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Recent advances in hepatic tissue engineering for the treatment of liver disease

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Abstract
Liver failure and chronic liver disease represent escalating global health burdens, exacerbated by donor organ shortages and the limitations of current transplant-based options. Although the liver possesses intrinsic regenerative capacity, chronic inflammation, fibrosis, and architectural disruption can inhibit complete repair, necessitating alternative therapeutic strategies. Hepatic tissue engineering has emerged as a multidisciplinary approach to reconstruct functional liver tissue by integrating stem cell biology, biomaterial science, and advanced bioprinting technologies. This review synthesizes recent advances in stem cell-derived regeneration, focusing on mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and liver stem/progenitor cells (LSPCs). MSCs primarily exert immunomodulatory and paracrine effects that remodel fibrotic microenvironments, whereas iPSCs offer scalable, patient-specific hepatocyte-like cells with evolving strategies to improve maturation and safety. LSPCs demonstrate strong lineage commitment and engraftment potential but remain constrained by limited availability and expansion challenges. Complementing cellular approaches, scaffold technologies include decellularized extracellular matrices, synthetic polymers, and emerging biomaterials such as plant-derived, silk-based, and nanostructured systems, providing critical structural, biochemical, and mechanical cues for hepatic organization and vascular integration. In parallel, emerging strategies utilizing ectopic transplantation sites, particularly lymph nodes, highlight the importance of vascularized, immunologically permissive niches for hepatocyte engraftment and expansion, offering a solution to early graft failure caused by insufficient perfusion. Advanced platforms including 3D bioprinting, organoids, and liver-on-a-chip systems enable precise spatial patterning, multicellular coordination, and dynamic microenvironmental control, enhancing metabolic functionality and disease-modeling capacity. Despite these advances, barriers including inadequate vascularization, immune incompatibility, incomplete cellular maturation, and lack of manufacturing standardization continue to limit clinical translation. Integrative strategies combining complementary stem cell populations, bioactive scaffolds, programmable biofabrication technologies, and biologically derived expansion niches represent the most promising pathway toward clinically viable liver reconstruction.

Keywords
Hepatic tissue engineering, Liver regeneration, Stem cell therapy, Biomaterial scaffolds, Liver organoids, 3D bioprinting, Liver-on-a-chip, Induced pluripotent stem cells, Lymph node-based hepatocyte engraftment, Regenerative medicine

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1. Introduction

Metabolic-dysfunction-associated fatty liver disease (MAFLD), including its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), along with alcohol-associated liver disease and cirrhosis, all represent the primary drivers of chronic liver failure worldwide (1). Despite the liver's intrinsic regenerative potential, endogenous repair mechanisms can be overwhelmed by these complications, leading to an irreversible decline in hepatic function (2). Global incidence of cirrhosis-related liver failure has increased by 58.21% between 1990 and 2021 (3), and as projected by the Bayesian Age-Period-Cohort, prevalence is expected to double by 2050 (4). Once cirrhosis progresses to end-stage liver disease (Figure 1), transplantation remains the only definitive therapy, but even this treatment option remains constrained by donor organ scarcity, immune rejection, immunosuppression, and care inequity (5).

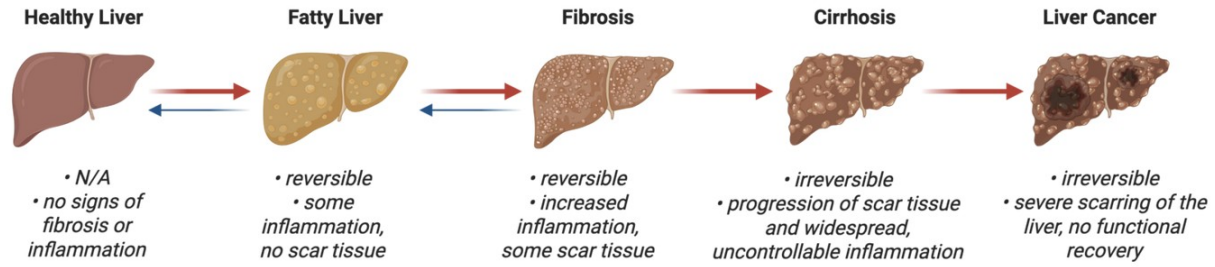

Figure 1. Schematic of the progression and stages of liver failure. This figure was created with BioRender.com

Current clinical interventions, including pharmacological therapies, artificial liver support systems, and surgical transplantation, fail to provide scalable, long-term solutions that restore native hepatic architecture and function (6). Thus, there remains an urgent need for regenerative strategies that move beyond organ replacement toward biological reconstruction.

Recent advances in hepatic tissue engineering have introduced regenerative platforms grounded in three primary stem cell populations: mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and liver stem/progenitor cells (LSPCs). Each population offers distinct advantages in differentiation potential, immunomodulatory capacity, scalability, and long-term application (7). Further, innovations in biomaterial scaffolds and bio-fabrication technologies have enabled increasingly sophisticated and functional reconstruction of the hepatic microenvironment (7). This review aims to synthesize recent advances in hepatic tissue engineering strategies, with a focus on stem cell-based therapies and biomaterials for liver regeneration. Based on significant gaps and developments in current research on cellular engineering, biomaterial science, and 3D bioprinting, this paper evaluates emerging regenerative models and offers insights into future directions to enable clinical translation.

2. Pathophysiology of liver disease

In the healthy liver, hepatocytes coordinate metabolic regulation, detoxification, and

biosynthesis (8). Non-parenchymal cells, including Kupffer cells, hepatic stellate cells, and sinusoidal endothelial cells, maintain immune surveillance, regulate vascular function, and maintain extracellular matrix homeostasis (9). This multicellular organization supports a highly specialized, metabolically compartmentalized microenvironment characterized by specific cellular signaling and zonation, defined as the heterogeneous distribution of hepatocytes along the liver's central axis, which spatially diversifies metabolic enzyme expression and functional capacity for detoxification, gluconeogenesis, and lipid metabolism (10).

In chronic fibrotic liver disease, including MAFLD, MASH, and cirrhosis, the liver's complex architecture is disrupted by progressive inflammation, fibrosis, and vascular injury (Figure 1). Hepatocyte loss, sinusoidal capillarization, defined as the loss of fenestrae pores vital for metabolic function (11), and immune dysregulation further impair regenerative signaling pathways. Specifically, the chronology of liver failure begins as MAFLD, interchangeable with its derivative MASLD, which is hepatocyte-centered metabolic dysfunction, characterized by hepatic steatosis, or excess triglyceride accumulation in hepatocytes (11). It then progresses to MASH through inflammatory amplification and stellate cell activation, leading to overproduction of extracellular matrix and fibrotic scarring (12). Finally, fibrosis irreversibly advances toward cirrhosis with multicellular disruption and the formation of regenerative nodules without functional integration; that is, the structure of the damaged organ may remodel itself without repair mechanisms to precisely restore liver function (13).In addition to architectural disruption, liver disease is considered to comprise a thorough failure in regenerative signaling stability. In healthy tissue, hepatocyte proliferation is orchestrated by tightly regulated pathways, including Wnt/β-Catenin signaling, which regulates intercellular adhesion and functional properties (14). Other pathways that support liver function include Hippo-YAP/TAZ, which represses the co-activators YAP and TAZ, which are responsible for liver growth and structural expansion (15); Notch for sugar and fat metabolism (16); and HGF/c-Met signaling, which suppresses apoptosis to promote hepatocyte proliferation, survival, and protection of liver tissues (17).

On the other hand, chronic inflammation and fibrotic remodeling, typical of liver deterioration, disrupt the regulation of these pathways, creating a microenvironment that permits regenerative scarring, a repair mechanism in which excess collagen is deposited in response to chronic injury or inflammation (18). In liver disease, sustained activation of transforming growth factor-ß (TGF-ß) signaling inhibits functional regeneration by suppressing hepatocyte proliferation and inducing apoptosis, rather than signaling repair to combat metastasis through maladaptive repair or carcinogenic signaling (19). Additionally, vascular remodeling in disease-afflicted livers disrupts oxygen and nutrient gradients that are crucial for zonation-specific gene expression. That is, hypoxia in regions with high fibrosis further alters cellular metabolism by triggering angiogenesis, thereby reinforcing pathological complexity (20). These insights highlight why regenerative strategies must extend beyond hepatocyte replacement alone toward restoring multicellular communication, vascular integrity, and

naturally occurring biomechanical cues to achieve durable functional recovery.

3. Hepatic tissue engineering

Hepatic tissue engineering integrates cellular biology, biomaterials, and biofabrication technologies to reconstruct and simulate functional liver environments that support regeneration, restore metabolic activity, and achieve long-term viability (21). Thus, rather than fully replacing the liver organ through surgical transplantation, hepatic regenerative strategies aim to recreate the cellular and structural conditions necessary for endogenous-like tissue restoration, which will then integrate directly into the prepared microenvironment (22).

3.1. Role of Stem cells in hepatic tissue engineering

3.1.1. *Mesenchymal Stem Cells (MSCs)*

MSCs exhibit strong immunomodulatory and paracrine signaling properties, supporting hepatocyte survival and regeneration through cytokine release rather than solely relying on directed differentiation (23). Sources of MSCs vary depending on independent success metrics and optimal functions (Table 1). Low immunogenicity enables allogeneic transplantation potential, while their high compatibility with complex bioscaffolding systems allows integration into pre-engineered grafts (24). Furthermore, MSC colonization of decellularized liver scaffolds increased expression of adhesion molecules and proangiogenic factors in the liver, indicating enhanced functionalization of the generated liver (25). However, limited hepatic maturation and functional specialization constrain their capacity for complete liver reconstruction (24).

Beyond their well-documented immunomodulatory effects, MSCs exert regenerative influence primarily through a complex secretome comprising cytokines, extracellular vesicles, miRNAs, and growth factors that promote and regulate angiogenesis, apoptosis, and inflammatory responses (26). This paracrine activity regulates the inflammation distinct to injured liver tissue by suppressing pro-fibrotic macrophage phenotypes and diminishing hepatic stellate cell activation (26). These features present MSCs less as direct tissue replacements and more as critical biological actors capable of reprogramming hostile microenvironments into conditions more favorable for functional regeneration and regulation. Furthermore, emerging evidence suggests that MSC-derived exosomes in a three-dimensional structure mediate hepatoprotection, or the ability of foreign substances to guard the liver against stress, inflammation, and repair damage, by upregulating YAP/TAZ and autophagy signaling in tissue-engineered liver complex (27). These nanoscale, acellular vesicles also deliver regulatory RNAs and proteins that influence resistance to apoptosis, oxidative stress responses, and angiogenesis (28). Exosomes derived from mesenchymal stem cells thus constitute attractive therapeutic candidates that can bypass several safety concerns associated with live-cell transplantation. Essentially, MSC secretomes can not only demonstrate therapeutic benefit in early-stage fibrosis and acute injury models but also have the potential to reverse cirrhosis based on their anti-fibrotic, antioxidant, and trophic-factor-producing capacities (29).

Table 1. This table compares the main sources of mesenchymal stem cells used in current hepatic tissue engineering approaches, along with tailored efficacy metrics of proliferation potential, extraction invasiveness, potential immune effects, and key characteristics (1).

1A: Mesenchymal Stem Cells (MSCs) Regenerative Features → Potential Sources ↓	Potential for Proliferation	Invasiveness of Extraction	Immune Effects	Key Characteristics
Bone Marrow	Very low • <~0.01% of nucleated cells	Yes • Uses aspiration techniques	Strong	• Osteogenic potential • Substantial clinical research
Adipose Tissue	High	No • Minimally invasive liposuction	Moderate	• Effective proliferation • High yield for scalability • Reception to directed differentiation
Umbilical Cord Blood (endothelial cells)	Very high	No • Collection from perinatal tissues	Lower • Anti inflammatory/ antifibrotic impact	• Maintains phenotype • Allogeneic usage • Good stemness markers

MSCs, when integrated into bioengineering constructs, exhibit strong adaptability within three-dimensional (3D) scaffolds, particularly when mechanical cues further enhance output and function. MSCs' immunoregulatory responses can also be manipulated by specific modifications to the scaffold, including stiffness, porosity, and biochemical composition, all of which have been shown to influence MSC behavior (30). Despite these advantages, though, the absence of robust hepatocyte-like and thus specific metabolic function constrains the potential of MSCs' application to supportive rather than reconstructive roles (25). These findings suggest that MSCs should be used in conjunction with other treatments within multicellular regenerative frameworks and not as standalone solutions.

3.1.2. *Induced Pluripotent Stem Cells (iPSCs)*

iPSCs offer unparalleled potential for differentiation, enabling directed hepatic lineage specification through controlled signaling pathways (31). Their patient-specific origin (Table 2) and differentiability support personalized regenerative medicine models, thereby reducing the risk of immune rejection. Most notably, concerns about iPSCs' potential for tumorigenicity (the tendency of transplanted cells, tissues, or organs to induce cancer within an organism) had led to the pursuit of safer approaches, such as adenoviral vectors, synthetic mRNAs, and diverse plasmid architectures, to enhance the integrity of iPSC programming (32). However, considerations regarding the repercussions of iPSC implementation include genomic instability and functional immaturity, which remain major barriers to clinical application (33). Current research focuses on enhancing differentiation specificity for the liver organ and its associated diverse microenvironment, while maintaining long-term functional stability and capacity (7).

iPSCs are the most versatile and theoretically complete solution for hepatic tissue engineering, owing to their capacity for unlimited self-renewal and directed differentiation into hepatocyte-like cells (HLCs) (31). By

recapitulating embryonic liver development through staged exposure to signaling cues such as Activin A, BMP4, FGF, and HGF, researchers have achieved a sophisticated hepatic phenotype in human iPSC-derived hepatic stellate cells that exhibit key liver-specific functions (34). Specifically, the hallmarks essential to the liver's metabolic competence were measured, including albumin secretion, tissue repair and structural balance, lipid transport, and necessary inflammatory responses (34).

However, iPSC-derived hepatocytes frequently retain fetal-like characteristics, limiting their long-term functional stability. Transcriptomic and epigenetic analyses reveal incomplete maturation profiles, particularly in drug-metabolism and stress-response pathways (35). Addressing this limitation has become a central focus of current research, with strategies including prolonged culture, hydrogel integrations, and "organ-on-a-chip" frameworks. Further, co-culture of HLCs with multiple cell types, including non-parenchymal liver cells, liver sinusoidal endothelial cells, hepatic stellate cells, or mesenchymal stromal cells, has been shown to improve metabolic activity and mimicry of HLCs because these cell-cell interactions emit needed paracrine signals for function and polarization cues in the presence of growth factors like VEGF and HGF (35).

Table 2. This table compares the main sources of induced pluripotent stem cells used in current hepatic tissue engineering approaches, along with tailored efficacy metrics of invasiveness, culture-specific selectivity, costs, general efficiency, and reprogramming time (26).

1B: Induced Pluripotent Stem Cells (iPSCs) Regenerative Features → Potential Sources ↓	Invasiveness	Selectivity Under Culture	Costs	Efficiency	Reprogra-mming Time
Hair Follicles (keratinocytes)	No	High convenience	Low	High	2-3 weeks
Umbilical Cord Blood (endothelial cells)	Yes	Some convenience	High	Moderate	2-4 weeks
Skin Biopsy (fibroblasts)	Yes	No conve-nience	Very low	Moderate	3-5 weeks

3.1.3. *Liver Stem/Progenitor Cells (LSPCs)*

LSPCs possess inherent hepatic lineage commitment, like iPSCs, which facilitates efficient integration into native liver micro-niches (36), with regenerative features specific to cell sources (Table 3). Their physiological relevance would thus offer advantages in functional maturation and regenerative signaling. However, limited availability, challenges associated with traditional cell therapy complications, and difficulties with *ex vivo* expansion would limit their widespread clinical applicability (37).

Unlike pluripotent or multipotent alternatives, LSPCs are also inherently primed for hepatic differentiation, enabling more efficient functional integration upon transplantation. Their responsiveness to endogenous regenerative cues enables them to participate directly in tissue remodeling, particularly in periportal regions, where progenitor activation is most prominent during injury (38).

Functionally, LSPCs demonstrate superior engraftment efficiency and metabolic integration compared to other stem cell types (39). When introduced into injured liver models, they promote bile duct formation, hepatocyte polarization, and interactions with sinusoidal endothelial cells, thereby mimicking hepatocyte function (1). These properties position LSPCs as highly attractive candidates for reconstructing native-like hepatic microarchitecture. LSPCs' dependence on specific niche signals enhances sensitivity and reduces their capabilities in pathological environments characterized by fibrosis and chronic inflammation (40).

The major limitation of LSPCs in general lies in their clinical scalability. Isolation yields remain low, and ex vivo expansion often leads to phenotypic drift or senescence (41). Furthermore, donor variability, tissue-sourcing inconsistencies, and the tendency for highly variable arrangements of LSPCs within *in vivo* structures (42) warrant significant consideration before proceeding with clinical translation. As a result, current applications of LSPCs are largely confined to experimental models or combined approaches in which they are embedded within engineered scaffolds. To mitigate some feasibility-related side effects, future research on LSPCs should establish safe protocols for genetic modification (37).

Table 3. This table compares the main sources of liver stem/progenitor cells used in current hepatic tissue engineering approaches, along with tailored efficacy metrics of reprogramming capacity and regenerative efficiency (36).

1C: Liver Stem/Progenitor Cells (LSPCs) Regenerative Features → Potential Source ↓	Reprogramming Inputs	Regenerative Efficiency
Mouse Embryonic Fibroblasts	• cumulative transcription factor expression	• bilineage differentiation • hepatocyte functionality
Canal of Hering	• cholangiocytes • activated liver progenitor cell expansion	• repair liver injury with influx of liver-specific cells to damaged area • develop hepatocytes and growth factors to respond to inflammation

3.2. Current avenues and areas of expansion in hepatic tissue engineering

Interestingly, hepatic tissue engineering research is shifting away from reliance on a single stem cell population toward integrated multicellular systems that more closely reflect the complexity of the native liver (43). Co-culture models incorporating hepatocyte-like cells, endothelial cells, and supportive stromal populations have demonstrated improved vascularization, metabolic stability, and long-term viability (35). Within these systems, MSCs often function as immunomodulatory stabilizers, iPSC-derived hepatocytes provide a scalable parenchymal mass, and LSPCs contribute lineage-specific maturation signals (1, 7).

Based on these integrations, successful liver regeneration is unlikely to arise from the rigid application of any single cellular solution. Ultimately, translating stem cell biology and

tissue engineering to rescue liver failure and disease will depend on integrating complementary stem cell populations within microenvironments that consistently guide differentiation, integration, and function over time. In the meantime, the diversity of origins (Tables 1-3) for potential stem cell collection remains a significant advantage for exploring stem cell applications today.

4. Role of bioengineered scaffold structures in hepatic tissue engineering

Scaffolds serve as structural frameworks that replicate the extracellular matrix architecture, providing biochemical, mechanical, and spatial cues essential for tissue organization. However, cellular potential alone is insufficient without structural support, as hepatocyte function is tightly regulated by extracellular and biomechanical cues. One such structure is the decellularized liver matrix scaffold (Figure 2), which entails removing cellular components that reduce organ function, leaving behind extracellular matrices that populate vascular networks with structural proteins and independent growth factors. Afterwards, recellularization returns nuclear materials from the recipient to the prepared space, which most consistently include differentiated stem cells precisely positioned to reconstruct organ networks around fully functional parenchyma and the vascular tree of the renewed liver (44).

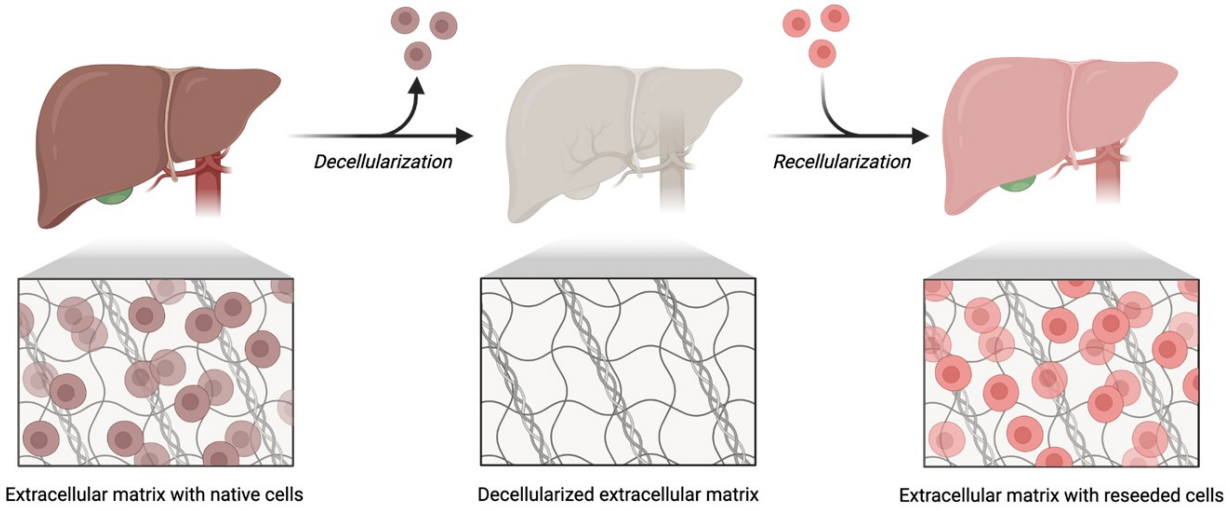

Figure 2. Visualization of liver decellularization and recellularization. Created with BioRender.com

In addition to the decellularized matrix structure, unique hybrids can also serve as scaffolds, often comprising naturally occurring biomaterials, synthetic polymers, and unconventional substrates such as plant-derived, silk-based, and nanomaterial systems (45). Each of these materials, when accommodated into select scaffolds, results in diverse augmentations of liver function post-regeneration without structural focuses.

At a functional level, scaffolds must fulfill three simultaneous roles: [1] mechanical support to preserve tissue architecture (46), [2] biochemical signaling through matrix-bound ligands and growth factors (47), and [3] spatial

organization that enables polarized hepatocyte function and vascular perfusion (48). In hepatic applications, scaffold failure in any of these domains can compromise overall construct viability and, in turn, reverse or even worsen liver-failure-related complications. This highlights the need for materials that balance structural integrity with biological permissiveness.

4.1. Why liver regeneration is uniquely difficult
Liver regeneration presents unique engineering challenges due to the liver's exceptionally dense and complex vascular network. Vascularization —the physiological process by which new blood vessels form to supply tissues with oxygen and nutrients—is essential for maintaining the viability and function of regenerating tissue. However, excessive or dysregulated angiogenesis may also contribute to tumorigenesis and cancer progression. To address this challenge, researchers have explored the integration of pre-vascularized scaffolds into engineered tissue constructs, allowing vascular networks to be established through induced angiogenesis prior to implantation (49).

As previously stated, zonation-complicated architecture should be considered to mimic tissue structure and increase the success of organ replication (50), in conjunction with the liver's mechanical softness, characterized by viscosity and elasticity, with measurable correlations with fibrosis stages and inflammation intensity. Effective scaffolds must support vascular integration, maintain low mechanical stiffness, enable equitable nutrient diffusion, and preserve microstructural organization. This is especially important, as structure and function often go hand in hand and are directly proportional to each other's success capacity in cellular processes. Recent scaffold innovations increasingly focus on bioactive surfaces, growth-factor integration, and microchannel vascular networks (51) to address these challenges.

In addition to vascular and mechanical challenges, hepatic regeneration is complicated by the liver's exceptionally high metabolic demand. Hepatocytes require continuous oxygenation and substrate availability to sustain detoxification and biosynthetic functions (52). Even brief ischemic periods following implantation can result in widespread cell death, making rapid anastomosis with host vasculature essential (53). Furthermore, bile canaliculi formation and drainage, which are often overlooked in early-stage scaffold construction, are critical for long-term functional integration (54) and remain a significant engineering bottleneck.

These challenges collectively explain why partial functional restoration has been achieved more readily and thus is more frequently documented than whole-organ replacement. In addition, the factors mentioned above explain why scaffold-based approaches increasingly prioritize more specialized, size-proportional functional units to recreate damaged liver microenvironments.

4.2. The importance of biomaterials in forming scaffolds in hepatic tissue engineering
While decellularized liver matrices and natural or biosynthetic polymers remain the dominant scaffold platforms in hepatic tissue engineering, growing attention has shifted toward unconventional biomaterials that challenge traditional assumptions about tissue-specificity

and material origin. Specifically, these biomaterials are often derived from non-mammalian, non-hepatic, or non-biological sources to meet the crucial functional requirements of liver scaffolds (45). These could include facilitating structural integrity, vascular guidance, and biochemical signaling, all without directly replicating native liver extracellular composition (47).

4.2.1. *Plant-derived scaffolds*

They feature intrinsic vascular architecture. These structures are among the most extensively studied unconventional platforms. Through decellularization of plant tissues, leaf venation networks can be preserved and repurposed as perfusable channels for mammalian cell culture (55). For example, spinach-leaf derived scaffolds maintain cellular perfusion in intact vascular networks (55). These naturally occurring microchannel networks closely approximate the branching geometry required for hepatic vascularization, offering a low-cost, highly scalable alternative to synthetic microfabrication. When functionalized with liver-specific extracellular matrix proteins, plant-derived scaffolds have demonstrated compatibility with hepatocyte adhesion and survival (56). However, the absence of native biochemical cues necessitates extensive surface modification, and long-term integration remains limited by mechanical and immunological considerations.

4.2.2. *Silk-based biomaterials*

These biomaterials offer a distinct advantage due to their tunable mechanical properties and established biocompatibility. Silk fibroin scaffolds can be engineered to match the low stiffness characteristic of healthy liver tissue while maintaining structural stability during implantation (57). For example, longitudinal assessment of liver–scaffold integration demonstrated that by day 14, host hepatic cells had infiltrated the acellular scaffold and become extensively integrated within its architecture (57). Their slow degradation kinetics enable sustained support during tissue remodeling, and chemical functionalization allows incorporation of hepatogenic growth factors (58). Unlike other biomaterials, silk scaffolds integrate well with intrinsic biological signaling pathways, such as activation of the Wnt pathway. Furthermore, silk fibroin scaffolds are responsive, regulating cell proliferation and downregulating Th-17 cell differentiation and the Th-1 immune response pathways (57).

4.2.3. *Paper-based and cellulose-derived scaffolds*

These scaffolds allow precise control over surface features of liver hybrids while reducing unnecessary signaling and outperforming conventional monolayer cultures when seeding and supporting hepatocyte growth. While paper substrates boast a strong resistance to degradation and polymer residues that mimic the liver's functionally required tissue stiffness, elements of cellulosic fibers and regions of electrostatic interactions allow for microfluidic manipulation of liver regeneration (59). Cellular morphologies after paper implementation grow more complex over time, regaining proper functionality and necessary networks (60). To enhance adhesion and protein adsorption, direct ECM protein coating and chemical modifications can be applied to the paper substrate to induce stronger covalent binding and scaffold efficacy, thereby creating a favorable environment for deployed cells (45).

4.2.4. *Nanomaterial-based scaffolds*

Scaffolds derived from nanomaterials introduce nanoscale topographical cues that influence hepatocyte polarity, cytoskeletal organization, and metabolic function (61). Such materials can include graphene, nanofibrous polymers, and hybrid composites. Electrospun nanofibers closely resemble the fibrillar structure of native extracellular matrix and promote enhanced cell attachment and function (62). Nanomaterial-based scaffolds resist decomposition and regulate infiltration and independence, enabling more complete and thorough growth of hepatic implants mediated by NGO (nano-graphene oxide) transplantation after 5 and 10 days (63). Additionally, nanomaterials enable high surface-area-to-volume ratios for growth-factor loading and controlled release, thereby positively facilitating the regeneration of hepatic functional capacity. Another benefit is high porosity, which facilitates greater diffusion of oxygen and nutrients; however, this is offset by concerns about the cytotoxicity and instability of nanomaterials in the human body (45). For this reason, regulatory approval and questions about biodegradation currently limit their clinical readiness.

Table 4. This table compares biomaterial integrations, summarized by efficacy metrics for each scaffold type, and measures regenerative success (45).

Scaffold Success Efficacy Metrics → Type of Biomaterial ↓	Measured Synthesis Rates	Surface Recog-nition	Cell Density & Distribution	Biocom-patibility
Plant-Based	• High albumin synthesis • High ammonia/α-fetoprotein secretion → High metabolism	• Awareness of galactose improves binding and long-term maintenance of cell-ECM communication	• Exceeds other biological polymer options → More scalable and high confidence	• Satisfies optimal ratio of remaining DNA → High water and porosity capacity for absorption
Silk-Based	• Long-term albumin/urea synthesis and CYP activity • Metabolic plasticity affected by hormone imbalances	• High expression of cholangiocyte genes when stimulated by liver ECM cues receptive to low content and detoxification	• Mimicked the natural parenchyme-mesenchyme arrangement in hepatic networks → Good response	• Later in growth, immune presence dwindles in number • Lack of mechanical stability
Paper-Based	• Consistent albumin and urea production is maintained after higher interaction between functional HepG2 cells	• Cell-adhesive proteins and surface nanoparticles can be covalently bonded to paper for improved biofunction	• After reducing diameter of filter paper, density increases for higher scaffolding culture capacity	• Multiple layers initiate crucial oxygen gradients to increase activity of adhesive enzymes
Nanomaterial-Based	• Lack of enhancement due to lack of intracellular interaction and large surface area for non-essential complexity	• Nanoscale topography guides alignment of carbon-based substrates to support growth of functional hepatocytes	• Cellular aggregation increases due to hydrophobic property of carbon nanoma-terials	• Linked to molecular dynamics needed for biological processes • Supports different-iation

Collectively, unconventional biomaterials expand the design scope of hepatic scaffolds by prioritizing different aspects of functional recuperation over direct biological mimicry. While none currently surpass decellularized liver matrices in overall biological readiness and benefits, factors such as scalability, cost-effectiveness, and design flexibility position plant-, silk-, paper-, and nanomaterial-based substrates as valuable components of hybrid scaffold systems (Table 4).

5. Novel innovations in hepatic tissue engineering

5.1. 3D-bioprinted organoids: The cutting edge of Stem cells with biomaterial integration

The use of organoids in a three-dimensional hepatic environment is a promising avenue for future exploration. Traditional two-dimensional cultures fail to replicate the organ's native structure and crucial multicellular interactions required for function, thereby limiting their predictive power for drug testing and disease modeling. In contrast, modern bioprinting strategies combine cell spatial positioning and distribution with microfabrication to generate physiologically accurate liver reconstructions that support the complex tissue functions native to a healthy liver (64). Currently, the success of bioprinted hepatic organoids depends on the properties of bioinks, which provide biochemical cues that promote hepatic differentiation and functional stability. Liver-specific bioinks are composed of hepatocytes, endothelial cells, and supportive matrix components, such as collagen, laminin, and gelatin methacrylate (GelMA), in pre-designed architectures (65). The mechanical properties of these bioinks, namely stiffness and viscoelasticity, help regulate hepatocyte behavior. Liver constructs enriched with these architectures demonstrate sustained metabolic activity, albumin synthesis, and enzymatic functions relevant to human drug metabolism, making them valuable models for pharmacological and toxicological analyses (66). Furthermore, advances in vascularization, which pose a major challenge for producing viable large tissues, have been achieved by integrating synthetic vascular networks into bioprinted constructs, thereby greatly improving nutrient and oxygen delivery throughout engineered tissues (67).

Liver organoids are self-organizing, three-dimensional cellular aggregates that retain many aspects of liver biology. When coupled with bioprinting, these organ replicas can be positioned and patterned within scaffolds that enhance maturation and functionality when structurally identical to original healthy tissues. Bioprinted liver organoids composed of multiple cell types, like hepatocytes and endothelial progenitors, exhibit enhanced secretion of liver-specific proteins, drug-metabolizing enzymes, and bile acids compared with traditional organoid cultures (64). The combination of bioprinting and organoid technology removes a key confounding variable in organoid experimentation, that is, variability in size and, essentially, by enabling controlled occupation of cellular space and scalable production of uniform tissue units, hepatic organoids can more consistently mimic *in vivo* environments for medicinal assistance, screening, and disease modeling (68).

5.2. Liver-on-a-Chip and microphysiological platforms for liver tissues

Integrating bioprinting with microfluidic algorithms and concepts yields liver-on-a-chip

systems that are complex microphysiological platforms that closely mimic the liver's dynamic flow and microenvironmental cues. Specifically, livers-on-a-chip insert a small number of liver cells onto chips that include human hepatocytes, primary human cells, immortalized human cell lines, and others that specialize in forming a 3D arrangement and in specialized biomechanics (69). These systems are also hosts of permeable channels for functional diffusion and respond well to environments analogous to those of the liver, accessible by biosensory signaling (70), which enables continuous nutrient supply, waste removal, and real-time monitoring of physiological parameters such as oxygen levels, pH, and biomarkers. Specifically, embedded sensor technologies further enable the characterization of tissue health and metabolic responses, thereby enhancing the analytical power of these platforms for drug development and toxicology.

Under perfusable-channel conditions, livers-on-a-chip additionally accelerate differentiation timelines and enhance hepatic functions, such as albumin production and cytochrome P450 activity (71). It is also possible that engineered hydrogels derived from decellularized liver extracellular matrix (dLECM) can be systematically tailored for microfluidically aligned livers-on-a-chip (72), thereby minimizing diffusion limitations and improving long-term tissue stability when combined with GelMA and other pro-hepatic factors, ultimately advancing the relevance of translational hepatic tissue engineering strategies.

5.3. Lymph node-based hepatocyte engraftment: a permissive expansion niche and its translational implications

A central limitation in hepatic tissue engineering is early graft failure due to insufficient vascularization, which results in ischemia and rapid loss of transplanted hepatocytes. While scaffold-based approaches aim to reconstruct liver architecture, they frequently fail at this initial survival stage. An alternative strategy that has emerged in preclinical and early clinical studies is the use of lymph nodes as ectopic sites for hepatocyte engraftment. Unlike engineered scaffolds, lymph nodes provide a pre-existing, highly vascularized stromal microenvironment that supports rapid cell survival and expansion (73).

Lymph nodes have been established as a biologically validated "permissive niche" for hepatocyte survival and expansion across multiple biological scales. Mechanistically, the success of lymph node engraftment arises from several convergent properties. First, the fibroblastic reticular cell (FRC) network provides a pre-formed extracellular matrix scaffold that supports immediate cell adhesion and prevents anoikis (74). Second, the dense vascular architecture, including high endothelial venules, enables rapid perfusion and minimizes the ischemic window that typically limits graft survival (75). Third, lymph nodes are intrinsically capable of dynamic remodeling and expansion, allowing transplanted hepatocytes to proliferate without the spatial and competitive constraints present in native liver tissue. Finally, the local immune environment exhibits a degree of tolerance that permits engraftment without triggering severe inflammatory or fibrotic responses (75).

Despite these advantages, lymph node–based hepatic tissue formation remains fundamentally limited in its capacity to recapitulate full liver

function. Ectopic hepatocyte clusters lack key architectural features of the native liver, including sinusoidal organization, metabolic zonation, and, critically, a functional biliary drainage system (76). As a result, while lymph node grafts can provide partial metabolic support, they are unlikely to achieve complete physiological replacement of liver function. This highlights a fundamental distinction between how lymph node niches that specialize in expansion characteristics that enable cell survival and proliferation, and the more functional niches that support full organ-level activity.

Lymph nodes effectively solve the problem of early vascularization and cell survival but fail to reproduce organ-specific architecture, whereas engineered scaffolds aim to reconstruct hepatic structure but are limited by poor initial engraftment. This dichotomy suggests that successful liver regeneration may require a staged or hybrid approach that integrates both paradigms.

One potential extension of this concept is the engineering of an autologous lymph node-derived stromal niche to enhance hepatocyte engraftment within the liver itself. In this framework, stromal cells or extracellular matrix components derived from patient-specific lymph nodes could be used to construct a permissive microenvironment that is implanted into the diseased liver alongside hepatocytes or induced pluripotent stem cell–derived hepatic cells (77). Such a niche would be expected to improve early survival by recapitulating the adhesion, vascularization, and immune-modulatory properties of lymph nodes. However, this strategy would remain constrained by the same limitations observed in ectopic lymph node grafts, particularly the absence of biliary integration and liver-specific architectural cues, unless combined with additional scaffold-based or biofabrication approaches.

6. Challenges and future directions

6.1 Challenges

The field of tissue engineering for the treatment of liver failure and disease faces broad obstacles, including but not limited to limitations in vascularization, immune rejection, and challenges in scale and clinical translation. Specifically for each section discussed in this paper, consideration of the ethical implications of stem cell sources, the need for standardized scaffold characterization, and maturation inconsistencies associated with bioprinting organoid-based strategies is necessary.

Another limitation is the presence of major barriers to achieving functional maturity and long-term stability. Individually, though, iPSC-derived hepatocyte-like cells frequently resemble fetal hepatocytes rather than fully mature adult liver cells, exhibiting incomplete metabolic competence (35). Furthermore, variability across donor lines and the lack of usable sources for differentiation introduce obstacles to reproducibility. Ethical considerations surrounding embryonic stem cells persist, whereas adult stem cell populations may exhibit limited expansion capacity and donor-dependent variability. Together, these issues hinder the reliable application of stem cell-derived hepatic constructs for clinical transplantation. Furthermore, immunogenicity and tumorigenic risk further complicate translation. Even autologous iPSC-derived cells may acquire mutations during reprogramming

or expansion, raising safety concerns. Residual undifferentiated pluripotent cells carry a risk of teratoma formation, necessitating stringent purification protocols (78). Additionally, integrating stem cell-derived hepatocytes into host tissue requires synchronized vascular and stromal support, which is difficult to achieve in isolation, especially in a separate *in vitro* environment. Thus, while stem cell platforms provide cellular versatility, their independent use remains insufficient for large-scale, clinically deployable liver regeneration.

Scaffold design for restoring hepatic function remains a fundamental challenge due to the structural and biochemical complexity of the native liver extracellular matrix (ECM). The liver's microarchitecture is defined by tightly coordinated zonation gradients, sinusoidal vascular networks, and region-specific mechanical properties, all of which are difficult to replicate using uniform biomaterials (50). Critically, these features' spatial and functional integration govern hepatocyte polarity, metabolic specialization, and overall tissue performance. Even decellularized ECM scaffolds, while biologically instructive, exhibit batch-to-batch variability and incomplete removal of immunogenic components, limiting reproducibility and clinical reliability. In contrast, synthetic scaffolds offer tunable mechanical properties and design flexibility but frequently lack the biochemical complexity required to sustain hepatocyte function and long-term metabolic stability. Thus, the central limitation here lies in current scaffold design: the inability to simultaneously achieve structural fidelity, biochemical signaling, and spatial organization within a single platform.

In addition, standardization remains another obstacle. Variability in porosity, stiffness, and degradation rate can all significantly alter cellular outcomes, yet consistent scaffold characterization protocols are lacking across laboratories (49). Furthermore, achieving adequate vascular infiltration within thick scaffolds remains a critical limitation, as diffusion constraints restrict construct size and long-term viability. Without reliable strategies to support perfusion and mechanical integration, scaffold-based constructs struggle to move beyond preclinical models.

Bioprinting and liver organoid systems provide the necessary spatial control and multicellular complexity for hepatic regeneration after the organ has been rendered incapable; however, they are constrained by reproducibility and maturation inconsistencies. Printed constructs often lack sufficient vascular integration, leading to necrotic cores in larger tissues (79). Resolution limitations in extrusion-based systems restrict accurate recreation of sinusoidal networks, while shear stress during printing can compromise cell viability (79). While bioprinting and organoids are powerful experimental tools for specialized disease modeling, translating microscale constructs remains underdeveloped because engineered tissues require both anastomosis facilitation and the precision of microscopic vascular networks to maintain structural and functional stability (79). Organoid systems, although self-organizing, exhibit heterogeneity in size, cellular composition, and functional output, leading to substantial experimental variability that remains unreconciled.

Many organoid-based systems are optimized for disease modeling or drug testing rather than full-

organ regenerative therapy. The lack of suitable, naturally occurring materials for bioprinting, including angiogenic cues and growth factors, limits reproducibility due to substantial variability within and between batches (80). Until this is addressed, scaling and holistic applicability of bioprinting technology remain problematic.

6.2 Future directions

Future progress will likely involve integrating complementary stem cell populations, bioactive scaffold systems, and programmable biofabrication strategies to overcome each element's respective limitations and enhance translational viability. Again, for each distinct avenue of hepatic tissue engineering, supplementing with different stem cell populations, integrating diverse and novel scaffold materials, and incorporating 4D considerations into bioprinting strategies would greatly expand the scope of the role liver tissue engineering plays in hepatic repair.

Future progress in stem cell-mediated liver regeneration will likely depend on strategically supplementing current arrangements of an individual stem cell type with a combination of other stem cell cultures. Co-culture systems integrating iPSC-derived hepatocytes with endothelial progenitors, mesenchymal stromal cells, and immune-modulating populations may better recapitulate hepatic microenvironments. Advances in directed differentiation protocols, including temporally controlled growth factor exposure and biomechanical conditioning, may further enhance adult-like metabolic maturation and reduce fetal phenotypes. Genome editing technologies also offer potential to enhance safety and function. CRISPR-based correction of pathogenic mutations in cells could enable personalized regenerative therapies, while specialized gene circuits can be tuned to suppress tumorigenic pathways in post-differentiated stem cells to mitigate the risk of teratoma formation (81). Standardized differentiation benchmarks, including molecular-level transcriptomic and metabolic profiling (82), will be essential to ensure maintenance of reproducibility and ethical standards. Through multi-lineage integration and molecular refinement, stem cell platforms may further evolve into a more clinically robust cellular therapy.

Emerging scaffold innovations should integrate unconventional materials with bioactive coatings, rather than relying solely on traditional decellularized ECM components. However, the inclusion of familiar dECM with synthetic structural backbones will likely offer mechanical stability alongside biological functionality. Furthermore, the surfaces of functionally applied scaffolds would benefit from liver-specific adhesion motifs and growth-factor signaling to enhance and sustain hepatocyte function. Additionally, incorporating angiogenic factors or using microchannel fabrication techniques, such as microfluidic perfusion, may address longstanding constraints in vascularization and enhance the viability of thick constructs. Further, tracking degradation will be critical for translational scalability. Integration with microfluidic perfusion systems and prevascularization strategies may further enhance the viability of thick constructs. When scaffold evolution results in a seamless transition into existing architectures, with or without reduced impact on vascularization, scaffolding strategies will be ideally capable of

supporting diverse stem cell populations for the treatment of liver failure and disease.

While bioprinting has shown promise for microenvironmental control, four-dimensional (4D) expansions, in which constructs dynamically evolve over time in response to biological or environmental stimuli, should also be explored. In hepatic applications, 4D strategies may include bioinks that degrade in response to enzymatic activity, release growth factors in a temporally controlled manner, or undergo stiffness modulation as tissue maturation progresses. In fact, results have been measured, though they have been discussed only minimally in contemporary research. Specifically, such bioinks are most feasible when derived from smart materials, such as shape-memory polymers (SMPs) and shape-morphing hydrogels, that enable programmed dynamics in 4D constructs (83). These composite-integrative approaches would more closely mimic *in vivo* liver regeneration, in which ECM remodeling and signaling gradients evolve continuously. Although still in its early stages, 4D bioprinting holds promise for addressing one of the most persistent challenges in hepatic tissue engineering: the mismatch between early-stage cell survival requirements and later-stage functional maturation (84). By allowing constructs to transition from supportive, protective environments toward more permissive, physiologically relevant conditions, 4D systems may enhance long-term organoid viability and integration potential.

7. Conclusion

Hepatic tissue engineering has demonstrated substantial promise as a strategy for treating liver failure and disease beyond traditional approaches. The integration of stem cell-derived hepatic populations, advanced scaffold systems, and biofabrication technologies has enabled significant progress toward restoring functional liver tissue. These approaches move beyond simple cellular replacement toward reconstructing the complex microenvironment required for sustained hepatic function. However, despite rapid advancements across these domains, the field remains constrained by its fragmented approach to replicating liver complexity. Future progress will depend not on incremental improvements within individual components, but on the deliberate integration of cellular, structural, and microenvironmental design principles into cohesive, multi-scale systems. Future regenerative strategies may additionally depend on integrating permissive vascularized engraftment niches with scaffold-based architectural reconstruction approaches. In particular, lymph node–derived microenvironments and related stromal niche engineering strategies may help address one of the central limitations in hepatic tissue engineering: the mismatch between early hepatocyte survival and long-term organ-level functional integration. Such strategies must simultaneously address vascularization, cellular maturation, immune compatibility, and scalability to enable meaningful clinical translation. Only through this systems-level approach can hepatic tissue engineering transition from experimental models to clinically viable organ reconstruction. As the global burden of liver disease continues to rise, the challenge is no longer whether liver tissue can be engineered, but whether that can happen with the precision and complexity required to restore human liver function.

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