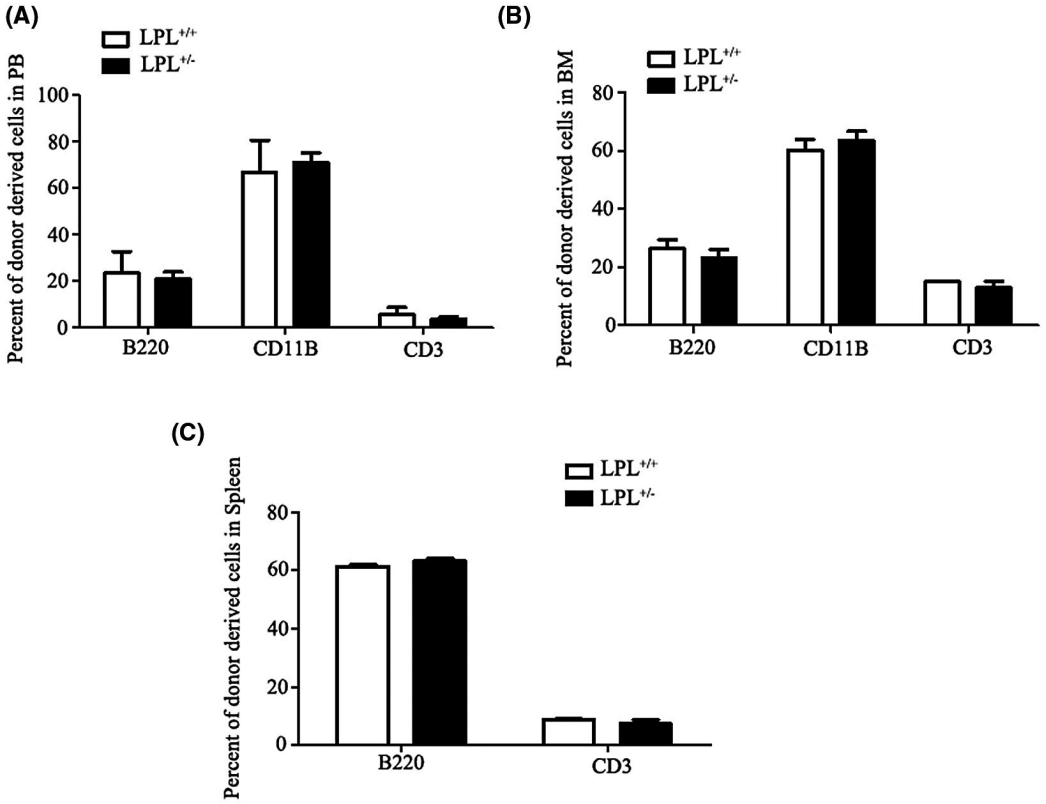


FIGURE 6 The LPL$^{+/-}$ microenvironment does not influence the frequency of B, T, or myeloid cells. (A) After cell transplantation for 4 months, frequency of RFP-derived T, B, and M cells in PB from LPL$^{+/+}$ or LPL$^{+/-}$ recipient mice. (C) Frequency of RFP-derived T, B, and M cells in BM of LPL$^{+/+}$ or LPL$^{+/-}$ recipient mice. (D) Frequency of RFP-derived T and B cells in spleen of LPL$^{+/+}$ or LPL$^{+/-}$ recipient mice (LPL$^{+/+}$ mice, $n = 6$; LPL$^{+/-}$ mice, $n = 6$). Data represent the mean ± SD

was promoted, resulting in alterations in the populations of T and B lymphocytes in the PB, BM, and spleen. However, there were no obvious changes in the HSC microenvironment in heterozygous LPL-knockout mice.

At both the mRNA and protein levels, expression of LPL is highly restricted to leukemic B cells.[18] In our study, we found that the percentage of B cells was highly increased in the PB, BM, and spleen in LPL$^{+/-}$ mice compared with their LPL$^{+/-}$ littermates. In further studies of the development of B cells, we found that the frequency of immature B cells clearly decreased, while the frequency of mature B cells increased in the LPL$^{+/-}$ mice, indicating that B cell development from the immature to mature phase is blocked by LPL deficiency. These results suggest that LPL participates in the development of B cells.

Heterozygous LPL-knockout mice have moderate hypertriglyceridemia, higher rates of glycolysis and glucose oxidation, as well as a reduction in total cholesterol.[19] Cholesterol homeostasis helps to maintain HSC quiescence.[20] Intracellular cholesterol accumulation lead to intrinsic cellular effects that promote HSC proliferation.[9] In this study, we observed increased clonogenic potential and cell cycle promotion in LPL$^{+/-}$ mice. These data indicate that LPL$^{+/-}$ induces intrinsic alterations in HSC. By transplantating BM cells from RFP transgenic mice into irradiated LPL$^{+/+}$ and LPL$^{+/-}$ littermates, we showed that there was no alteration in the BM microenvironment in LPL$^{+/-}$ mice.

In our research, LPL$^{+/-}$ mice blocked B cell development. Thus, LPL may be involved in B cell development. Research on LPL and B cell mainly focuses on B-CLL. LPL is a central enzyme in lipid metabolism; it participates in various solid and hematologic malignancies to provide an extra energy source for tumor cells. Some researchers have described a link between the expression of LPL in the tumor cell and a poor clinical outcome of patients suffering B-CLL.[21] LPL might play an important role in fatty acid metabolism and energy supply of B-CLL cells.[10] LPL could be critical for the proliferation and survival of the leukemic cells, but neither the function of LPL in B-CLL nor the molecular mechanisms regulating its synthesis are known.[10,12]

In summary, the current study reveals that HSC proliferation is inhibited in LPL$^{+/-}$ mice though upregulated expression of the p57^{KIP2} and p21$^{WAF1/CIP1}$ signaling pathways, without any effects on the BM microenvironment.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

All listed authors meet the requirements for authorship. CQ and LB conceived and designed the experiment. LB wrote the main manuscript text. GYS performed the experiments. XYL performed and analyzed the data and FACS. KYL performed the transplantation assays. YYH managed the mice. XPL performed the RT-PCR. All authors have read and approved the manuscript.

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