Wang *et al. Journal of Translational Medicine* (2025) 23:1409
https://doi.org/10.1186/s12967-025-07412-3

Journal of Translational Medicine

REVIEW Open Access

Liver regeneration: unraveling the molecular mechanisms and clinical application

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Abstract
The liver's exceptional capacity sets it apart from other organs in its response to various acute and chronic injuries, known as "liver regeneration". Liver regeneration is not driven by a single pathway, but is achieved through a multi-level network including hepatocyte dedifferentiation, liver progenitor cell (LPCs)activation, non-coding RNA regulation, and metabolic reprogramming. Moreover, liver regeneration research still faces challenges: precise regulation of regeneration termination signals, the tumorigenic risk of stem cell therapy, and immune rejection in personalized treatment, among other issues, need to be addressed urgently. In this review, we delineate the cellular dynamics of liver regeneration and synthesize numerous signaling pathways and factors that prominently contribute to liver regeneration alongside recent research advancements. As well as its current clinical application including molecular therapy, stem cell therapy, and the development of artificial livers. We also discuss some of the current problems and look forward to new treatments. By integrating findings from numerous studies, it provides a comprehensive understanding of liver regeneration, highlighting its significance in treating liver diseases and guiding future research.

Keywords Liver regeneration, Cell source, Clinical trial, Mechanisms, Novel clinical exploration

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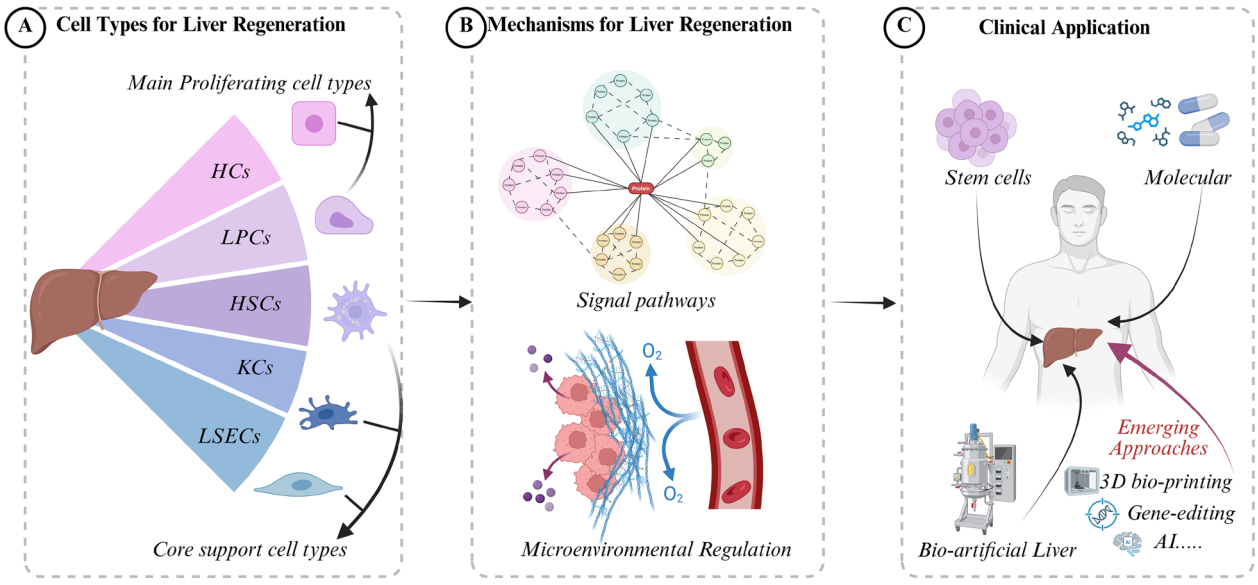
Graphical abstract



Introduction

The liver, a multifaceted organ, is central to regulating physiological processes including metabolism, detoxification, protein synthesis, and immune response. Various factors including viruses, alcohol, metabolites, toxins, and other pathogenic agents can compromise liver function, leading to acute or chronic injurys that may progress to liver disease [1]. Liver disease accounts for two million deaths annually and is responsible for 4% of all deaths. Deaths are largely attributable to complications of cirrhosis and hepatocellular carcinoma, with acute hepatitis accounting for a smaller proportion of deaths [2, 3]. The liver is unique in its ability to regenerate, even after significant damage or tissue loss. This regenerative capacity is crucial for recovery from various liver diseases and injuries. Once damaged, the liver initiates regeneration and hepatocytes proliferate, in order to restore the original form and function of the liver [4]. This regeneration process not only involves liver cells, but also complex interactions with adjacent cellular components. Multiple factors jointly contribute to the complexity of liver regeneration [5]. Given the multifactorial nature of the process, its precise mechanisms remain under investigation.

Although the mechanism of liver regeneration is extremely complex, the mainstream conclusion is that liver regeneration is mainly divided into three stages: initiation, proliferation and termination. In the initial stage, various factors trigger responses in liver cells and other non-parenchymal cells,such as Kupffer cells (KCs) in the liver release pro-inflammatory cytokines that promote the transition from G0 to G1 [6]. The next stage is hepatocyte proliferation driven by mitogen signaling molecules such as epidermal growth factor (EGF) and hepatocyte growth factor (HGF) [7]. While the mass of the regenerating liver approximates that of the original organ, the liver regeneration enters the termination stage. Throughout the entire liver regeneration process, the complex molecular mechanisms involved include the initiation and cessation of liver parenchymal cell proliferation, the transformation of non-liver parenchymal cells, and immune and metabolic influences, rendering liver regeneration a systematic tissue engineering process [8–10]. Furthermore, the zonated architecture of the liver [11] and the specificities of its pathologies, such as fatty liver and fibrosis [12, 13], also complicate liver regeneration. These are the diverse conditions encountered in liver regeneration research. Critically analyzing these issues and identifying the core common and distinct mechanisms presents a significant challenge to liver regeneration research and treatment. Given the complexity of basic theories, we are more looking forward to the clinical application of liver regeneration. How to transform basic knowledge into clinical practice and how clinical practice can feed back to the theoretical foundation are also important. Thus, liver regeneration stands as a pivotal subject not only in basic research but also in clinical investigation. Clarifying the regulatory factors and mechanisms in each stage of liver regeneration will provide new strategies for the application of liver regeneration.

In this review, we first delineate the cellular dynamics of liver regeneration and cell sources for regeneration. Subsequently, we summarize the current mechanisms related to liver regeneration, involving signaling pathways,

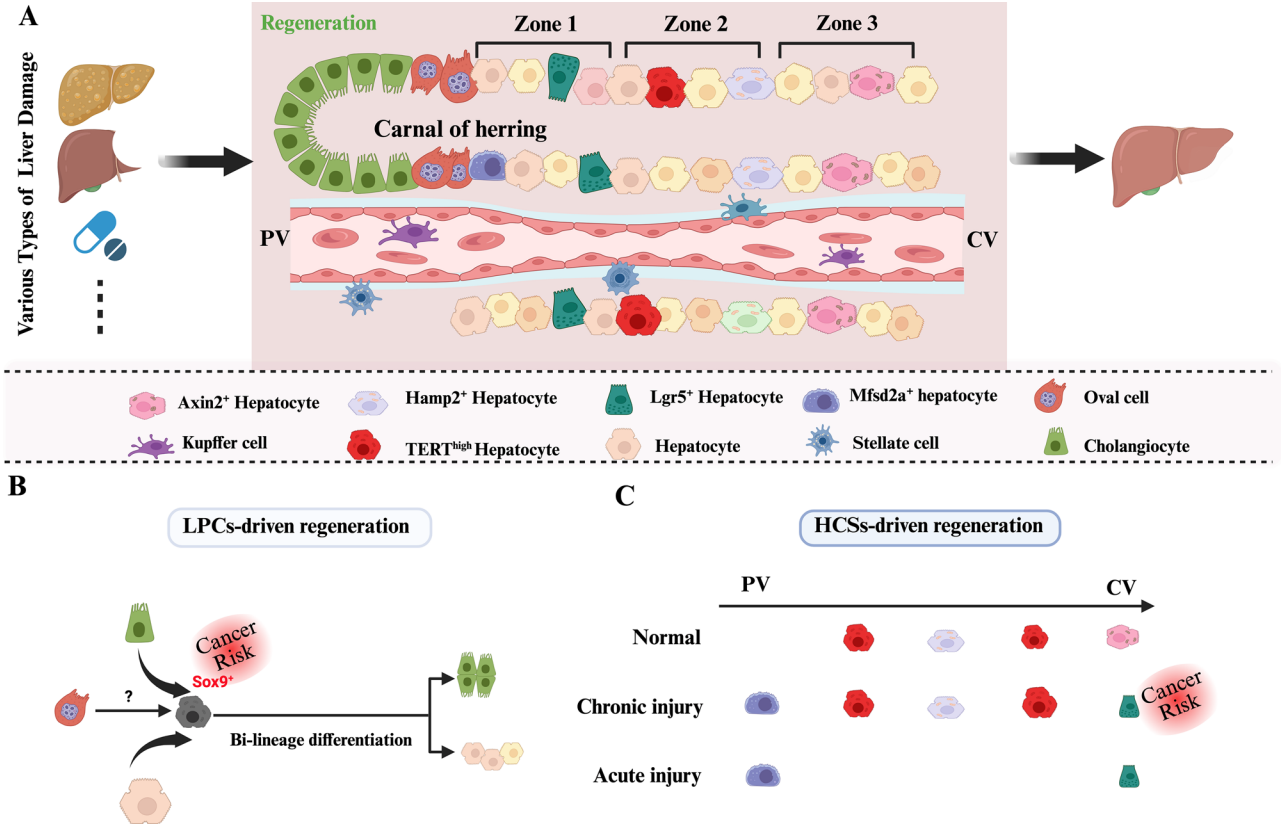


Fig. 1 Cell sources for liver regeneration based on the different cell types and distribution in different locations of the liver. (**A**) Under various types of injury, liver regeneration can be mobilized to a certain extent to restore liver function, including various types of hepatic parenchymal cells and non-hepatic parenchymal cells distributed in three different zones of blood oxygen concentration mediated by portal vein (PV) and central vein (CV). The known cell types for liver regeneration under acute and chronic stimuli are present. (**B**) Cells and proliferation methods involved in LPCs-driven regeneration. (**C**) Under different conditions of injury and stress, different cell types play a major role in HCSs-driven liver regeneration. Some cells that may be prone to cancer are labeled

growth factors, and other important substances related to liver regeneration alongside recent research advancements. Finally, we explore the clinical therapeutic applications for liver regeneration, including stem cell therapy, molecularly targeted drugs, artificial livers, and possible new directions related to such as three-dimensional (3D) bio-printing and AI assistance in the future.

Cell types for liver regeneration

The liver is composed of different types of cells, approximately 70% of which are hepatocytes (HCs), and other major non-parenchymal cells (NPCs) including liver sinusoidal endothelial cells (LSECs), hepatic stellate cells (HSCs), Kupffer cells (KCs), biliary epithelial cells (BECs), and liver progenitor cells (LPCs) [14]. Upon acute and chronic injury, hepatocytes can enter the cell cycle and restore structure and function through compensatory hyperplasia. When severe parenchymal damage impairs hepatocyte regeneration, liver progenitor cells (LPCs)—also known as oval cells—become the dominant contributors to hepatic regeneration [15, 16]. Hence, depending on the severity of damage and cell types involved, typically liver regeneration generally occurs via two types:HCs-driven and LPCs-driven (Fig. 1). With the advancement of biotechnology, especially the popularization of single-cell transcriptomics, spatial transcriptomics and lineage tracing genetic mice in recent years, the cell types in the liver have been characterized with higher resolution. Scientists have gained a deeper understanding of which cell group or the synergy of several types of cell groups contributes to the remarkable regenerative capacity of liver regeneration. There are also some controversies that require further research.

HCs-driven liver regeneration

The origin of hepatocytes in the physiological homeostasis of adult liver and the process of regeneration is an important and controversial scientific issue that needs to be solved urgently. Of course, it is relatively clear now that hepatocytes are the main cell type of the liver by the proliferation of pre-existing hepatocytes. When the regenerative capacity of hepatocytes is not severely compromised, newly formed hepatocytes derived from preexisting hepatocytes and that LPCs contributed

minimally to acute hepatocyte regeneration. In the uninjured liver, pericentral Axin2$^+$ cells possess the ability to differentiate into all hepatocyte subtypes along the lobule, including those surrounding the portal vein. This process is regulated by Wnt proteins derived from the central vein, which control the population dynamics of the pericentral Axin2$^+$ cells population [17]. But Wei et al. found that mid-lobular zone 2 cells marked by Hamp2 expand in number during normal homeostasis and were driven by the IGFBP2-mTOR-CCND1 axis. Neither zone 1 nor zone 3 located cells is responsible for the regeneration. They also confirmed the zone 3 Axin2$^+$ cells expansion in normal homeostasis but is specifically observed in Axin2-CreER; tdTomato mice, not in multiple other CreER mice they constructed [18]. Pu et al. reported that zone 1 Mfsd2a$^+$ population decreases during liver homeostasis. Nevertheless, liver regeneration induced by partial hepatectomy significantly stimulates the expansion of the Mfsd2a$^+$ periportal hepatocytes. Meanwhile, during CCl_4-induced chronic injury, the Mfsd2a$^+$ hepatocyte population expands and completely replaces the pericentral hepatocyte population throughout the whole liver [19]. Lin et al. utilized Tert$^{CreERT2/+}$Rosa26$^{LSL\text{-}Tomato/+}$ mice to reveal that TERT^{High} hepatocytes derived clonal expansion by a self-renewal in normal homeostasis and chronic injury induced by CCL_4 and DDC (3,5-diethoxycarbonyl-1,4-dihydrocollidine) diet. Unlike the above studies where the zone distribution of the cell types involved is clearly defined, TERT^{High} hepatocytes were distributed throughout all lobular zones [20]. Ang et al. have confirmed that Lgr5$^+$ pericentral hepatocytes are self-maintained in normal liver regeneration. But Lgr5$^+$ hepatocytes can be replenished by Lgr5$^-$ cells upon pericentral liver injuries indicating that a local niche actively defines the property of Lgr5$^+$ hepatocytes. They also identified Lgr5$^+$ pericentral hepatocytes were as major cells of origin in DEN-induced HCC development [21]. Recently, Sutton et al. used a combination of single-nucleus RNA-sequencing (snRNA-seq), spatial transcriptomics, and multiplex single molecule florescence in situ hybridization identified a novel migratory ANXA2$^+$ hepatocytes in the peri-necrotic areas of liver tissue contribute to liver regeneration [22].

LPCs-driven liver regeneration

When HCs-driven liver regeneration is compromised, LPCs-driven liver regeneration becomes the main means of replenishing liver cells. BECs can dedifferentiate into LPCs. Then, these LPCs differentiate into hepatocytes [16]. In addition to this BECs-to-LPCs dedifferentiation, hepatocytes also can dedifferentiate into LPCs and later redifferentiateinto hepatocytes [23]. So, the LPCs express both markers of hepatocyte (KRT8, KRT18, and albumin) and BEC (KRT7, KRT19, EpCAM, and SOX9) [24–26]. Activation of LPCs has been extensively investigated using animal models of chronic liver injury. During MCD (Methionine and Choline Deficient) diets induced chronic injury in Ikkβ$^{\triangle}$Hep mice, dying mature hepatocytes produce Hedgehog ligands which promote the compensatory outgrowth of LPCs and myofibroblasts [27]. In DDC diets induced chronic injury in Survivin$^{\triangle}$Hep mice, causing loss of liver mass and inflammation, LPCs were activated to proliferate and expand in number (Fig. 1) [28].

Other contributing cell types

With the development of technologies such as single-cell sequencing, accumulating evidence indicates that, beyondthese two classic proliferation methods, other types of cells especially LSECs and immune cells, also play an important role in liver regeneration. Hu et al. utilized single-cell spatial transcriptomics reveals a dynamic control of metabolic zonation and liver regeneration by endothelial cells (ECs) Wnt2 and Wnt9b [9]. Shi et al. also revealed LSECs contribute to hepatocyte regeneration via a Tie2/Wnt signaling pathway by scRNA-seq technology [29]. Brazovskaja et al. further explored the cellular states in this paradigm of human liver regeneration through single-cell and mononuclear transcriptomics of healthy, enlarged (regenerative), and atrophied (embolic) human liver biopsies. The analysis focused on five major cell populations—hepatocytes, cholangiocytes (bile duct epithelial cells), endothelial cells, mesenchymal cells, and immune cells—revealing alterations in cell-type proportions, hepatocyte zonation, and intercellular communication in the regenerating human liver [30]. Therefore, with the development of technology, there are more and more in-depth means to explore the complex process of liver regeneration, which involves the expression of various cells in different times and spaces and the mutual antagonism and cooperation. The entire blueprint of liver regeneration will be drawn in more detail to develop better clinical applications in the future.

Mechanisms of liver regeneration

Building on investigations into the cellular origins ofliver regeneration, a series of regulatory networks such as signaling pathways and growth factors are crucial to liver regeneration. A clear understanding of these mechanisms, accelerate the clinical application of drugs and other treatments and save more patients with liver damage is an urgent matter. For example, the rate of post-hepatectomy liver failure (PHLF) after major liver resection is reported to range from1.2 and 32% across different cohorts [31]. The regenerative capacity of the remaining liver is a major determinant of postoperativeliver failure. The regeneration of post-hepatectomy liver is a complex, but well-orchestrated, series of events initiated by several

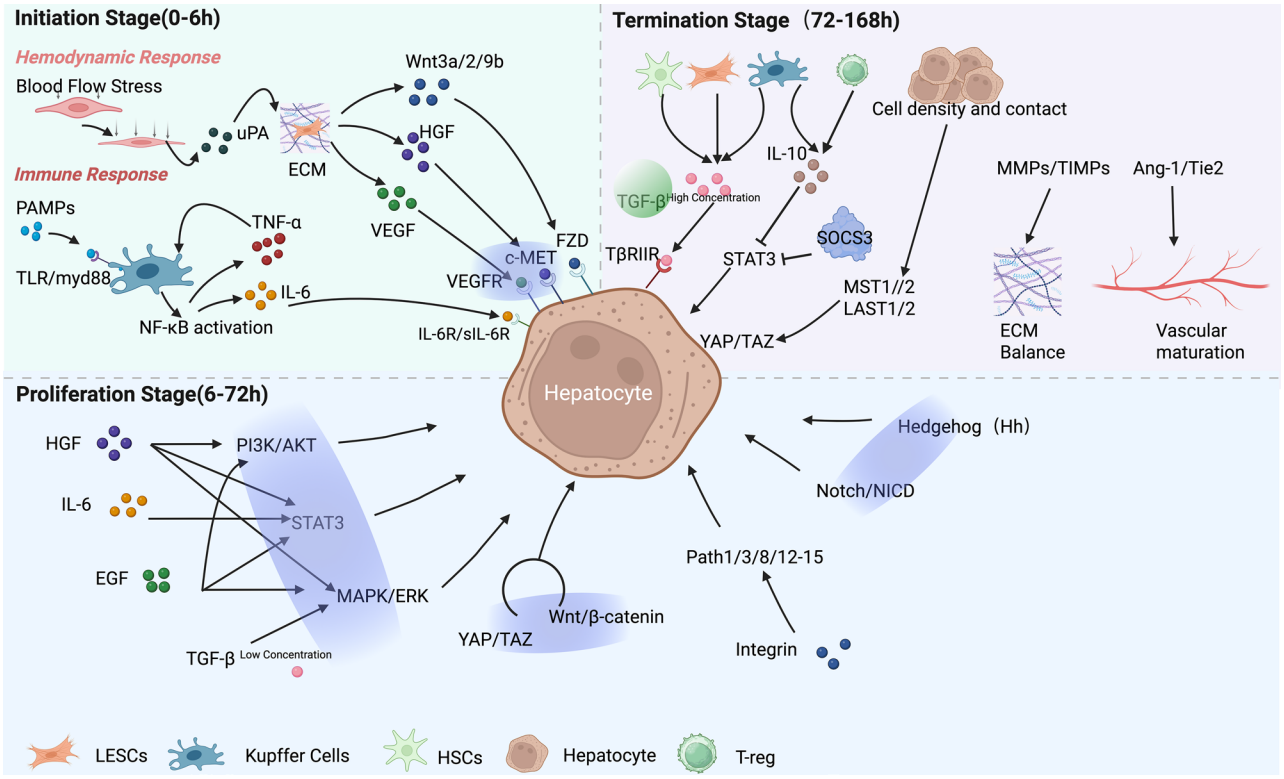


Fig. 2 The transition of liver cells from a resting state to a proliferative state and their recovery to a resting state require the coordination of multiple signaling pathways. Different stages of liver regeneration involve in very complex pathways and factors. These pathways and factors mainly play a major role at a certain stage, or throughout the entire process of liver regeneration, and have opposite effects under the influence of different regulatory factors at each stage, such as the IL6–STAT3 signaling pathway. At the same time, each pathway has a synergistic effect, such as the VEGFR and c-MET signaling pathways in the initial stage of the liver, and the Hippo and Wnt signaling pathways in the proliferation stage

autocrine, paracrine, and endocrine hepatotropic factors [32]. Therefore, in this part we mainly review signaling pathways, growth factors, and other currents mechanisms related to liver regeneration.

As research progresses, genes and signaling pathways associated with liver regeneration have been identified, which are involved in different stages and different cell types of liver regeneration. They play a key role in the regulation of liver regeneration through multiple biologically active signaling cascades (Fig. 2).

TLR signaling pathway

Toll-like receptors (TLRs) constitute a primary defense against infectious pathogens by detecting diverse pathogen- or damage-associated molecular patterns (PAMPs/DAMPs) and are evolutionarily conserved pattern-recognition receptors (PRRs).The TLR4/MyD88 signaling pathway triggers inflammatory responses and induce the production of numerous pro-inflammatory factors, suggesting its potential involvement in early liver regeneration [33]. Following partial hepatectomy, TLRs expressed on Kupffer cells (KCs) in the liver recognize pathogen-associated molecular patterns (PAMPs), including bacterial lipopolysaccharide (LPS), lipoteichoic acid and nucleic acids. TLRs such as the TLR2, TLR4, TLR5 and TLR9 mediate the activation of NF-κB via the MyD88, leading to the production of inflammatory cytokines TNF-α, IL1β and IL-6. It is notable that insufficient IL-6 in myd88$^{-/-}$ mice leads to impaired hepatocyte proliferation, highlighting the importance role of this signaling pathway [33–36].

Recent investigations have highlighted the distinct rolesof specific TLR subtypes in liver regeneration. Inhibition of TLR4 and TLR5 has been shown to impede liver regeneration post-injury by activating signal transducer and activator of transcription 3 (STAT3), emphasizing the role of inflammatory factors in the early stages of liver regeneration [37, 38]. TLR3, however, signals exclusively through Toll-interleukin-1 receptor (TIR)-domain-containing adaptor-inducing IFN-β (TRIF), distinguishing it from other isoforms [35]. Previous studies have demonstrated that intraperitoneal administration of the TLR3 ligand poly (I:C) suppresses liver regeneration in mice [39]. Subsequent research by Elina Zorde-Kovalevsky et al. revealed that TLR3 signaling delayed hepatocyte proliferation after post-hepatectomy (PH), accompanied by enhanced NF-κB activation in Kupffer cells of TLR3$^{-/-}$ mice, whereas TLR3 signaling in liver parenchymal cells

contributes to early hepatocyte proliferation [40]. Collectively, the intricate mechanism of TLRs orchestrates the orderly progression of early liver regeneration.

NF-κB pathway

At the initial stage of liver regeneration, LPS, TNF-α and intercellular adhesion molecule-1 (ICAM-1) jointly act to activate the NF-κB pathway in KCs. Activated KCs secrete large quantities inflammatory mediators such as TNF-α and IL-6 and release them. TNF-α reinforces NF-κB activation in an autocrine feedback loop, thereby amplifying the expression and secretion of TNF-α and IL-6. IL-6, in turn, activates the signal cascades that promotes the growth and proliferation of neighboring hepatocytes.

Upon cytokine stimulation, NF-κB activation extends to hepatocytes, promoting the activation of the IκB kinase (IKK) complex, triggering the phosphorylation, ubiquitination and subsequent degradation of IκB, thereby promoting the release of NF-κB dimers and nuclear translocation through a series of post-translational modifications [41]. Nuclear NF-κB subsequently upregulates the gene expression of IL-1, IL-6, vascular endothelial growth factor (VEGF), and vascular cell adhesion molecule-1 (VCAM-1), creating favorable conditions for liver regeneration. In addition, Four-and-a-half LIM-only protein 2 (FHL2) plays a pivotal role in liver regeneration by activating the NF-κB pathway [42]. Conversely, Pellino1 is a key regulatory factor that can activate NF-κB signal transduction during liver regeneration, and microRNA-21 is negatively correlated with Pelino1 (Peli 1). The upregulation of microRNA-21 hinders the signal transduction of NF-κB at the initial stage of regeneration [43]. In contrast, the signaling cascade of NF-κB-inducing kinase (NIK) and its downstream effector IKKα inhibit the JAK2/STAT3 pathway, thereby suppressing hepatocyte proliferation [44]. Together, these biphasic regulatory signaling pathways involving activation and inhibition form the basis of complex regulation during liver regeneration.

IL-6 pathway

IL-6, as an inflammatory mediator, is involved in the production of pro-inflammatory and pro-angiogenic factors, such as IL-8, granulocyte-macrophage colony-stimulating factor (GMCSF) and VEGF. It has been confirmed that IL-6 plays a pivotal role in liver regeneration with early data demonstrating impaired liver cell regeneration in IL-6 knockout mice. Single-cell RNA sequencing and in vivo screening experiments further revealed the mechanism by which IL-6 activates injury-specific enhancers and promotes hepatocyte dedifferentiation [45, 46]. After liver resection or liver injury, gut-derived factors such as LPS promote the synthesis and secretion of IL-6 by activating liver-resident KCs. Subsequent IL-6 signaling is conducted through the classical or trans-signaling pathway.

IL-6 classic signaling pathway

IL-6/JAK/STAT3 pathway is regarded asa classical signal pathway. IL-6 can activate JAK/STAT, MAPK and PI3K/AKT signal pathways. Among them, IL-6/JAK/STAT3 pathway plays the predominantrole in liver regeneration [47]. Upon binding of IL-6 binds its receptor (IL-6 R) on the target cell membrane, a complex forms with glycoprotein 130 (Gp130), which activates JAK and subsequent phosphorylation of signal transducers and activators of transcription STATs proteins. STAT3 is the downstream effector of this pathway and plays a vital role in promoting liver regeneration. This has been demonstrated by its contribution to hepatocyte mitosis and its protective effects during acute hepatic injury. Activated STAT3 can also regulate IL-6 signaling by inducing the expression of suppressor of cytokine signaling-3 (SOCS3) and establishing a negative feedback loop [48]. IL-6/STAT3 signaling transduction can be enhanced by anti-inflammatory factor A20 and promote liver regeneration. Collectively, these results confirmed the importance of IL-6/STAT3 pathway in liver regeneration [49].

IL-6 trans-signaling

IL-6 trans-signaling is regarded as a key pathophysiological mechanism regulating diverse cellular responses. Expression of the IL-6 R is limited to select cell types, including hepatocytes, some immune cells, epithelial cells such as BECs, as well as non-epithelial cells like HSCs. Consequently, in other cellular contexts, IL-6 signaling primarily occurs through the trans-signaling pathway. In this process, IL-6 R on the cell membrane is cleaved by metalloprotease ADAM17. The resulting soluble IL-6 R (sIL-6 R) binds IL-6, forming IL-6/sIL-6 R complex. Gp130 binds to it and initiates downstream signal transduction [50, 51]. Recent studies have emphasized the importance of trans-signaling in liver regeneration. The level of sIL-6 R increased significantly after partial hepatectomy. It binds to IL-6 and stimulates liver regeneration through trans-signal transduction. Importantly, this signaling pathway is the predominantmode of IL-6 mediated liver regeneration.

PI3K/AKT/mTOR pathway

mTOR plays a prominent role in the positive regulation of liver regeneration. Phosphorylated tuberous sclerosis complex 2 (TSC2) increase in isolated primary hepatocytes as early as 2 hours after 70% hepatectomy and reached the peak at 6 hours, which indicated that PI3K/AKT/mTOR pathway was activated in the early regeneration stage [52]. Glycine promotes hepatocyte

proliferation by enhancing AKT/mTOR activation, thereby exerting a protective effect against liver injury [53]. Additionally, microRNA-21 (miR-21) mediates Cyclin D1 translation to, alleviatingRas homologous gene family member B (Rhob)-mediated inhibition of AKT1/mTORC1, thus promoting liver regeneration [54]. In the zebrafish model, farnesoid X receptor (FXR) agonists are inhibitors of BECsdriven liver regeneration, and activation of FXR impairs liver progenitor cell-mediated liver regeneration through the PTEN-PI3K-AKT-mTOR axis [55]. Historically, research has primarily focused on the role of mTORC1 in liver regeneration. However, recent studies confirm that mTORC2 plays an important role in enhancing liver regeneration by promoting fatty acid oxidation, and has become a key molecule of liver regeneration [56–58]. AKT inhibits cell proliferation through FoxO1, which is a negative regulation of liver regeneration. Under normal conditions, AKT1 and AKT2 are expressed in the liver. Loss of AKT impairs liver regeneration and increases mortality in mice, and FoxO1 knockout can restore the mitotic reaction of hepatocytes after partial hepatectomy [59].

Ras/Raf/MEK/ERK pathway

Upon extracellular stimulation, Ras initiates Raf dimerization and kinase activation, resulting in the phosphorylation of serine residues on the dual-specificity kinase MEK1/2. Subsequent phosphorylation at$Thr^{202/185}$ and $Tyr^{204/187}$ on MEK1/2 activates the downstream ERK1/2. Activated ERK1/2 then phosphorylates various substrates located in the cell membrane, organelles and cytoplasm, exerting functions related to cell proliferation and growth.

Following partial hepatectomy hepatectomy, the MEK/ERK cascade undergoes rapid and transient activation within 30 minutes to 4 hours, which is consistent with the early G1 phase of hepatocytes. The induction of Cyclin D1 further confirmes this activation and promoted the replication of hepatocyte DNA [60]. The growth hormone receptor (GHR) knockout mice have clarified the pivotal role of ERK1/2 in promoting the progression of hepatocyte cell cycle from the G1 phase to the S phase by transducing the signal of epidermal growth factor receptor (EGFR) [61]. Serum and glucocorticoid-induced protein kinase 1 (SGK1) phosphorylates ERK2 in a serum-dependent manner, enhancing ERK signaling activation and promoting liver regeneration by increasing ERK2 activity and the formation of the MEK/ERK complex formation [62]. Given that Ras can activate the Raf/MEK/ERK and PI3K/Akt pathways, their crosstalk is tightly regulated during the regeneration process, and both of these pathways are essential for hepatocyte replication and proliferation.

Hedgehog (Hh) signaling pathway

Hh signaling pathway is a highly conserved cascade that transduces signals from the cell membrane to the nucleus. This pathway can be activated by three ligands: sonic hedgehog (Shh), the Indian hedgehog (Ihh), and the desert hedgehog (Dhh). In the absence of Hh ligands, patched (Ptch) inhibits the activity of Smoothened (Smo) by preventing its accumulation within cilia. Subsequently, the full-length glioma-associated oncogene (GliFL) protein, after being phosphorylated by protein kinase A (PKA), glycogen synthase kinase-3 (GSK3), and casein kinase 1 (CK1), undergoes proteolytic cleavage to produce Gli repressor (GliR) [63]. After Ptch binds to the Hh ligand, the inhibition of Smo is alleviated, signaling suppressor of fused (Sufu) releases the Gli activator (GliA), thereby activating the expressions of the target genes [64].

In the healthy adult liver, Hh signaling remains largely quiescent, with mature hepatocytes expressing Hh ligands at minimal levels. Previous studies have shown that the lack of Ptch expression in liver parenchymal cells further prevents the activation of the Hh signaling pathway [65, 66]. However, during the process of liver regeneration, mature hepatocytes are significantly lost after 70% partial hepatectomy. Consequently,Hh pathway is activated in the stages of liver regeneration and proliferation. Glypican-3 proteoglycan (GPC3) binds Hh on the cell membrane and competes with Hh receptor Patched for Hh binding, thus inhibiting Hh pathway. Reduced binding of Ihh to GPC3 and increased interaction between Shh and Gli1/Gli2 lead to upregulation of downstream effector mRNA levels. In addition, during the whole process of liver regeneration, the expression of Smo exceeds Ptch, which further supports the activation of Hh pathway [67, 68]. The complex interaction between Hh signaling pathway and other pathways will affect liver regeneration. Hh signaling can activate Yap1, which is the transcription cofactor and end effector of the Hippo pathway, indicating that Yap1 is the downstream effector of the Hh pathway [69]. Furthermore, molecules such as miR-182-5p [70] and JNK1 [71] enhance liver regeneration through the Hh pathway. miR-182-5p overexpression promotes Hh ligand expression in HSCs, activating Hh signaling in hepatocytes and stimulating hepatocyte proliferation. Similarly, increased JNK1 expression markedlyenhances liver regeneration through the Hh pathway.

Notch signaling pathway

The Notch signaling pathway is an evolutionarily conserved mechanism in multicellular organisms that governs cell fate determination of cell fate during development and maintaining tissue homeostasis in adults. This pathway comprisesNotch receptors, Notch ligands, CBF1/Suppressor of Hairless/LAG-1 (CSL) DNA-binding

proteins, and downstream target genes, coordinating cellular responses that are crucial for tissue morphogenesis and function [72]. The Notch receptors are type I transmembrane proteins comprising extracellular and intracellular domains. To date, four Notch receptors (Notch1, Notch2, Notch3, Notch4) and two ligand families (Jagged (JAG) –1, 2 and δ -like ligands (DLL) –1, 3, 4) have been identified [73]. Ligand-receptor binding initiates proteolytic cleavage and the release of the Notch intracellular domain (NICD), which is transferred to the nucleus. There, NICD binds to CSL DNA-binding proteins to activate the transcription of target genes [74].

The Notch signaling pathway is indispensable for bile duct morphogenesis [75] and plays a key role in liver regeneration. In the early stage of liver regeneration, the Notch signaling is activated. Activated NICD in hepatocytes peaks within 15 minutes after partial hepatectomy, accompanied by upregulation of Notch1 and its ligand Jagged1 on the fourth postoperative day [76]. Recent studies have shown that the rapid upregulation of Notch3 and Jagged-2 expressions promotes the vigorous proliferation of bile duct epithelial cells [77]. The γ-secretase inhibitor FLI-06 to inhibit Notch signaling diminishes the mitogen levels of HGF and EGF, significantly impair the liver's proliferative ability, and emphasize the role of Notch in liver regeneration [78]. Additionally, Notch signaling attenuates the inflammatory response elicited by TNF-α, IL-1, and IL-6 from KCs. Jagged1-mediated myeloid Notch1 pathway attenuates liver ischemia/reperfusion injury, modulating macrophage/neutrophil trafficking and proinflammatory mediator expression [79]. However, during later stages of liver regeneration, shear stress-induced LSECs senescence inhibits liver regeneration via activating endothelial Notch signaling [80], demonstrating the dual role of Notch in liver regeneration.

Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway is renowned for its pivotal role in liver growth, development, and regeneration, orchestrating cell proliferation, cell-cell adhesion, and tissue integrity.

Canonical Wnt/β-catenin signaling

In the absence of Wnt signaling, β-catenin forms a degradation complex with Axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3β (GSK3β), and casein kinase 1α (CK1α), causing β-catenin phosphorylation and its cytoplasmic retention [81]. Upon Wnt ligand binding to Frizzled (FZD) and co-receptor LRP5/6, intracellular Disheveled (DVL) activation prevents β-catenin phosphorylation, leading toits accumulation in the cytoplasm [82, 83]. Subsequent nuclear translocation of β-catenin initiates downstream target gene transcription.

Wnt/β-catenin signaling not only governs liver development but also crucially exerts critical influence liver regeneration [84, 85]. Following partial hepatectomy, macrophage-derived Wnt ligands activate the canonical pathway.Rodent studies post-PH observed a rapid 2.5-fold increase in β-catenin levels, followed by transient phosphorylation and subsequent downregulation [86]. However, during the proliferation phase, β-catenin reactivation triggers nuclear translocation and activation of downstream target genes, including Cyclin D1, a key regulator of the G1/S cell cycle transition. Elevated Cyclin D1 expression post-PH correlates with increased S-phase hepatocytes, with β-catenin overexpression enhancing liver regeneration [86–88]. Furthermore, Wnt/β-catenin signaling regulates other cell cycle proteins; hepatocyte-specific conditional Ctnnb1 knockout delays liver regeneration, associated with decreased Cyclin A and E expression [89, 90].

Non-canonical Wnt signaling

Certain Wnt ligands activate pathways independent of β-catenin, collectively referred to as non-canonical Wnt signaling. In this pathway, Wnt interacts solely with the FZD receptor complex subunit, operating independently of LRP5/6. Non-canonical Wnt signaling diverges into two principal branches: (1) the Wnt/Ca^{2+} pathway, acting through Ca^{2+} -dependent kinases, calmodulin, and the transcription factor NF-AT; and (2) the planar cell polarity (PCP) pathway, in which Wnt ligands bind Frizzled–Ror2–DVL complexes to activate either RhoA–ROCK or Rac–JNK cascades, thereby regulating cell polarity and migration [91].

Recent studies have elucidated the involvement of the noncanonical Wnt pathway in liver regeneration. Notably, Wnt5a has emerged as a prototypical ligand in this context. Binding of Wnt5a to Frizzled-2 and Ror2 activates either the Wnt/Ca^{2+} pathway or Rac signal transduction [92]. Early studies demonstrated that Wnt5a inhibits canonical Wnt/β-catenin signaling by promoting β-catenin degradation [93]. Given β-catenin's pivotal role as a pro-proliferative signaling factor in liver regeneration, the negative regulation of β-catenin by Wnt5a may contribute to the termination of liver regeneration. In a recent study by Jing Yang et al. demonstratedthat Wnt5a suppressed canonical Wnt/β-catenin signaling in cultured primary hepatocytes and significantly impeded the proliferation of HepG2 hepatocytes [94]. Intriguingly, the expression levels of Wnt5a and Frizzled-2 exhibited a marked increase at 24 hours post-partial hepatectomy, suggesting the initiation of termination mechanisms at an early stage [94]. Consequently, liver regeneration appears to be tightly regulated, transitioning from positive to negative regulation to ensure its proper initiation and cessation.

Hippo signaling

The Hippo signaling pathway, an evolutionarily conserved regulatory cascade, controls organ size by modulating cell proliferation, apoptosis, as well as stem cell self-renewal. At its core, the Hippo pathway comprises a kinase cascade involving mammalian Ste20-like kinases 1/2 (Mst1/2) and Salvador 1 (SAV1), which phosphorylate and activate large tumor suppressor 1/2 (LATS1/2) complex. Subsequently, LATS1/2 kinases phosphorylate and inhibit the transcriptional co-activators Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ), major downstream effectors of the Hippo pathway [95, 96]. Whendephosphorylation, YAP/TAZ translocate from the cytoplasm to the nucleus, where they co-activate transcription factors such as transcriptional enhancer factor domain family member (TEAD) 1–4, regulating genes involved in hepatocyte growth, proliferation, and dedifferentiation [97].

During the early phases of liver regeneration, the Hippo pathway activity is suppressed, resulting in elevated YAP and TAZ activation. Studies have demonstrated significant upregulation of YAP protein expression within 3 days post-partial hepatectomy compared to resting liver tissue. Subsequent YAP interacts with TEAD to foster liver regeneration [98, 99]. Deletion of YAP in hepatocytes markedly inhibits liver regeneration following partial hepatectomy [100]. Additionally, TAZ, another downstream effector, promotes liver regeneration by stimulating IL-6-induced hepatocyte proliferation and inhibiting cell death post-injury. The loss of both YAP and TAZ results in a delay in liver regeneration [101]. Following the completion of liver regeneration, the Hippo pathway is reactivated, and levels of active core Hippo kinase Mst1/2 and inactive phosphorylated YAP return to quiescent liver tissue levels.

TGF-β signaling

The inhibitory role of TGF-β in liver regeneration is well established.it transiently suppresses early hepatocyte proliferation responses. Recent studies suggest that the transient inhibition induced by TGF-β early in proliferation may modulate macrophage activation status, affecting the inflammatory response crucial for early liver regeneration coordination [102]. Subsequently, TGF-β expression markedlyincreases in the later stages, contributing to liver regeneration termination [103]. Inhibition of TGF-βR1 or TGF-βR2 signaling prolongs hepatocyte proliferation and enhances liver regeneration after acute injury [102, 104]. Additionally, TGF-β/Smad pathway inhibitors, SnoN and Ski, are upregulated during liver regeneration, promoting regeneration by interacting with Smad proteins. Notably, inhibitory complexes decrease significantly post-liver mass restitution, potentially contributing to TGF-β/Smad pathway inhibition in hepatocytes [105]. Conversely, Ahnak, another TGF-β signaling inhibitor, exerts opposing effects on liver regeneration [103]. These findings underscore the negative regulatory role of TGF-β/Smad in liver regeneration. Intriguingly, intact TGF-β-mediated signaling may not be essential for liver regeneration inhibition, as compensatory activin A signaling may augment [106].

Crosstalk between signal pathways

As discussed above, liver regeneration involves many signaling pathways, and there will be cross-talk between them. This intricate interplay further increases the complexity of regulatory network. There is strong evidence that YAP, a key effector of the Hippo pathway, interacts with β-catenin signaling to promote hepatocyte proliferation during regeneration. YAP activation upregulatesWnt target genes, while β-catenin nuclear translocation is enhanced when Hippo signaling is suppressed [107]. Notch plays a dual role by controlling biliary versus hepatocyte lineage specification and interacting with Wnt/YAP pathways. Activation of Notch suppresses hepatocyte proliferation while promoting ductal reactions, especially in chronic injury [108]. EGFR signaling is activated early during regeneration and promotes hepatocyte entry into the cell cycle. This pathway can synergize with Wnt/β-catenin signaling by enhancing β-catenin stability via GSK-3β inhibition [109]. TGF-β signaling, generally inhibitory to proliferation, acts as a braking mechanism in later phases of regeneration. It can antagonize Wnt and YAP activity, contributing to regeneration termination and fibrosis prevention. Crosstalk with Hippo/YAP has been observed in the context of tissue remodeling [110]. The PI3K/AKT/mTOR axis is central to hepatocyte survival and metabolism. It interacts positively with EGFR signaling and is also modulated by insulin and cytokine signals during regeneration [5]. The JAK/STAT3 pathway, activated primarily by IL-6 and related cytokines, plays an early and essential role in liver regeneration. STAT3 activation promotes expression of cyclins and anti-apoptotic genes. Importantly, this pathway crosstalk with EGFR/PI3K signaling by inducing HGF and TGF-α, creating a feed-forward loop [111]. Following liver injury, Kupffer cells and infiltrating immune cells release TNF-α and IL-6, activating NF-κB in hepatocytes. NF-κB then promotes survival by inducing anti-apoptotic genes and synergizing with JAK/STAT3, mTOR, and Wnt signaling [112]. The Notch and Hedgehog pathways interact to control the fate of key cell types involved in adult liver repair by modulating epithelial-to-mesenchymal-like/mesenchymal-to epithelial-like transitions [113]. Liver regeneration is a model of signal integration, not simple sequential activation. Crosstalk between mitogenic, metabolic, anti-apoptotic, and inflammatory signals ensure robust, adaptive regeneration while preventing

overgrowth and tumorigenesis. A comprehensive understanding of these signaling networks not only provides insight into liver physiology but also reveals promising therapeutic targets for chronic liver injury, fibrosis, and hepatocarcinogenesis.

Liver microenvironment

In the last part of the chapter on the source of liver regeneration cells, we briefly introduced some immune cells and other types of cells, other than liver parenchymal cells and LPCs. These cells are not the main source cells of liver regeneration but important microenvironment regulating cells, and they are also an important part of the liver regeneration mechanism. The immune or metabolic microenvironment of liver is actually crucial for liver regeneration and is also the latest research hotspot. Therefore, we have summarized the research and mechanisms in this part.

Immune microenvironment

Immune factors are involved throughout all phases of liver regeneration. As illustrated in the above mechanism, classic IL-6 and TNF family factors play an important role in the initiation, proliferation and termination stages of liver regeneration by affecting various signaling pathways. Beyondthese classic immune factors, several newly identified immune-liver regeneration crosstalk factors that deserve attention. A study published in Immunity recently demonstrated that the ACh produced by a hepatic subset of ChAT+ B cells is a key factor in liver regeneration. These lymphocytes mediate bi-axial regulation that reduces IFNγ production by CD8+ T cells but stimulates IL-6 synthesis by Kupffer cells, with both effects on promoting hepatocyte survival and proliferation [114]. Another interesting research published in Nature recently revealed Glutamate metabolically reprograms bone-marrow-derived macrophages in liver to stabilize HIF1α, which transcriptionally activates WNT3 to promote YAP1-dependent hepatocyte proliferation, boosting liver regeneration [115]. Liu et al. revealed that environmental eustress promotes liver regeneration via the sympathetic regulation of type 1 innate lymphoid cells to increase IL-22 in mice [116].

Metabolic microenvironment

Alterations in the hepatic microenvironment—including changes in blood flow, oxygen tension, and disturbances in glucose and lipid metabolism—form a regulatory network that profoundly influences the regenerative process.

Among them, the microenvironment of lipid metabolism is a hot topic of current research. The lipid accumulation during liver regeneration peaks in 12–24 hours after hepatectomy, reaching as high as three to four times in triglyceride content, and gradually decreases to the basal level at 72 h post-surgery [117]. This phenomenon has been discovered for more than 50 years, but still very interesting and worthy of attention. One of the research directions is that the microenvironment of lipid metabolism is closely linked to the energy issues of liver regeneration. However, at present, the detailed relationship between its specific metabolic microenvironment changes with liver regeneration still needs further exploration. Recently, Llorens-Giralt et al. provided a genome-wide atlas of enhancer-gene interactions during liver regeneration. Their results indicate that hepatic regeneration involves the repression of enhancers regulating liver-specific metabolic functions, particularly those involved in lipid metabolism [118]. L-carnitine, an endogenous cofactor in fatty acid metabolism, promotes liver regeneration by enhancing lipid catabolism following hepatectomy [119]. Prostaglandin PGE2 is a lipid signaling molecule. The enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH), which acts in vivo as a negative regulator of prostaglandin levels and activity can negatively regulate liver regeneration. Inhibitor of 15-PGDH (SW033291) increases prostaglandin PGE2 can promote liver regeneration [120]. Chen et al. through in vivo CRISPR screening, identify mesoderm induction early response 1 (MIER1) as a key epigenetic regulator that bridges the acute lipid accumulation and cell cycle gene expression during liver regeneration in male animals [121].

At the same time, the immune and metabolic microenvironments regulating factors also interact, such as Deng et al. revealed a LIFR–STAT3–CXCL1–CXCR2 axis and a LIFR–STAT3–cholesterol–ERRα–hepatocyte growth factor axis that form bidirectional hepatocyte–neutrophil cross-talk to repair and regenerate the liver [122]. This is also the case with the previously mentioned glutamate, recently published in Nature, regulating macrophage reprogramming to promote liver regeneration [115].

Liver fibrosis

Hepatic fibrosis is the healing response that occurs as a result of acute or chronic liver damage [123]. It is a repair process, dynamic and potentially reversible, that is associated with liver regeneration [8, 124]. Damage-induced matrix deposition is a transient phenomenon of the regenerative response, and successful healing entails its eventual removal [10]. Liver fibrosis not only affects the function of the liver itself, but also brings various complications. For example, spontaneous bacterial peritonitis (SBP) is a serious complication of liver cirrhosis with a high recurrence rate and a marked increase in mortality [125]. HSCs have a central pathogenetic role in the development of liver fibrosis [126]. But recent research published in Nature revealed that when precisely eliminate HSCs in mice, an unexpected chain reaction occurred:

the liver volume shrank by 15%. This study suggests existing anti-fibrotic treatments may inadvertently destroy the liver's key system for repairing itself [127]. At the same time, there has been a major breakthrough in clinical application recently. Semaglutide recently achieved the endpoint of "disappearance of fatty liver and inflammation without worsening fibrosis, and promotion of liver cell regeneration" in a Phase III clinical trial, with approximately 62.9% of patients receiving semaglutide achieving this endpoint, compared to approximately 34.3% of patients receiving placebo [128]. Semaglutide received accelerated approval in August 2025 for MASH with fibrosis, becoming the second FDA-approved treatment after resmetirom.

Liver fibrosis and regeneration represent two opposing yet interdependent processes that jointly determine hepatic outcome following injury. Under physiological conditions, liver regeneration restores tissue integrity and function through well-orchestrated activation of hepatocytes, liver progenitor cells, and stromal networks. However, persistent injury or dysregulated repair shifts this balance toward fibrogenesis, characterized by excessive extracellular matrix deposition and activation of hepatic stellate cells. Increasing evidence suggests that the molecular networks driving regeneration—such as TGF-β/Smad [129], Wnt/β-catenin [91], Hippo/YAP [12], and Hedgehog [65] pathways—also participate in fibrotic remodeling, with their temporal and spatial regulation determining whether recovery or scarring predominates. Transient activation of these pathways promotes hepatocyte proliferation and matrix remodeling, whereas chronic or uncontrolled activation leads to pathological fibrosis. Thus, fibrosis can be viewed as a maladaptive form of regeneration. Emerging research indicates that restoring regenerative microenvironments—via metabolic reprogramming [8], immune modulation [124], or matrix softening [30]—can revert fibrosis and re-engage endogenous repair mechanisms. Understanding the dynamic crosstalk between regenerative and fibrogenic signaling provides a conceptual framework for developing antifibrotic therapies that not only halt progression but also re-activate functional regeneration, offering new hope for patients with chronic liver disease.

Clinical treatment for liver regeneration

Building upon advances in basic research on the mechanisms of liver regeneration, significant progress has been achieved in translating these findings into clinical applications. Some promising progress has been made in clinical treatment, including stem cell transplantation, molecular targeted therapy, bioartificial liver support systems and other novel methods. However, due to the complexity of liver regeneration, further research is needed to clinically address key clinical barriers in liver regeneration. Various treatment methods that have achieved certain breakthroughs have their own advantages and limitations. Clinical methods for liver regeneration are generally still limited (Fig. 3).

Stem cell transplantation related treatments

Stem cell transplantation offers a promising avenue for liver regeneration by replacing damaged liver cells or stimulating the liver's own regenerative capacity. Different types of stem cells, including mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), LPCs, and even hematopoietic stem/progenitor cells (HSPCs), have shown potential in promoting liver repair and regeneration in basic and clinical research.

MSCs

Among them, MSCs have attracted considerable attention for their capacity to promote liver regeneration.After partial hepatectomy, the transplanted MSCs demonstrate an affinity for periportal localization and improve metabolism by reducing fat accumulation in hepatocytes, and promote liver regeneration in the mouse model [130, 131]. In the experimental model of liver failure, MSCs transplantation improves acute liver failure (ALF) by activating the β-catenin pathway, enhancing liver glycogen reserve and promoting hepatocyte proliferation.

In clinical evaluations, MSCs therapy is similar to rituximab in reducing the incidence of acute rejection after liver transplantation in patients with severe liver failure. Moreover, MSC therapy effectively reduces postoperative infection ratesand alleviating biliary complications [132]. Furthermore, among patients with ischemic biliary tract diseases after liver transplantation, the two-year survival rate of transplanted human umbilical cord blood MSCs is relatively high, which indicates the clinical practicability of MSCs treatment [133]. In addition, MSCs and their secreted derivatives, such as extracellular vesicles and conditioned media, effectively attenuate hepatic injury and stimulate regeneration [134]. Actually, there are still obstacles to translating MSCs-based treatments into clinical outcomes, including considerations of immune compatibility, stability, heterogeneity and differentiation potential.

ESCs

ESCs, derived from human or other mammalian embryos, are a type of stem cell with the potential to differentiate [135]. Based on this characteristic, they are a potential tool for treating liver damage. Kuai et al. induced rhesus monkey ESCs towards hepatocyte-like cells (HLCs) by a four-step differentiation process. The differentiated cells displayed morphological features, gene expression patterns and metabolic activities

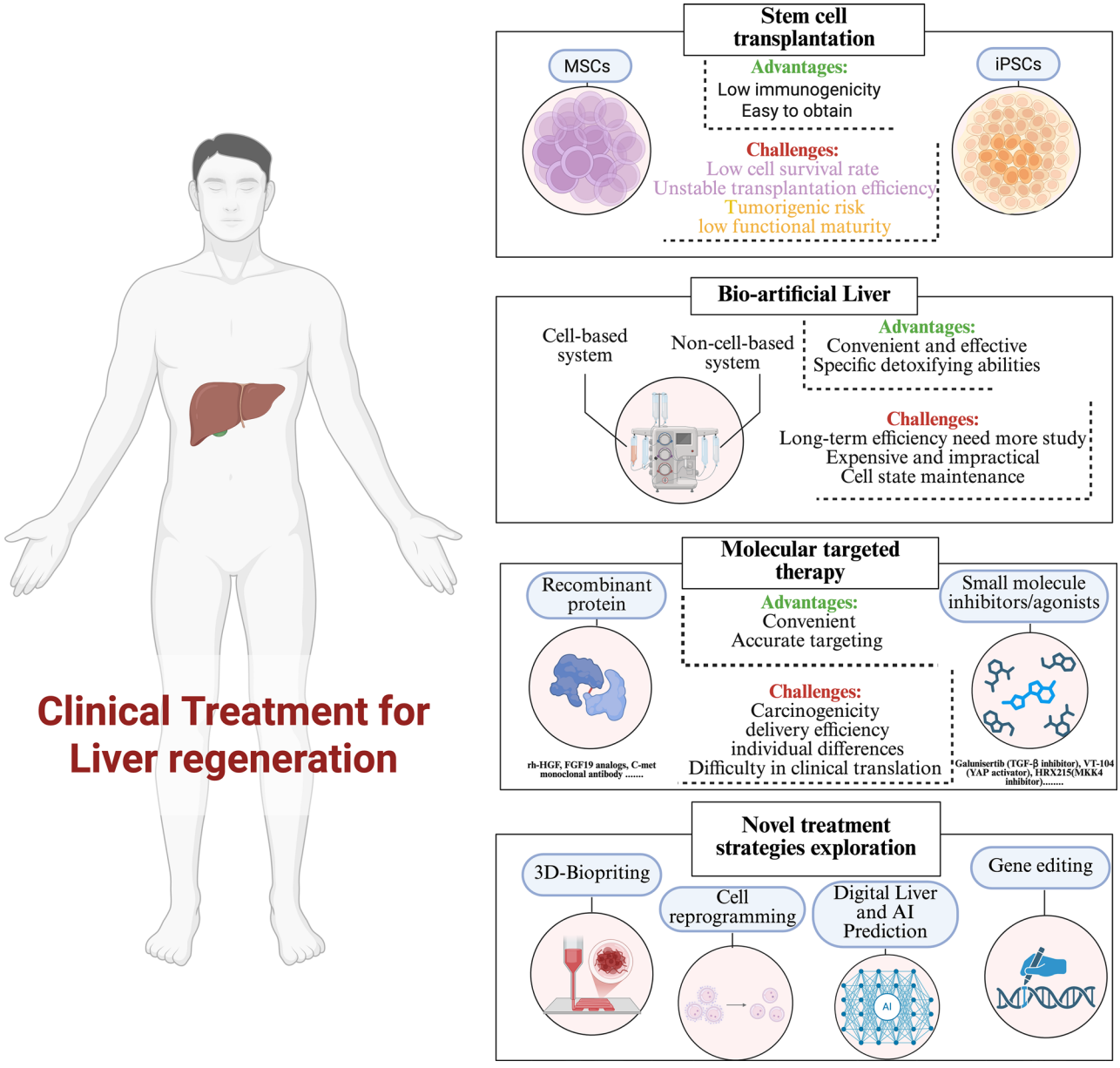


Fig. 3 How to effectively enhance the function of liver regeneration after clinical liver resection is extremely important for the patient's condition. Currently, some results have been achieved in stem cell transplantation and drugs, bio-artificial liver, which is beneficial for clinical application. However, these treatments have their own advantages and limitations. In the future, with the development of technology, methods such as cell reprogramming, 3D bioprinting, and AI assistance will also achieve some preliminary results in liver regeneration treatment, which may provide everyone with more diversified treatment options in the future

characteristic of hepatocytes [136]. Currently, the safety and function assessment of HLCs are generally in mice. Tolosa et al. evaluated the ability of a European human ESC line (VAL9) to generate hepatocytes after transplantation into mice with acetaminophen-induced acute liver failure [137]. Dong et al. reported that HLCs derived from human ESCs benefit the recovery of injured liver tissues in mice, through cell replacement and delivering trophic factors that support liver regeneration [138]. However, Clinical applications of ESCs evoke ethical concerns regarding their origin from human embryos and hepatocarcinogenesis in vivo [139, 140]. Notably, a recent phase I clinical trial involving nine patients with cirrhosis demonstrated that human amniotic epithelial cell (hAEC) transplantation was safe and well tolerated [141].

iPSCs

The advent of iPSCs represents a pioneering milestone in regenerative medicine. Takahashi and Yamanaka first

reprogrammed mice fibroblasts into iPSCs by introducing four key transcription factors: octamer-binding transcription factor 3/4 (Oct3/4), sex-determining region Y-box 2 (SRY-Sox2), Kruppel-like factor 4 (Klf4) and cellular myelocytomatosis (c-Myc), collectively referred to as OSKM [142]. iPSCs have attracted considerable attention in the fields of liver diseases and regeneration. iPSCs from mice can differentiate into functional hepatocyte-like cells and exhibit hepatocyte-specific functions, such as albumin secretion, glycogen storage and cytochrome activity induction [143]. Furthermore, there have been innovative strategies for utilizing the regenerative potential of iPSCs in preclinical models of liver injury. In a mouse model of acute liver failure, iPSCs with continuous HGF release delivered by carboxymethyl hexamethyl chitosan hydrogel (CHC) have been shown to alleviate necrotic liver regions [144]. Similarly, human induced pluripotent stem cell-derived hepatocyte-like cell (iPS-HLC) sheets are affixed to the liver surface of mice afflicted with liver injury by cell sheet engineering techniques, successfully reducing the fatal acute liver injury caused by CCl_4 infusion [145]. Concurrently, investigations have elucidated that human iPSCs lines have the ability to differentiate into cells with hepatocyte characteristics [146]. Despite these strides, challenges persist in the clinical application of iPSCs-based therapies. For example, the tumorigenic potential of c-Myc and the limitations of complex liver reconstruction are important issues that need to be addressed. In this context, the cultivation of liver organoids has emerged as a promising avenue for investigating disease models and facilitating liver regeneration. By culturing stem cells in a 3D environment, liver organoids recapitulate the differentiation potential of cells from all three germ layers, offering versatile platforms for drug screening and potentially serving as a novel approach for liver transplantation therapy.

LPCs

LPCs can differentiate into mature liver cells or bile duct cells during liver injury, thereby promoting tissue repair in liver regeneration, demonstrating the therapeutic potential of LPCs in the field of regenerative medicine. When ICAM-1–enriched LPC clones were transplanted into nude mice subjected to 70% partial hepatectomy, the donor cells successfully engrafted within the hepatic parenchyma and expressed key hepatocyte markers, including hepatocyte nuclear factor 4α (HNF4α), CCAAT/enhancer-binding protein α (C/EBPα), and carbamoyl phosphate synthase I (CPS1).This result demonstrates the potential of LPCs for generating mature hepatocytes in vitro, bringing hope to regenerative therapy [147]. Furthermore, transplantation of LPCs into the livers of Mdm2-deficient mice significantly restored hepatic parenchyma, regenerated hepatocytes and biliary epithelium, and demonstrated dual-lineage differentiation, leading to marked structural and functional recovery of the injured liver [148]. Clinical studies have also revealed the therapeutic effect of LPCs transplantation. Continuous transplantation of hepatocytes and LPCs into patients with ornithine carbamate transferase (OTC) deficiency revealed that hepatocyte transplantation failed to cure the patients, but short-term clinical improvement occurred in the patients after LPCs transplantation, indicating the therapeutic potential of LPCs in the clinical setting [149]. Overall, these findings confirm the potential and prospects of LPCs transplantation as a treatment for liver diseases and liver regeneration. However, clinical trials are still lacking at present, and further exploration and large-scale research are needed to comprehensively evaluate its efficacy and safety in diverse clinical contexts.

HSPCs

HSPCs originate from the embryonic liver and mainly exist in adult bone marrow. Bone marrow transplantation studies on mice lacking of fumarate acetoacetate hydrolase (FAH) revealed the liver and hematopoietic reconstitution potential of high-purity HSPCs, demonstrating their ability to differentiate into functional hepatocytes in vivo [150]. Furthermore, the transplantation of hematopoietic stem cells into mouse liver injury models showed significant plasticity, and HSPCs exhibited hepatocyte characteristics resistant to injury escalation [151]. CD39 has the ability to mobilize HSPCs, thereby promoting liver regeneration after partial hepatectomy in mouse models and humans [152]. It is notable that routine autopsy analyses of liver tissues from hematopoietic cell transplantation recipients and donors have revealed evidence of hepatocyte remodeling mediated by hematopoietic stem cells, which is attributed to the fusion and proliferation between bone marrow monocytes and host hepatocytes. However, the potential mechanism of liver regeneration mediated by HSPCs and its clinical applications deserve further rigorous testing. Harnessing the regenerative potential of HSPCs may thus represent a promising future strategy for liver tissue repair.

Despite rapid advances in regenerative biology, the clinical translation of liver regeneration strategies particularly involving iPSC-derived hepatocyte sheets and LPCs transplantation remains limited. Although manipulation of iPSCs holds substantial promise for regenerative medicine, current clinical trials of stem cell–based transplantation have yielded unsatisfactory outcomes [153]. Stem cell transplantation will encounter safety issues such as angiogenesis, carcinogenesis, and immune disorders and others challenges include defining optimal cell sources, expansion protocols, and delivery routes, as well as understanding long-term fate and host responses. As of now, translation to human trials has been slow, with

only a handful of early-phase trials (e.g., Japan's CiRA and OrganTech collaborations) reaching the regulatory stage. No Phase III clinical trials have conclusively demonstrated therapeutic efficacy of either strategy in human patients, underscoring the urgent need for standardized clinical evaluation and long-term outcome monitoring. The immunogenicity of MSCs once believed immune-privileged has been increasingly recognized in allogeneic settings, potentially limiting repeated transplantation [154]. Factors added to induce differentiation of stem cells can also cause various problems. The hepatotoxicity of TGF-β inhibitors, while attractive for modulating fibrotic signaling, remains a critical safety concern due to their broad regulatory roles in homeostasis and regeneration [129]. Similarly, β-catenin pathway activation, commonly used to enhance hepatic differentiation, may inadvertently promote hepatoblastoma or HCC-like transformation if not precisely regulated [155]. Maximizing the translational potential of stem cell therapies for liver regeneration demands an integrated approach that balances efficacy, safety, and manufacturability. Advances in bioengineering, cell sorting, genomic editing, and clinical trial design will be key to overcoming current barriers and realizing the promise of regenerative liver medicine.

Molecular therapy

Translating mechanistic insights from basic research into clinical practice remains a major challenge. Numerous attempts have been made to develop pharmacological agents and biologics that enhance liver regeneration in response to injury or surgical resection. Although several compounds and recombinant proteins have shown robust efficacy in cell culture and animal models, their clinical performance has been far more complex. Here, we summarize emerging drugs with demonstrated or potential clinical utility for promoting hepatic regeneration in humans. HRX215 has recently emerged as one of the most promising pharmacological candidates for promoting liver regeneration. In 2013, Lars Zender's team published a paper in the journal Cell [156]. Through in vivo RNAi screening, they found that MKK4 is the main regulator of liver regeneration and that inhibiting MKK4 can significantly improve the regenerative capacity of hepatocytes. In addition, they established a company called HepaRegeniX, which is committed to developing MKK4 inhibitors for the treatment of liver diseases. In 2024, they reported the development and functional characterization of the first-in-class MKK4 small molecule inhibitor HRX215, demonstrating that the drug can prevent post-hepatectomy liver failure and enable pigs to survive in a liver resection model with a mortality rate of 85%. Moreover, data from a Phase I clinical trial involving 48 healthy volunteers supported the safety and tolerability of HRX215. These findings suggest that HRX215 may represent a viable treatment option for human patients with PHLF and post-transplant small liver syndrome [157].

Another noteworthy pharmacological agent is Resmetirom, a selective thyroid hormone receptor-β (THR-β) agonist, which in 2024 became the first FDA-approved therapy for patients with metabolic-associated steatohepatitis (MASH) and hepatic fibrosis. In a large phase III study involving 1,444 participants, patients received either 80 mg or 100 mg of Resmetirom, or a placebo, once daily for 52 weeks. In addition to improving fat metabolism, Resmetirom has been found to reduce inflammatory responses and fibrotic processes in the liver. This is important for preventing MASH from progressing to more serious liver diseases, such as cirrhosis and liver cancer. By reducing inflammation and inhibiting fibrosis, Resmetirom helps maintain the integrity and function of the liver structure [158]. Although the drug was not developed specifically for liver regeneration, thyroid hormones play a critical role in liver regeneration [159]. Therefore, it has great potential as an auxiliary drug for liver regeneration.

Based on the complex regulatory mechanism of liver regeneration, the effect of molecularly targeted drugs alone may be weak to a certain extent. Therefore, in clinical advancement and application, many signaling pathway inhibitors and activators have not achieved good clinical results. However, we have also summarized various drugs currently under development that have achieved certain results in mouse or big animals' experiments. With further analysis of liver regeneration, perhaps these drugs will shine in the clinic after better optimization or combination.

Existing studies have found that the pathogenic bacterium Listeria monocytogenes can produce Internalin B (InlB) protein, which stimulates HGF by interacting with the HGF receptor (HGFR), thereby activating the HGFR-controlled signaling pathway and promoting hepatocyte proliferation [160]. Enhancing Wnt/β-catenin signaling has also been proven to be beneficial for liver regeneration. Wnt agonist compound can increase the expression of Cyclin D1 in rat liver transplantation donors and alleviate hepatocyte injury and liver injury induced by liver ischemia/reperfusion [161–163]. Furthermore, Morita et al. demonstrated that glycyrrhizin acid (GL), a traditional Chinese medicine, promotes liver differentiation through β-catenin Notch signaling [164]. Activation of the β-catenin pathway by thyroid hormone receptor β agonists also upregulates Cyclin D1 expression in mice undergoing partial hepatectomy [165]. Similarly, Niu et al. injected the Toll-like receptor-5 agonist CBLB502 into mice with liver injury induced by cisplatin chemotherapy and observed activation of the transcription factor NF-κB through the TLR5/MyD88 pathway, leading to liver

Table 1 Signal molecule related drugs

Signaling Pathway	Drug/Compound	Role in liver regeneration	Reference
MKK4	HRX215 (MKK4 inhibitor)	prevent post-hepatectomy liver failure	[157]
THR-β	Resmetirom (thyroid hormone receptor-β agonist)	reduce inflammatory and fibrotic processes	[158]
HGF/c-Met	InternalinB	promotes hepatocyte proliferation	[160]
Wnt/β-catenin	Modified pyrimidine compound (2-amino-4-[3,4-(methylenedioxy) benzylamino]-6-(3-methoxyphenyl) pyrimidine)	attenuates hepatic injury and apoptosis	[152]
	Triiodothyronine (T3)	promotes hepatocyte proliferation	[159]
	GC-1 (thyroid hormone receptor β agonist)	promotes hepatocyte proliferation	[159]
	Glycyrrhizin (GL)	promotes liver differentiation	[164]
TLR/Myd88	CBLB502 (Toll-like receptor-5 agonist)	protects the liver	[166]
STAT3	Pioglitazone	promotes hepatocyte proliferation	[168]
TGF-β	Galunisertib (TGFβR1 inhibitor)	promotes hepatocyte proliferation	[154]
Hippo/YAP	XMU-MP-1 (MST1/2 inhibitor)	promotes hepatic repair and regeneration	[170]
	TRULI (Lats kinase inhibitor)	facilitates liver regeneration	[171]
	TCPOBOP (CAR agonist)	induces hepatomegaly and liver regeneration	[172]
MAPK/ERK	71D6 (MET agonistic antibody)	promotes liver proliferation	[167]
HDAC	Valproic Acid	induce hepatocyte cycle arrest	[173]
	Phenylbutyrate	Inhibit protein synthesis	[174]
PI3K/Akt/mTOR	β-glucoceramide	inhibits the expression of early adipogenic genes	[175]

protection [166]. The mesenchymal-epithelial transition factor (MET) agonistic antibody 71D6 promotes liver proliferation after hepatectomy by activating the ERK signaling pathway [167]. Pioglitazone, a thiazolidinedione derivative, ameliorates liver regeneration failure in obese, diabetic mice and prevents abnormal increases in phosphorylated signal transducers and STAT3 and SOCS3 mRNA levels in the liver, thereby promoting Cyclin D1 expression and hepatocyte proliferation [168]. Moreover, by reducing the inhibitory effect of TGF-β and promoting the proliferation of hepatocytes in the resected liver, some progress has also been made in the research. Galunisterib, as a specific TGF-βR1 inhibitor, can increase the levels of cyclin E1 and CDK2 in mice after partial hepatectomy, thereby exerting the effect of promoting hepatocyte proliferation [129]. Silymarin modulating influence of TNF-α cytokine genetic polymorphism can promote liver regeneration [169]. Another approach is to promote liver regeneration by inhibiting the Hippo signaling pathway. It has been confirmed that inhibiting Mst1/2 can promote hepatocyte proliferation and liver regeneration in mice after partial hepatectomy [170]. TRULI, an inhibitor of Lats kinase, which is a small molecule drug can activate the Yap target gene in the liver and promote liver regeneration [171]. The constitutive androstane receptor (CAR) agonist TCPOBOP induces hepatomegaly and liver regeneration by promoting YAP translocation and interacting with the YAP signaling pathway [172].

More deeply, there are also some drugs that have inhibitory effects on liver regeneration. The research on these drugs also helps reveal the mechanism of liver regeneration from another aspect. The antiepileptic drug valproic acid (VPA) has hepatotoxic side effects. It can inhibit liver regeneration and induce hepatocyte cycle arrest. The speculated mechanism is related to its inhibition of histone deacetylase (HDAC) and its target genes [173]. Influencing liver regeneration by regulating metabolic pathways is also the pharmacological action pathway of many drugs. Phenylbutyrate is clinically used to treat urea cycle disorders and maintain normal liver metabolism. However, it has the opposite effect on liver regeneration. Benzoate treatment of mice after partial hepatectomy, shows the specific activity of liver DNA and the protein synthesis rate decreased, with inhibited liver regeneration [174]. β-glucoceramide significantly inhibits the expression of early adipo-genic genes during liver regeneration in mice and is considered a potential target for the treatment of liver diseases [175]. Based on these findings, drugs developed from promoting proliferation-related signaling pathways and metabolic pathways to provide the energy required for hepatocyte proliferation can also be regarded as a promising liver regeneration strategy (Table 1). Therefore, it is necessary to conduct further research and exploration on these mechanisms in order to develop effective therapeutic drugs.

Bio-artificial liver (BAL)

Tissue engineering is a particularly promising clinical treatment method for liver regeneration. A bio-artificial liver is a device or system designed to support or replace the function of a failing liver, particularly in cases of acute liver failure, cirrhosis, or liver disease. BAL can serve as a bridge while waiting for a liver transplant or, in some cases, promote regeneration of the liver itself [176]. BAL

devices powered by new technologies have been modified to increase cell numbers and improve detoxification in large animal model and patients with ALF. The device developed by Chen et al. named spheroid reservoir bio-artificial liver (SRBAL) demonstrated powerful performance in survival improvement and ammonia detoxification in medical and surgical ALF pigs with potential benefits in stimulating hepatocyte regeneration [177]. Li et al. developed an extracorporeal liver support device called air-liquid interactive bioartificial liver (Ali-BAL) that exhibited a powerful capacity to support liver function by detoxification of ammonia, promotion of native liver regeneration, and suppression of inflammation, leading to marked recovery and survival of pigs with ALF [178]. Wang et al. developed human-induced hepatocytes-BAL (hiHep-BAL) showed toxin transparency and promotion of liver regeneration in preclinical experiments in pigs, and after adjuvant treatment with hiHep-BAL in in a small sample of seven patients with liver damage, the patients' livers showed better regenerative activity [179]. But, BAL (including biological and non-biological types) have some inherent defects and complications. Non-biological artificial livers mainly suffer from coagulation problems, hypotension, and equipment-related problems. Bioartificial livers face challenges such as cell stability and limited material exchange capabilities. A longer period of research is needed in the future to make it truly serve clinical purposes.

Current clinical trials on liver regeneration

A growing number of translational studies are advancing the concept of liver regeneration from experimental biology into human clinical application. These efforts encompass stem-cell–based therapies, bio-artificial support systems, molecular activators, and metabolic modulators that either directly stimulate hepatocyte proliferation or restore a regenerative microenvironment.

Among the cell-based approaches, umbilical cord–derived mesenchymal stem cell (MSC) infusion (NCT05985863, China) has entered a multicenter Phase II randomized controlled trial for acute-on-chronic liver failure (ACLF), aiming to verify the observed benefits in MELD score reduction and short-term survival. Similarly, autologous MSC combined with $CD34^+$ hematopoietic stem cell (HSC) infusion (NCT04243681, India) has completed a Phase I/II study demonstrating procedural safety after hepatic-artery infusion in decompensated cirrhosis, though efficacy still requires validation in larger cohorts.

To bridge critical liver failure and support endogenous regeneration, the HepaCure bio-artificial liver device (NCT05989958, China) integrates hiHep cell-based bioreactors with double plasma molecular adsorption (DPMAS). This Phase I/II trial evaluates safety, tolerability, and regenerative outcomes in ACLF, representing a hybrid strategy between mechanical detoxification and biologic restoration. A conceptually distinct but equally regenerative strategy is tested by LyGenesis, which uses allogeneic hepatocyte transplantation into lymph nodes (NCT04496479, USA). The ongoing Phase IIa dose-escalation trial has dosed its first patient, and interim data suggest the feasibility of ectopic "mini-liver" formation within lymphatic niches.

At the molecular level, HRX-215, a selective MKK4 inhibitor (EudraCT 2021-000193-28, Europe), has completed its first-in-human Phase I trial, showing excellent safety and pharmacokinetics, and has progressed to Phase Ib/IIa studies for accelerating post-hepatectomy liver regeneration. In metabolic-associated liver disease, Resmetirom, a thyroid hormone receptor-β (THR-β) agonist (NCT04197479, MAESTRO-NAFLD-1), became in March 2024 the first FDA-approved therapy for non-cirrhotic MASH with F2–F3 fibrosis, having achieved histologic resolution of steatohepatitis and fibrosis improvement at 52 weeks. A parallel avenue is explored by Semaglutide, a GLP-1 receptor agonist (NCT04822181, Phase III), which demonstrated significant steatohepatitis resolution without fibrosis worsening and marked weight loss in interim analyses; regulatory review remains ongoing.

Collectively, these trials delineate a continuum of regenerative medicine—from cellular and bio-engineered to pharmacologic and metabolic modalities—marking a transition from supportive care toward true restoration of hepatic architecture and function in human disease

Novel treatment therapies exploration

As artificial intelligence (AI) technology goes from concept to explosion, in this era we may be able to examine the nature of biology from another perspective. Especially in recent years, AI technology has been increasingly integrated into biological research. Generative AI methods can even create designs, such as small-molecule drugs and proteins, by analyzing diverse data modalities, including images and sequences [180]. Digital cells, digital liver, digital human body, if there is enough information, computer calculations will be able to simulate the entire liver or other organs in the future [181]. With the assistance of AI, the cost of trial and error is drastically reduced. We may also be able to understand liver regeneration more systematically and the exploration of treatment methods will also develop rapidly. Of course, AI will also involve many issues such as ethics and safety.

The large-scale production of human derived liver cells is rewriting the history of liver disease treatment. With the advancement of technology iteration and industrialization, patients with cirrhosis and liver failure can regain new life and reverse fibrosis by injecting humanized liver

cells with differentiation function. 3D bioprinting is also showing great promise in the field of liver regeneration and disease modeling. It involves using 3D printing technology to create functional liver tissue, which can be used for drug screening, disease modeling, and potentially, as a substitute for liver transplants [115, 182]. At the same time, the application of nanomaterials combined with 3D bioprinting in liver regeneration mainly focuses on constructing biological scaffolds that are closer to the natural liver structure, promoting the growth and differentiation of hepatocytes, and achieving liver function recovery [183]. Nanomaterials can be specifically targeted to liver tissue or hepatocytes by surface modification and functionalization, increasing the delivery of medications and reducing their adverse effects that can be a potential tool for promote liver regeneration [184]. The simultaneous application of regenerative medicine and nanotechnology can be an ideal approach in tissue regeneration [185]. As we reviewed previously, the molecular changes and immune and other microenvironmental changes are actually due to various types of cells. Therefore, cell reprogramming in the body is an ideal method to permanently change gene expression. With the development and advancement of gene editing technologies such as Crispr/Cas9, it may also play an important role in the field of liver regeneration as a cell reprogramming tool in the future. Recently, Zhang et al. utilized CRISPR-Cas9-mediated gene correction of patient-derived hepatocytes for treatment of inherited liver diseases [186]. This strategy holds promise for the treatment of human liver diseases. Although new technical means provide good directions for future liver regeneration and related liver disease treatment, they are also faced with ethical, safety and other systemic issues.

Future perspectives

Looking ahead, future research on liver regeneration will increasingly emphasize the integration of multi-omics, precision intervention, and translational validation. With the rapid development of single-cell sequencing, spatial transcriptomics, and proteomics, it is now possible to construct high-resolution cellular maps of the regenerating liver and identify novel niche-dependent interactions among hepatocytes, stellate cells, and immune cells. These approaches will help to uncover the hierarchical control of regeneration and to clarify why regenerative potential declines under pathological conditions such as fibrosis or chronic inflammation. Moreover, combining multi-omics data with computational and AI-driven modeling will allow the prediction of regenerative outcomes and the identification of key regulatory nodes that could be targeted therapeutically.

On the clinical side, the translation of basic discoveries into effective therapies remains a major challenge.

Future directions should focus on the precise and safe modulation of regeneration-related pathways—such as IL-6/STAT3, Wnt/β-catenin, Hippo/YAP, and TGF-β/Smad—through spatiotemporal gene editing, nanocarrier-based delivery systems, and pathway-specific small molecules. Stem cell and organoid technologies are expected to advance from preclinical validation toward standardized, patient-specific applications, aided by 3D bioprinting and biomaterial scaffolds that enhance cell engraftment and vascularization. In parallel, AI-assisted drug discovery and digital-twin modeling could shorten the translational gap between laboratory findings and clinical implementation. Establishing large-scale registries, multicenter clinical trials, and international ethical frameworks will be essential to ensure the safety, reproducibility, and accessibility of regenerative therapies. Collectively, these multidisciplinary strategies will transform liver regeneration research from descriptive biology into a predictive, controllable, and patient-tailored medical discipline, accelerating the development of curative interventions for acute and chronic liver diseases.

Conclusion

In this review we delve deeply into the regeneration mechanism of the liver and the clinical treatment. We emphasize the synergistic effects among different cell populations in the liver and their interactions for improving treatment methods. We elaborate on the complexity and importance of the main signaling pathways and microenvironments mechanism involved in liver regeneration. It is certain that liver regeneration is a complex process composed of signal networks and their mutual coordination. Therefore, we believe that there is no single factor that can completely prevent or promote liver regeneration. However, it must be recognized that the three traditional stages of liver regeneration are not absolutely isolated but relative and combined. Each stage interacts with each other and forms a complete coordination mechanism. Liver regeneration is a highly refined dynamic balance rather than a static process. Given the complexity of liver regeneration, informatics-based engineering approaches are essential. Future research should further integrate multi-omics data, such as transcriptomics, proteomics, and metabolomics. Single-cell sequencing and spatial transcriptomics technologies with higher resolution and coverage can be used to identify local cellular responses, comprehensively mapping the interplay between different signaling pathways. This will help identify potential targets for more precise regulation of liver regeneration, thereby synergistically improving overall liver function and regeneration.

Another concern is that liver regeneration is not a problem that can be characterized by a single static time point. It involves metabolic reprogramming,

epigenetic modifications, and the synergistic and antagonistic effects of immune function. Current research, such as using a single time point for autopsy after mouse hepatectomy [57, 119, 187], misses a significant amount of information. Therefore, there is an urgent need to develop advanced dynamic models that more accurately simulate the human or mammalian liver. Organ-on-a-chip, 3D bioprinting, and digital livers may be promising options, but they still require extensive data accumulation. Furthermore, effectively bridging the gap between scientific research and clinical application depends on translational research, which requires interdisciplinary collaboration across fields such as molecular biology, pharmacology, bioengineering, and clinical medicine. By developing specific drugs and improving drug delivery systems, future research aims to create new therapies suitable for widespread clinical application.

Despite remarkable advances in understanding the molecular and cellular basis of liver regeneration, translating these discoveries into clinical practice remains an ongoing challenge. The intricate interplay of immune, metabolic, vascular, and stem-cell–related mechanisms render liver regeneration a highly context-dependent process, complicating therapeutic manipulation. Findings derived from rodent models often fail to recapitulate the complex pathophysiology of human liver injury, where chronic inflammation, fibrosis, and metabolic dysregulation coexist. Moreover, interventions that activate pro-regenerative signaling pathways—such as Wnt/β-catenin, Hippo/YAP, or TGF-β inhibition—carry oncogenic or fibrogenic risks when applied long-term, underscoring the delicate balance between regeneration and malignant transformation. Stem-cell–based strategies, though promising, face issues of immune compatibility, differentiation stability, and tumorigenic potential, while pharmacological agents encounter metabolic clearance and microenvironmental heterogeneity that limit efficacy. In addition, the lack of robust translational models, standardized outcome metrics, and ethically feasible clinical trial designs further restricts the pace of clinical translation. Therefore, future progress will depend on integrative approaches that combine multi-omics profiling, systems biology, bioengineering, and precision pharmacology to establish safer, patient-tailored regenerative interventions. Such interdisciplinary strategies are crucial to bridging the gap between mechanistic insights and effective therapies for human liver regeneration.

Basic experiments have yielded numerous findings, yet their clinical application is indispensable for meaningful impact. Hence, we present a summary of clinically relevant cell transplantation methods and drugs, bioartifical liver, and potential therapeutic strategies. Nevertheless, clinical data and treatments for enhancing liver regeneration capacity remain scant. The journey from fundamental research to clinical application is protracted, underscoring the need for continued efforts to bridge this gap. The breakthrough in the field of liver regeneration relies on scientific innovation and the construction of a global ethical framework, ultimately achieving a leap from myth to reality for the "Prometheus liver".

Abbreviations

KCs	Kupffer cells
EGF	Epidermal growth factor
HGF	Hepatocyte growth factor
3D	Three-dimensional
HCs	Hepatocytes
NPCs	Nonparenchymal cells
LSECs	Liver sinusoidal endothelial cells
HSCs	Hepatic stellate cells
BECs	Biliary epithelial cells
LPCs	Liver progenitor cells
snRNA-seq	Single-nucleus RNA-sequencing
ECs	Endothelial cells
PV	Portal vein
CV	Central vein
PHLF	Post-hepatectomy liver failure
TLRs	Toll-like receptors
PAMPs	Pathogen-associated molecular patterns
LPS	Lipopolysaccharide
STAT3	Signal transducer and activator of transcription 3
TIR	Toll-interleukin-1 receptor
TRIF	TIR-domain-containing adaptor-inducing IFN-β
ICAM-1	Intercellular adhesion molecule-1
PH	Post-hepatectomy
IKK	IκB kinase
VEGF	Vascular endothelial growth factor
VCAM-1	Vascular cell adhesion molecule-1
FHL2	Four-and-a-half LIM-only protein 2
Peli 1	Pelino1
NIK	NF-κB-inducing kinase
GMCSF	Granulocyte-macrophage colony-stimulating factor
IL-6 R	IL-6 receptor
Gp130	Glycoprotein 130
SOCS3	Suppressor of cytokine signaling-3
sIL-6 R	Soluble IL-6 R
TSC2	Tuberous sclerosis complex 2
miR-21	microRNA-21
Rhob	Ras homologous gene family member B
FXR	Farnesol X receptor
GHR	Growth hormone receptor
EGFR	Epidermal growth factor receptor
SGK1	Serum and glucocorticoid-induced protein kinase 1
Hh	Hedgehog
Shh	Sonic hedgehog
Ihh	Indian hedgehog
Dhh	Desert hedgehog
Ptch	Patched
Smo	Smoothened
GliFL	Full-length glioma-associated oncogene
PKA	Protein kinase A
GSK3	Glycogen synthase kinase-3
CK1	Casein kinase 1
GliR	Gli repressor
Sufu	Suppressor of fused
GliA	Gli activator
GPC3	Glypican-3 proteoglycan
CSL	CBF1/Suppressor of Hairless/LAG-1
NICD	Notch intracellular domain
APC	Adenomatous polyposis coli
GSK3β	Glycogen synthase kinase 3β
CK1α	Casein kinase 1α
FZD	Frizzled
DVL	Disheveled

PCP	Planar cell polarity
Mst1/2	Mammalian Ste20-like kinases 1/2
SAV1	Salvador 1
LATS1/2	Large tumor suppressor 1/2
YAP	Yes-associated protein
TAZ	Transcriptional co-activator with PDZ-binding motif
TEAD	Transcriptional enhancer factor domain family member
15-PGDH	15-hydroxyprostaglandin dehydrogenase
MIER1	Mesoderm induction early response 1
SBP	Spontaneous bacterial peritonitis
MSCs	Mesenchymal stem cells
ESCs	Embryonic stem cells
iPSCs	Induced pluripotent stem cells
HSPCs	Hematopoietic stem/progenitor cells
ALF	Acute liver failure
HLCs	Hepatocyte-like cells
hAEC	Human amniotic epithelial cell
Oct3/4	Octamer-binding transcription factor 3/4
SRY-Sox2	Sex-determining region Y-box 2
Klf4	Kruppel-like factor 4
c-Myc	Cellular myelocytomatosis
CHC	Carboxymethyl hexamethyl chitosan hydrogel
OTC	Ornithine carbamate transferase
FAH	Fumarate acetoacetate hydrolase
InlB	Internalin B
HGFR	HGF receptor
GL	Glycyrrhizin acid
MET	Mesenchymal-epithelial transition factor
CAR	Constitutive androstane receptor
VPA	Valproic acid
HDAC	Histone deacetylase
BAL	Bio-artificial liver
SRBAL	Spheroid reservoir bio-artificial liver
Ali-BAL	Air-liquid interactive bioartificial liver
AI	Artificial intelligence

Acknowledgements
Not applicable.

Author contributions
NW and CZ, MHG collected, analyzed, interpreted data and wrote the manuscript, BL and JS served as the principal supervisor and funder of the study, and checked manuscript. RJJ & JLB reviewed the manuscript and make some suggestions for the manuscript.

Funding
This study was funded by National Natural Science Foundation of China (No. 82201817, No. 82301010) and Youth Talent Cultivation Fund Project of Dalian Medical University (No. 510016).

Data availability
This review is based on previously published studies and publicly available resources. No new data or materials were generated or analyzed in this study.

Declarations

Ethics approval and consent to participate
This article does not involve any studies with human or animal subjects.

Consent for publication
Not applicable.

Competing interests
The authors declare no conflicts of interest.

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Received: 29 May 2025 / Accepted: 29 October 2025
Published online: 19 December 2025

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