



Activated hepatic stellate cells are required for Hippo–YAP activation and functional liver regeneration following portal vein ligation in mice

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ABSTRACT

Portal vein ligation (PVL), a preoperative strategy to induce compensatory liver regeneration, is widely applied in clinical practice; however, the cellular and molecular mechanisms underlying PVL-induced liver regeneration remain incompletely understood. Hepatic stellate cells (HSCs), known for their collagen gene expression even in early activation states, have emerged as potential regulators of liver regeneration. To elucidate their role in PVL-induced regeneration, we established a murine PVL model and used Col1a1-GFP reporter mice to visualize collagen gene-expressing HSCs. These cells showed a transient increase after PVL, suggesting activation in response to altered portal flow. To investigate their functional contribution, we selectively ablated activated HSCs using Col1a2-Cre/ERT × ROSA-DTA mice. Despite preservation of total liver mass, activated HSC-deficient mice regenerated their livers through a strikingly different mechanism: hepatocyte proliferation was enhanced, whereas hepatocyte hypertrophy was impaired, resulting in numerous small hepatocytes. Mechanistically, depletion of activated HSCs markedly suppressed YAP nuclear localization and reduced expression of canonical YAP target genes (*Cyr61*, *Ctgf*), indicating impaired activation of the Hippo–YAP pathway, whereas mTOR signaling and growth factors remained unchanged. Bulk RNA sequencing further revealed diminished enrichment of metabolic pathways in activated HSC-deficient livers, suggesting impeded functional maturation of hepatocytes. These findings identify activated HSCs as essential mediators of Hippo–YAP-driven hepatocyte hypertrophy and functional maturation after PVL. By redefining activated HSCs as pro-regenerative regulators, this work provides a mechanistic foundation for strategies to enhance preoperative liver regeneration in clinical settings.

1. Introduction

The liver has a remarkable regenerative capacity [1]. Surgical resection induces compensatory regeneration of the remnant liver. This phenomenon is well documented in patients undergoing hepatic lobectomy for tumor removal or living donor liver transplantation. However, when the residual liver volume falls below 30 %, postoperative liver failure frequently occurs due to insufficient regeneration. To overcome this limitation, portal vein ligation (PVL) — a procedure that redirects portal blood flow to the remnant liver to promote regeneration — has

been used clinically since the 1980s [2,3]. Despite its widespread application, the cellular and molecular mechanisms underlying PVL-induced liver regeneration remain poorly understood, largely because of the technical challenges in establishing a reproducible and reliable mouse PVL model suitable for mechanistic studies [4].

Liver regeneration is a complex process involving hepatocytes and non-parenchymal cells, including cholangiocytes, sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells (HSCs) [5]. HSCs have traditionally been regarded as key contributors to liver fibrosis. However, recent evidences indicate that they also play an important role in

Abbreviations: GFP, green fluorescent protein; HSC, hepatic stellate cell; ICG, indocyanine green; LW/BW, liver-to-body weight; POD, postoperative days; PVL, portal vein ligation; RT-qPCR, quantitative reverse transcription polymerase chain reaction.

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liver regeneration. HSCs are activated after partial hepatectomy and may contribute to tissue remodeling during regeneration [6]. Signaling pathways such as the mTOR and Hippo-YAP, which regulate cell growth and proliferation, have been implicated in liver regeneration [7,8]; however, their involvement in this process following PVL has scarcely been reported.

Clinically, PVL has the potential to induce the rapid regeneration of the remnant liver, which could expand surgical indications for patients with extensive hepatic tumors and enable curative resection in cases that would otherwise be inoperable. A deeper comprehension of the mechanisms underlying liver regeneration after PVL may therefore provide molecular insight for therapeutic strategies to enhance liver regeneration and improve surgical outcomes.

In this study, we established a reproducible mouse PVL model and employed collagen GFP reporter mice to visualize the dynamics of HSCs during regeneration. We further investigated the functional contribution of these cells by analyzing liver regeneration in conditional knockout mice lacking collagen gene-expressing cells.

2. Methods

2.1. Animals

The following male mouse strains were used: 6–8 weeks old collagen 1 α 1-green fluorescent protein (Col-GFP) mice, which express GFP under the control of the Col1 α 1 promoter and thereby label collagen gene-expressing cells [9]; collagen 1 α 2-Cre/ERT mice (Col1 α 2^{Cre-ERT}) [The Jackson Laboratory, stock no.029567] and Rosa26^{fllox-Stop-fllox-DTA} (ROSA-DTA) [The Jackson Laboratory, stock no.009669], which enable tamoxifen-inducible ablation of collagen-expressing cells. All animals were maintained under specific pathogen-free conditions in the animal facility at Kyoto University.

2.2. Portal vein ligation

Anesthesia was induced and maintained with inhaled isoflurane during PVL. A midline upper abdominal incision was made to expose the hepatoduodenal ligament and portal structures. For PVL, the right branch was identified at the first major bifurcation of the main portal vein, and the left branch was carefully isolated and doubly ligated with an 8-0 nonabsorbable monofilament suture. Notably, portal venous anatomy differs between mice and humans: in mice, the left branch supplies the left, middle, and caudate lobes, which are collectively referred to as the left lobes. A detailed description of the surgical procedure is provided in the Supplementary Movie. In sham-operated controls (CTRL), the hepatoduodenal ligament was similarly exposed; however, the portal vein was not ligated.

2.3. Tamoxifen-induced ablation and sample collection

For the conditional ablation model, experimental littermates carrying Col1 α 2^{Cre-ERT} crossed with ROSA-DTA mice (Col1 α 2-DTA) served as the aHSC Δ group, and littermates lacking Cre (Col1 α 2-CreERT(-)) served as controls. Tamoxifen (1 mg in 100 μ l corn oil) was administered daily by intraperitoneal injection to both groups from five days before PVL until two days after PVL, according to a previously described protocol [6].

Mice were euthanized on postoperative days (POD) 3, 7, 14, and 28 after PVL. At each designated time point, the body and liver weights were recorded, and liver tissues were harvested for subsequent analyses.

2.4. Immunohistochemical staining

Formalin-fixed, paraffin-embedded liver specimens (4 μ m thick) were deparaffinized, treated to quench endogenous peroxidase activity, and subjected to heat-induced antigen retrieval. Sections were then

incubated with primary antibodies overnight at 4 °C, developed with DAB chromogen, and counterstained with hematoxylin. The antibodies are listed in [Supplementary Table 1](#). Quantification of Ki67-positive nuclei and YAP nuclear localization was performed in three randomly selected fields at 400 $\times$ magnification.

2.5. Immunofluorescent staining

Frozen liver sections (4 μ m thick) were incubated with primary antibodies overnight at 4 °C, followed by Alexa Fluor-conjugated secondary antibodies, and examined using a fluorescence microscope. GFP-positive areas were quantified from three randomly selected fields at 200 $\times$ magnification using ImageJ software. Hepatocyte size was assessed by the number of nuclei per unit area in three randomly selected fields at 400 $\times$ magnification and visualized by phalloidin staining (Thermo Fisher Scientific).

2.6. Quantitative reverse transcription polymerase chain reaction (RT-qPCR)

Total RNA was extracted from the right lobe of the liver using TRIzol reagent (Thermo Fisher Scientific) and purified with an RNA purification kit (QIAGEN). cDNA was synthesized using random primers, and RT-qPCR was performed with SYBR Green. Gene expression levels were quantified using the $\Delta\Delta$ Ct method, with 18S rRNA serving as the internal control. Primer sequences are listed in the [Supplementary Table 2](#).

2.7. Western blotting

Liver tissue samples from the right lobe were homogenized, and total protein was extracted. Equal amounts of protein (10 μ g per lane) were separated by SDS-PAGE and transferred onto nitrocellulose membranes. Membranes were incubated with primary antibodies overnight at 4 °C, followed by HRP-conjugated secondary antibodies for 1 h. Signals were detected using a chemiluminescent HRP substrate. β -actin was used as the loading control. Band intensities were quantified using ImageJ software [10].

2.8. RNA sequencing and bioinformatic analysis

Total RNA was extracted as described in the RT-qPCR section. Sequencing libraries were prepared and sequenced on the Illumina NovaSeq 6000 platform. Raw read counts were processed using the DESeq2 package in R to identify differentially expressed genes (DEGs). DEGs were subjected to Gene Ontology (GO) enrichment analysis. A heatmap of the top 50 DEGs was generated using the pheatmap package in R, based on genes with an adjusted p value < 0.05. The datasets generated and analyzed during the present study are available from the corresponding author upon reasonable request.

2.9. Statistical analysis

Data are presented as mean $\pm$ standard deviations (SD). Comparisons between two groups were performed using Student's t -test, and those between more than three groups were compared using ANOVA and Tukey's test. Statistical significance was defined as p < 0.05. All statistical analyses were performed in R (version 4.4.2).

2.10. Study approval

All the experiments were conducted in accordance with, and approved by the Animal Research Committee of the Graduate School of Medicine at Kyoto University (approval date: September 28, 2022; approval number: MedKyo 22601, 23142, 24035, and 25160).

3. Results

3.1. Establishment and validation of a mouse portal vein ligation model

To validate the PVL procedure in Col-GFP mice, the left portal branch was doubly ligated (Fig. 1A), and indocyanine green (ICG) was injected peripherally through the penile vein. Near-infrared imaging with the LIGHTVISION2 system (Shimadzu) revealed strong fluorescence in the right lobe, whereas the ligated left lobes exhibited no detectable fluorescence (Fig. 1B). This confirmed interruption of portal blood flow to the left lobes and its diversion exclusively to the right lobe.

Following PVL, the non-ligated right lobe, which received all portal blood flow, exhibited progressive regeneration, with the liver-to-body weight (LW/BW) ratio increasing significantly from POD 3 to POD 7 and continuing to increase gradually thereafter (Fig. 1C). In contrast, the ligated left lobes underwent atrophy. As a result of these reciprocal changes, the total-lobe LW/BW ratio remained relatively constant throughout the 28-day observation period (Fig. 1D). This is consistent with the maintenance of overall liver mass homeostasis observed clinically.

3.2. Transient increase in collagen gene-expressing cells with characteristics of hepatic stellate cells

The number of GFP-positive cells, identified as collagen gene-expressing cells, was quantified in the non-ligated right lobe at each postoperative time point. In the PVL group, the proportion of GFP-positive cells increased significantly on POD 3 and again on POD 14, with the highest incidence observed on POD 3 (Fig. 1E). In contrast, the frequency of GFP-positive cells remained low and unchanged across all time points in the CTRL group.

To further characterize these GFP-positive cells, immunofluorescence staining was performed on POD 3 liver sections. GFP-positive cells colocalized with desmin, a marker of HSCs. A subset of these cells also expressed α -SMA, indicating partial activation (Fig. 1F). These findings suggest that GFP-positive cells predominantly comprised HSCs. Consistent with these histological observations, RT-qPCR analysis revealed significant upregulation of profibrogenic genes, including *Col1a1*, *Timp1*, and *Acta2* in the right lobe on POD 3 compared with sham-operated controls (Fig. 1G).

3.3. Hepatocyte size and proliferation during PVL-induced liver regeneration

Liver regeneration following PVL was characterized by two distinct phenomena: an increase in hepatocyte size and a concomitant rise in hepatocyte proliferation. Hepatocyte size was assessed by phalloidin staining and quantitatively analyzed in the central vein (CV) and portal vein (PV) regions (Fig. 2A and B). In both regions, hepatocyte size progressively increased, reaching a peak on POD 14 (Fig. 2C). Hepatocyte proliferation was evaluated by Ki67 immunostaining. The proportion of Ki67-positive hepatocytes was highest on POD 3 in both CV and PV regions. It then declined rapidly but remained above baseline levels even on POD 28 (Fig. 2D).

3.4. Hepatic stellate cell depletion enhances hepatocyte proliferation but impairs hepatocyte hypertrophy after PVL

To determine the functional role of collagen gene-expressing HSCs in the liver regeneration after PVL, Col1a2^{Cre-ERT} mice were crossed with ROSA-DTA mice to generate activated HSC-depleted mice (aHSC^Δ group), in which tamoxifen treatment induces DTA-mediated ablation of collagen-expressing HSCs (Fig. 3A). TUNEL staining revealed increased apoptotic cells within the hepatic sinusoids on POD 7 in the aHSC^Δ group (Fig. 3B), confirming successful depletion of activated HSCs.

Despite the absence of activated HSCs, the LW/BW ratio of the non-

ligated right lobe was comparable between the aHSC^Δ and CTRL groups throughout the observation period (Fig. 3C). However, the cellular composition of regeneration differed markedly. Phalloidin staining demonstrated that hepatocyte size on POD 14 was significantly smaller in the aHSC^Δ group, indicating impaired hepatocyte hypertrophy (Fig. 3D).

In contrast, hepatocyte proliferation was more pronounced in the aHSC^Δ group: Ki67 staining showed a significantly higher proportion of proliferating hepatocytes on POD 7, with this difference diminishing by POD 14 (Fig. 3E). Similar findings were observed in PV regions (Supplementary Fig. 1A and B).

These findings demonstrate that liver regeneration proceeds through a distinct mode when activated HSCs are absent: the liver achieves normal overall mass not by hepatocyte hypertrophy, but by generating a large number of smaller hepatocytes. This shift from hypertrophic to proliferative regeneration highlights a critical role for collagen gene-expressing HSCs in supporting hepatocyte hypertrophy during PVL-induced liver regeneration.

3.5. Hepatic stellate cells are required for hippo-yap activation in PVL-induced liver regeneration

The Hippo signaling pathway is a major regulator of organ size, tissue homeostasis, and regenerative responses [11,12]. In this pathway, the transcriptional coactivator YAP undergoes dephosphorylation and nuclear translocation, where it forms a YAP/TEAD complex [13] to induce target genes such as *Cyr61* and *Ctgf* [14]. Immunostaining revealed that nuclear localization of YAP was markedly reduced in the aHSC^Δ group compared with the CTRL group (Fig. 4A). Consistent with this, RT-qPCR demonstrated significantly lower expression of the YAP target genes *Cyr61* and *Ctgf* in the aHSC^Δ group on POD 7 (Fig. 4B).

We also examined alternative pathways that may contribute to liver regeneration. Components of the mTOR pathway (AKT and mTOR/p70S6K/S6RP) showed no significant differences between the two groups (Supplementary Fig. 2A and B), nor were there meaningful changes in growth factor gene expression such as *Hgf* (Supplementary Fig. 2C). These results suggest that impaired hepatocyte hypertrophy in activated HSC-deficient livers was associated primarily with reduced Hippo-YAP signaling rather than alterations in mTOR activity or growth factor availability.

3.6. RNA-seq analysis suggests altered hepatocyte function in activated hepatic stellate cell-depleted regeneration

To further define the molecular consequences of activated HSC depletion, bulk RNA sequencing was performed on right-lobe tissues from CTRL and aHSC^Δ mice on POD 7. A heatmap of the top 50 differentially expressed genes revealed distinct transcriptomic profiles between the two groups (Fig. 4C). Gene Ontology enrichment analysis demonstrated that compared with the aHSC^Δ group, metabolic processes and oxidoreductase activity were significantly enriched in the CTRL group within the Biological Process and Molecular Function categories. These findings indicate potential impairment of functional maturation in the absence of activated HSCs (Fig. 4D).

4. Discussion

Preoperative PVL is a clinically established strategy to prevent postoperative liver failure in patients undergoing major hepatectomy. By redirecting portal flow away from the lobe scheduled for resection, the future liver remnant undergoes compensatory regeneration over several weeks [15]. However, the mechanisms driving PVL-induced regeneration have remained unclear, partly due to the difficulty of establishing reproducible murine PVL models [4]. In the present study, we successfully developed a reliable mouse PVL model and directly visualized portal perfusion territories using ICG fluorescence. All mice

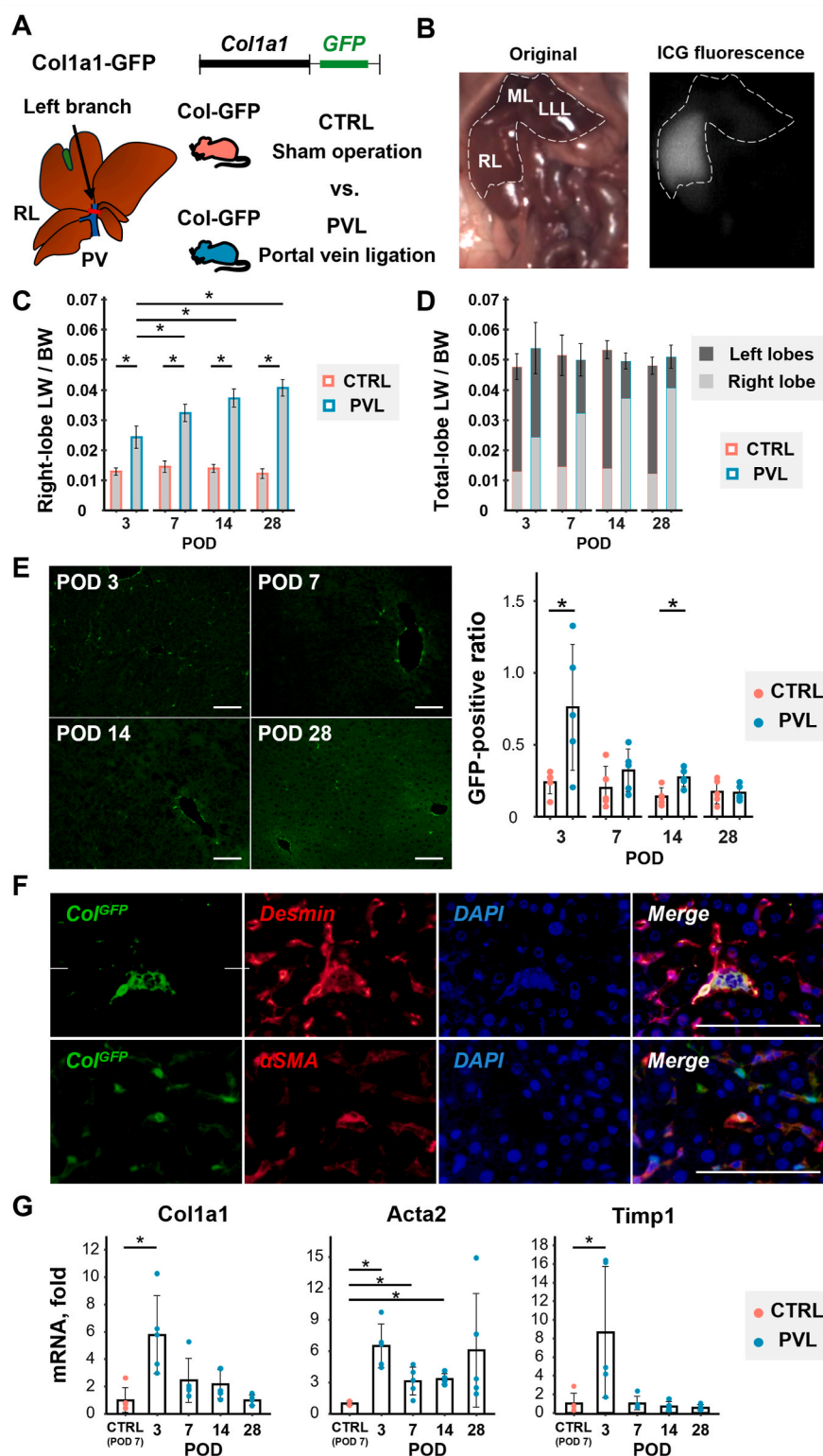


Fig. 1. Transient increase of collagen gene-expressing cells after PVL (A) Schematic overview of the experimental design, including the genetic structure of the Col1a1-GFP reporter mouse and the double ligation site of the left portal vein (red line). (B) Visualization of portal venous perfusion following indocyanine green (ICG) injection. ICG fluorescence was detected only in the right lobe. The white dotted line outlines the liver surface. (C) Time course of right-lobe LW/BW ratio. (D) Time course of total-lobe LW/BW ratio. (E) Representative GFP fluorescence images of liver tissue at each postoperative time point, with quantitative comparison between CTRL and PVL groups. (F) Immunofluorescent images of POD 3 liver showing colocalization of GFP with stellate cell markers (Desmin and αSMA). (G) RT-qPCR analysis of profibrogenic gene expression in CTRL and PVL groups. Scale bars: 100 μm **p* < 0.05. Abbreviations: GFP, green fluorescent protein; HSC, hepatic stellate cell; LW/BW, liver-to-body weight; PVL, portal vein ligation. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

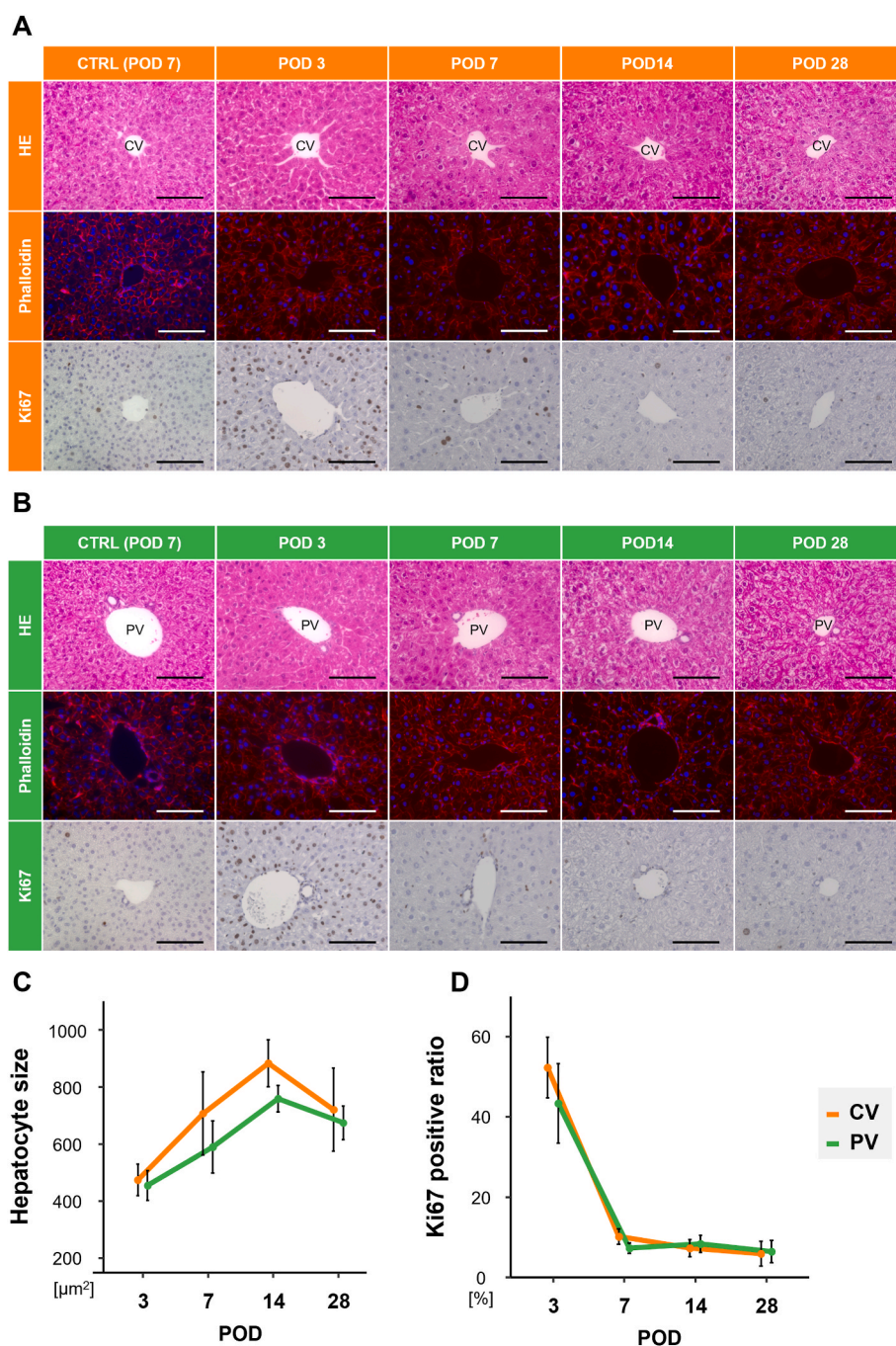


Fig. 2. Temporal changes in hepatocytes following PVL (A, B) Representative sections of the PVL model in the central vein (CV) and portal vein (PV) regions, stained with hematoxylin and eosin (HE), phalloidin, and Ki67. (C) Quantification of hepatocyte size over time in the CV and PV regions. (D) Ki67-positive hepatocyte ratios over time in the CV and PV regions. Scale bars: 100 μ m. Abbreviations: CV, central vein; HE, hematoxylin and eosin; PV, portal vein; PVL, portal vein ligation.

survived the procedure, underscoring both the safety and reproducibility of the model.

HSCs have traditionally been recognized for their role in liver fibrosis, becoming activated by inflammatory signals and producing extracellular matrix components. However, recent work has revealed important physiological functions of quiescent HSCs. These cells surround hepatic sinusoids and regulate sinusoidal tone through contractile activity [16], and they are responsive to mechanical cues such as shear stress [17]. In our study, HSC activation was observed as a transient increase in collagen gene-expressing HSCs after PVL in Col-GFP reporter mice, suggesting that changes in portal flow act as both mechanical and functional triggers for HSC activation.

HSCs are also known to secrete factors that influence hepatocytes, including hepatocyte growth factor (HGF), neurotrophin-3, and R-spondin 3, the latter of which activates Wnt signaling to promote hepatocyte proliferation and maintain liver homeostasis [18,19]. Moreover, the three-dimensional cytoplasmic processes of HSCs extend toward both sinusoidal endothelial cells and hepatocytes [20], implying direct structural and functional interactions. Based on these roles, we initially hypothesized that deletion of activated HSCs would impair liver regeneration after PVL. Surprisingly, however, liver mass in aHSC Δ mice recovered to levels comparable to controls, consistent with the robustness of the “Hepatostat”, a regulatory mechanism that maintains the LW/BW ratio across physiological and experimental conditions [21].

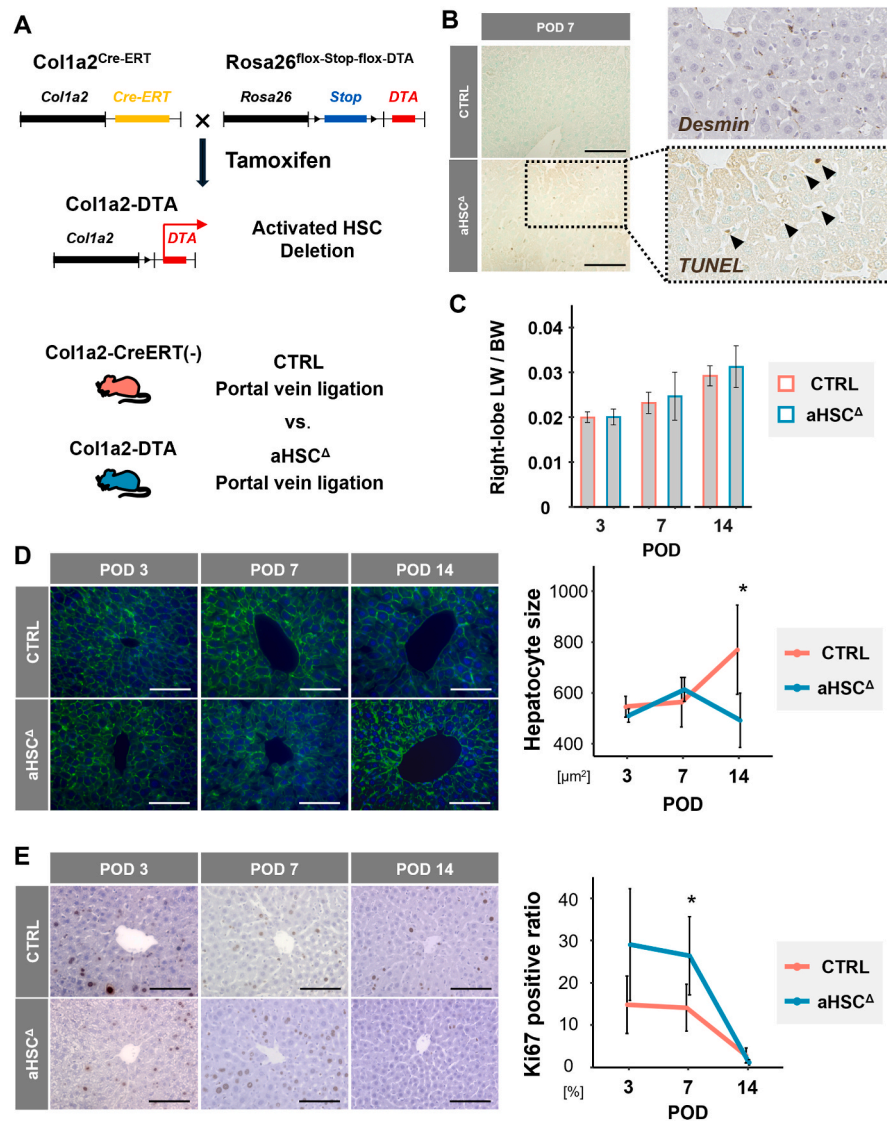


Fig. 3. PVL-induced compensatory changes in collagen gene-expressing cell-ablated (aHSC^Δ) mice (A) Schematic overview of experimental design. Top: genetic configuration of the *Col1a2*^{Cre-ERT} and *Rosa26*^{flox-Stop-flox-DTA} mice. Bottom: comparison of CTRL and aHSC^Δ groups (B) Left: TUNEL staining on POD 7 in CTRL and aHSC^Δ groups. Right: high-magnification images of desmin and TUNEL staining. Black arrowheads indicate TUNEL-positive cells. (C) Time course of the right-lobe LW/BW ratio. (D) Representative phalloidin staining of hepatocytes in the CV region. (E) Ki67-positive hepatocyte ratios in the CV region over time. Scale bars: 100 μ m **p* < 0.05. Abbreviations: CV, central vein; LW/BW, liver-to-body weight.

Importantly, the mode of regeneration differed markedly. In the absence of collagen gene-expressing HSCs, hepatocytes proliferated more vigorously yet failed to undergo normal hypertrophy, resulting in numerous small hepatocytes. These findings indicate that activated HSCs are dispensable for hepatocyte proliferation but indispensable for hepatocyte hypertrophy, a key component of PVL-induced liver regeneration.

To explore the mechanisms underlying impaired hepatocyte hypertrophy, we examined the Hippo-YAP signaling pathway, a central regulator of organ size [11,12]. In aHSC^Δ livers, YAP nuclear translocation and expression of canonical YAP target genes (*Cyr61*, *Ctgf*) were markedly reduced, demonstrating that activated HSCs are required for proper activation of Hippo-YAP signaling during PVL. Other pathways commonly implicated in liver regeneration, including mTOR signaling and growth factors such as HGF, were unchanged, highlighting the specificity of the HSC-Hippo axis in regulating hepatocyte size.

RNA-seq analysis further suggested that hepatocytes proliferating in the absence of activated HSCs exhibit reduced expression of metabolic

and oxidoreductase-related genes. These transcriptional changes raise the possibility that HSC-dependent signals are required not only for hepatocyte hypertrophy but also for the functional maturation of regenerated hepatocytes.

Taken together, our findings reveal a previously underappreciated regenerative role of activated HSCs in PVL-induced liver regeneration. Rather than acting solely as profibrotic cells, collagen gene-expressing HSCs appear to support hepatocyte hypertrophy through activation of Hippo-YAP signaling and may contribute to the functional quality of regenerated liver. These results suggest new avenues for enhancing preoperative liver regeneration through targeted modulation of HSC activity or HSC-hepatocyte signaling.

This study has limitations. PVL was performed in healthy mice, whereas in clinical settings, PVL is often applied to livers affected by chronic hepatitis or fibrosis. Future studies should examine PVL-induced regeneration in diseased livers and evaluate tissue function following HSC depletion. Additional work is also required to identify the paracrine signals through which activated HSCs regulate hepatocyte YAP activity

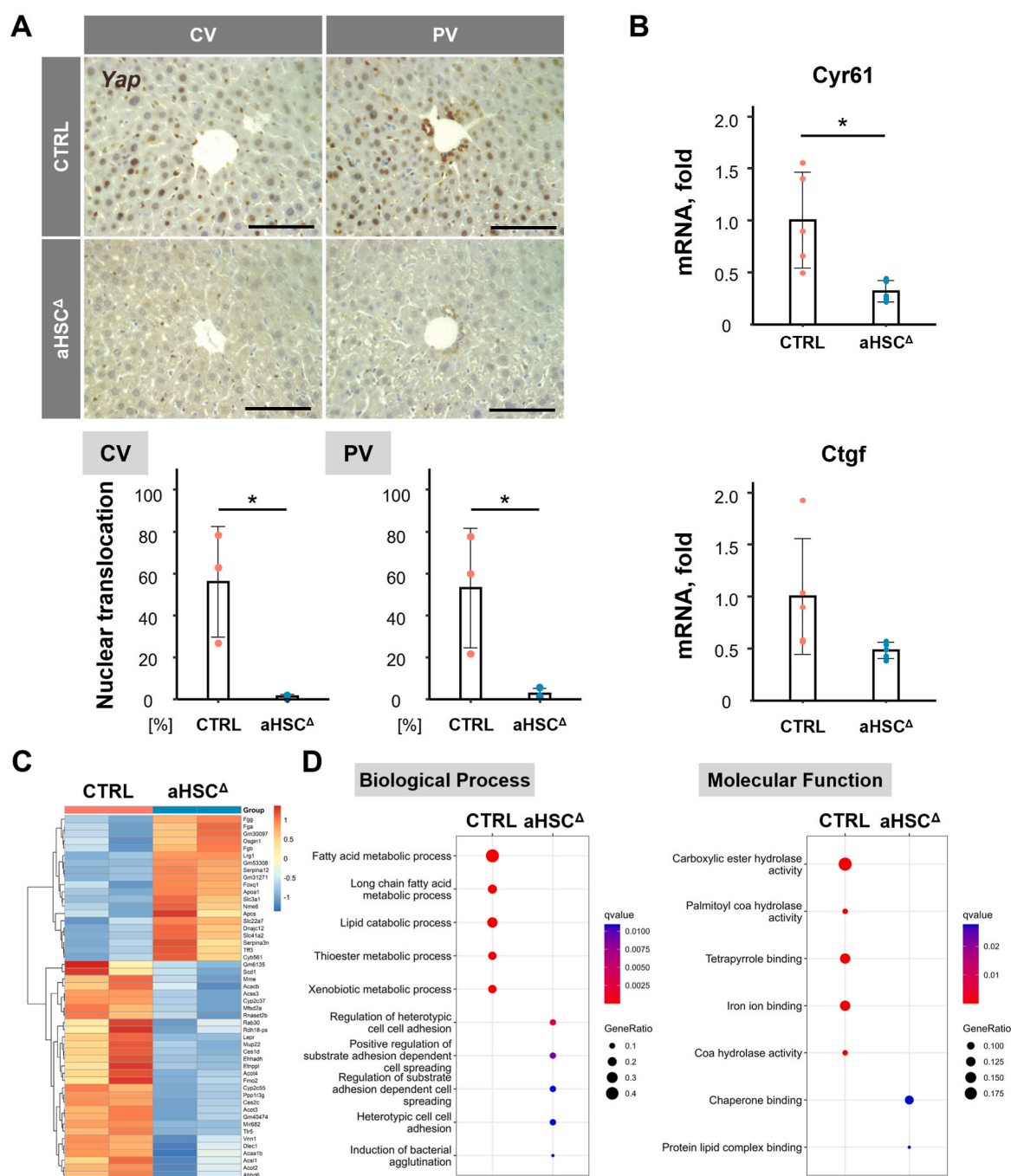


Fig. 4. PVL was associated with the Hippo-YAP signaling and altered transcriptomic profiles (A) Immunohistochemical staining of YAP in the CV and PV regions, with quantification of YAP nuclear translocation ($n = 3$). (B) RT-qPCR analysis of YAP target gene expression. (C) Heatmap of the top 50 differentially expressed genes (DEGs) in CTRL and aHSC^Δ groups. (D) Gene Ontology enrichment analysis of DEGs, shown for Biological Process and Molecular Function categories. Scale bars: 100 μ m * $p < 0.05$. Abbreviations: CV, central vein; DEGs, differentially expressed genes; HSC, hepatic stellate cell; PV, portal vein.

and to determine whether modulating these pathways may improve regenerative outcomes in patients undergoing PVL.

In conclusion, these results demonstrate that alterations in portal flow activate HSCs, which in turn enable hepatocyte hypertrophy through Hippo-YAP signaling. Liver regeneration following PVL relies on compensatory mechanisms, but efficient regeneration requires HSC-dependent signaling to support hepatocyte hypertrophy and functional maturation.

CRediT authorship contribution statement

Keisuke Okura: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Visualization, Writing – original draft. **Yukinori Koyama:** Conceptualization, Writing – review & editing, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration. **Takahiro Nishio:** Funding acquisition, Writing – review & editing, Data curation. **Yoshihiko Kurata:** Writing – review & editing. **Daichi Nakamura:** Writing – review & editing. **Hiroto**

Nishino: Writing – review & editing. **Tomoaki Yoh:** Writing – review & editing. **Masayuki Okuno:** Writing – review & editing. **Keiko Iwai-sako:** Writing – review & editing, Data curation. **Etsuro Hatano:** Supervision, Writing – review & editing.

Data statement

All relevant datasets supporting our findings are available from the corresponding author upon reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbrc.2025.153071>.

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