NARRATIVE REVIEWS

Cell Therapy in Advanced Cirrhosis: From Preclinical Evidence to Clinical Application

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End-stage liver disease (ESLD) presents a significant worldwide health and economic burden accounting for 4% of global deaths. When ESLD develops into liver failure, the only effective treatment is liver transplantation, which is limited by surgical and access barriers and significant posttransplant complications. Furthermore, the scarcity of suitable donors means many patients deteriorate or die while waiting for a transplant, highlighting the need for alternative therapeutic strategies. ESLD is characterized by a multifactorial pathophysiology driven by a complex interplay of extensive parenchymal damage, self-perpetuating chronic inflammation, and advanced fibrosis. Cell-based therapies have emerged as promising alternatives to restore liver function through either parenchymal replacement or microenvironment remodeling. While primary hepatocyte transplantation remains the benchmark for parenchymal replacement, emerging modalities have undergone substantial evolution, demonstrating an enhancement in the integration of the transplanted cells into the diseased liver tissue to ameliorate liver function. Despite these advances, suboptimal engraftment due to the negative effect of the liver dysfunctional microenvironment results in limited durability and functional impact of parenchymal replacement. As the negative role of the dysfunctional microenvironment in disease progression became clearer, the focus for disease-modifying cell therapy shifted toward microenvironment-remodeling therapies. Mesenchymal stromal cells, regulatory T cells, chimeric antigen receptor T cells, and regenerative macrophages have been recognized as powerful modalities, with the potential to offer durable restoration of liver function by exerting anti-inflammatory and antifibrotic effects, thereby favoring endogenous repair. In this review, we discuss these evolving platforms, delineate their mechanistic underpinnings, and define the opportunities and challenges that shape their translation into clinically viable alternatives for treating ESLD.

Keywords: Cirrhosis; Hepatic Decompensation; Inflammation; Fibrosis; Cell Therapy

Introduction

Liver disease is a major health burden accounting for 2 million deaths annually and responsible for 4% of all deaths worldwide.[1] End-stage liver disease (ESLD) is the terminal phase of progressive liver disease common to a variety of etiologies; including steatotic liver disease (SLD), viral hepatitis, and autoimmune liver diseases. For SLD, early pathophysiology is driven by metabolic dysfunction where impaired adipose tissue fat storage and insulin resistance increase the hepatic influx of fatty acids. As hepatic fat accumulates, hepatocytes undergo significant cellular stress, resulting in lipotoxicity, mitochondrial dysfunction, and oxidative stress. In addition, alcohol-related toxicity in etiologies such as alcohol-related liver disease and metabolic dysfunction–associated alcohol-related liver disease further contributes to the initiation of liver injury through increased oxidative stress, altered metabolism and increased lipid synthesis. Regardless of etiology, this process culminates in hepatocellular injury, activation of Kupffer cells (KCs; ie, resident macrophages) and downstream inflammatory pathways which sustain chronic inflammation and promote progressive fibrosis (scarring), ultimately altering hepatic architecture and impairing the liver's metabolic and detoxifying functions. Advanced scarring and increased intrahepatic vascular resistance (IHVR) drive the development of portal hypertension and its downstream consequences, including splanchnic vasodilation, ascites, variceal bleeding, hepatic encephalopathy, and multi-organ dysfunction.[2,3]

Abbreviations used in this paper: **BEC, biliary epithelial cell; CAID, cirrhosis-associated immune dysfunction; CAR-T, chimeric antigen receptor T cell; CQAs, critical quality attributes; CRS, cytokine release syndrome; CYP450, cytochrome P450; 3D, three-dimensional; ECM, extracellular matrix; ESLD, end-stage liver disease; EV, extracellular vesicle; FAP, fibroblast activation protein; GMP, good manufacturing practice; HCC, hepatocellular carcinoma; HepLPC, hepatocyte-derived liver progenitor-like cell; HLC, hepatocyte-like cell; HSC, hepatic stellate cell; IHVR, intrahepatic vascular resistance; IL-10, interleukin-10; iPSC, induced pluripotent stem cell; iPSC-HLC, induced pluripotent stem cell hepatocyte-like cell; KC, Kupffer cell; MELD, Model for End-Stage Liver Disease; MMP, matrix metalloproteinase; MSC, mesenchymal stromal cell; RM, regenerative macrophage; RMT, regenerative macrophage therapy; TGF-β, transforming growth factor-beta; Treg, regulatory T cell.**

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Despite advances in pharmacologic therapies and artificial liver support systems, orthotopic liver transplantation remains the only curative option for ESLD. Its clinical application is limited by access to liver transplant evaluation, contraindications to major surgery, persistent shortage of organs, complexity of the surgery, and substantial risk of posttransplant complications, resulting in a sharp imbalance between yearly deaths due to ESLD and transplant performed (~52K vs ~12K respectively in the United States—https://hrsa.unos.org/data/view-data-reports/national-data/). These data underscore the urgent need for the development of novel therapeutics that target both the underlying pathogenesis and progression of liver disease.

Cell therapy has emerged as a highly promising alternative for treating ESLD as it provides the potential to offer therapy to the large group of patients who cannot access liver transplantation, as well as to alleviate donor organ shortages and minimize dependence on invasive liver transplants.[4–6] Two main categories of cell therapies for ESLD will be reviewed as follows:

1. Cell therapies aimed at restoring parenchymal cells with autologous or allogeneic transplant of hepatocytes and/or biliary cells.
2. Cell therapies aimed at remodeling the hepatic microenvironment (ameliorating the inflammatory milieu) to drive liver regeneration.

A growing body of evidence suggests that transplantation of hepatocytes, as the main functional cell of the liver, could theoretically support liver regeneration through engraftment, proliferation, and replacement of the damaged cells. However, obtaining, producing, and successfully engrafting sufficient functional hepatocytes for clinical application remains a challenge, only partially mitigated by recent efforts to differentiate parenchymal cells from stem or stem-like cells, with and without the use of organoid technology or three-dimensional (3D)-printed scaffolds.[7–10] Therefore, interest has shifted toward cell therapies that can remodel the hepatic microenvironment, as these approaches offer the potential to reduce inflammation, reverse fibrosis, and stimulate hepatic regeneration (ie, proliferation of endogenous hepatocytes). These approaches often require lower transplanted cell numbers compared to hepatocyte replacement and offer the potential to restore liver function in the absence of large-scale engraftment.[4,5,11,12] Key remodeling cell types include regenerative macrophage therapy (RMT), bone marrow progenitors, mesenchymal stromal cells (MSCs), regulatory T cells (Tregs), and chimeric antigen receptor T cells (CAR-Ts). Tregs and CAR-T cells remain investigational therapies at preclinical. Preclinical and clinical evidence suggest that MSCs and RMT represent promising regenerative therapies for ESLD. The therapeutic benefit of MSCs is intrinsically linked to their broad immunomodulatory and paracrine effects, such as secreting trophic factors, cytokines, and extracellular vesicles (EVs) that reduce inflammation and fibrogenesis and support hepatocyte proliferation. RMT typically derived from autologous monocytes, promotes liver repair by secreting anti-inflammatory cytokines and producing matrix metalloproteinases (MMPs) that facilitate extracellular matrix (ECM) remodeling and fibrosis reduction.

The annual incidence of hepatocellular carcinoma (HCC) in patients with ESLD of various etiologies is 2%–4%.[13] HCC is the most prevalent form of primary liver cancer worldwide, and one with the highest mortality rate.[14] The global incidence of HCC is rising steeply, with projections indicating an increase to an estimated 22 million cases worldwide by 2030. While approved medical therapies exists for HCC, including multikinase inhibitors such as sorafenib and lenvatinib, and immune checkpoint inhibitors, the objective response rates for first-line regimens remain low (ranging 15%–30%).[15] Also in this case, the limited efficacy of approved therapies can be ascribed to perturbations in the tumor microenvironment, characterized by a highly immunosuppressive response.[16] Interestingly, therapeutics goals in HCC are the opposite as compared to those in ESLD: the need shifts from an anti-inflammatory and antifibrotic effect in ESLD to a pro-inflammatory and ECM remodeling limiting effect in HCC. Examples of cell therapy aiming to achieve such goals are cytokine-induced killer cell approaches, next-generation CAR-T cells, engineered natural killer cells, and emerging macrophage-based therapies. Due to the complexity of the pathogenetic mechanisms and the variety of approaches in current development in HCC and other liver cancers, we will focus herein on cell therapy for ESLD.

Before providing an in-depth review of cell therapy approaches in ESLD, we will review key pathogenetic mechanisms that cell therapies can target or leverage.

Pathophysiological Drivers of End-Stage Liver Disease

Regardless of underlying pathophysiology, the progression to ESLD follows a consistent trajectory involving persistent inflammation, progressive fibrogenesis, vascular remodeling, and systemic immune dysregulation, leading to low metabolic reserve, portal hypertension, and hepatic dysfunction, usually resulting in a decompensation event such as ascites, variceal bleeding, and/or hepatic encephalopathy.[2,3,6]

The pathogenesis of ESLD starts when multiple cycles of degeneration and regeneration drive the development of a chronically inflamed environment; insults of a diverse nature damage parenchymal cells, which then release danger-associated molecular patterns, such as high mobility group box 1 protein, resulting in the activation of KCs and scar-forming hepatic stellate cells (HSCs). Newly recruited immune cells, such as monocyte-derived macrophages, acquire an inflammatory phenotype and amplify the inflammatory and profibrogenic responses by production of tumor necrosis factor alpha, interleukin-1 beta, interleukin-6, reactive oxygen species, and transforming growth factor-β (TGF-β).[17,18]

HSCs occupy a central role in the mechanisms of liver fibrosis: in the healthy liver, quiescent HSCs store vitamin A and contribute to ECM homeostasis.[19] During chronic parenchymal damage, liver inflammation develops, resulting in HSC activation. Furthermore, TGF-β promotes alpha-smooth muscle actin upregulation, synthesis of fibrillar collagens (particularly types I and III), and fibronectin and other ECM components, leading to deposition and crosslinking of the collagen matrix. This remodeling process is dynamically regulated by MMPs and their tissue inhibitors of metalloproteinases; persistent inflammatory signaling favors tissue inhibitor of metalloproteinases expression and matrix accumulation over degradation. In parallel, activated HSCs secrete proangiogenic mediators such as vascular endothelial growth factor linking fibrogenesis to vascular remodeling.[20] Finally, chronic inflammation is supported via the chemokine ligand 2–driven monocyte recruitment, a well-defined feed-forward mechanism reinforcing inflammatory and fibrotic responses[21] (Figure). In summary, what begins as a normal wound-healing response becomes maladaptive when injury is repetitive or sustained, tipping the balance from regeneration toward fibrosis.

Over time, this continuous, inflammation-driven ECM deposition transforms the hepatic microvasculature, driving sinusoidal capillarization marked by loss of endothelial fenestrations, formation of a pathologic basement membrane, and, ultimately, the collapse of bidirectional exchange of blood between sinusoids and hepatocytes.[2,22] These alterations distort hepatic architecture, promote nodular regeneration and increase IHVR, ultimately increasing portal pressure. Therefore, hepatic inflammation not only promotes fibrosis but also amplifies portal hypertension and its downstream clinical sequelae in later stages of the disease. For instance, pathologic remodeling of the vascular bed results in blood being shunted away from the liver, contributing to the development of hepatic encephalopathy. Furthermore, it contributes to decrease in liver metabolic function, for example driving a marked reduction in the synthesis of clotting factors. Elevated portal pressure also leads to splanchnic congestion and intestinal barrier dysfunction, facilitating bacterial translocation and systemic exposure to pathogen-associated molecular patterns. Increased gut permeability is compounded by a decreased KC barrier function, which results in increased hepatic lipopolysaccharide exposure, and recruitment of innate immune cells from circulation, thus promoting further inflammatory cytokine release and intensifying sinusoidal vasoconstriction. This in turn provides the hemodynamic substrate for complications such as ascites and esophageal varices[23] (Figure).

Finally, cirrhosis-associated immune dysfunction (CAID), a hallmark of advanced cirrhosis, is characterized by the coexistence of systemic inflammation and immune deficiencies in the liver due to dysfunctional KCs. CAID development drive an inflammatory escalation, which further exacerbates endothelial activation, splanchnic vasodilation, and arterial hypovolemia, impairing renal perfusion and promoting acute kidney injury extending to, in the most severe cases, hepatorenal syndrome. CAID also further heightens portal pressure and increases the risk of variceal bleeding and neuroinflammatory mechanisms leading to hepatic encephalopathy. These processes also lead to systemic circulatory changes characteristic of advanced cirrhosis, including a hyperdynamic circulation with increased cardiac output, but reduced effective arterial blood volume. Compensatory mechanisms are activated to maintain circulatory stability, but over time these responses become insufficient as cardiac function deteriorates in cirrhotic cardiomyopathy, further worsening circulatory dysfunction and organ perfusion.[24,25]

In summary, decompensation reflects collapse of the fragile equilibrium between portal pressure and systemic inflammatory burden. Recurrent or severe decompensation episodes progressively diminish hepatic reserve, limit regeneration, and accelerate progression toward irreversible ESLD (Figure).[2]

In the next section, we will analyze cell therapies aimed at restoring the loss of parenchyma (hepatocyte or biliary cell transplantation) and those aimed at regulating the microenvironment to favor regeneration (Figure).

Cell Therapy as a Therapeutic Intervention to Restore Parenchymal Mass

Adult Hepatocytes

A therapeutic approach that has been under investigation since the 1970s is hepatocyte replacement therapy. Hepatocyte cell therapy aims to regenerate a functional liver by replacing damaged parenchyma with transplanted hepatocytes, which also offers an opportunity for genetic modification to enhance therapeutic effectiveness.[26] This approach has yielded promising results for the treatment of liver diseases, particularly as a bridging therapy for acute liver injury and metabolic diseases associated to single gene defects.[26,27] However, its therapeutic potential for definitive treatment of cirrhotic patients remains uncertain and hampered by many technical limitations. Although mature adult hepatocytes can improve survival and liver function in preclinical cirrhosis models,[28] translation into clinical benefit for cirrhotic patients has been limited. In 1992, the first autologous hepatocyte therapy was safely carried out in cirrhotic patients,[29] and the results showed that despite a good tolerability profile, very limited engraftment of cells was present 1 month postadministration, and no clinical benefit was observed.

The development of hepatocyte cell therapy has faced several biological, logistical, and technical hurdles; these include challenges in sourcing the appropriate cells, standardization of culture procedures, risk of liver-tropic virus transfer, and an inhospitable inflammatory and fibrotic environment hampering the probability of engraftment. Early efforts relied on adult hepatocytes isolated from donor livers unsuitable for transplantation. However, hepatocytes are notoriously difficult to handle, losing their phenotype quickly

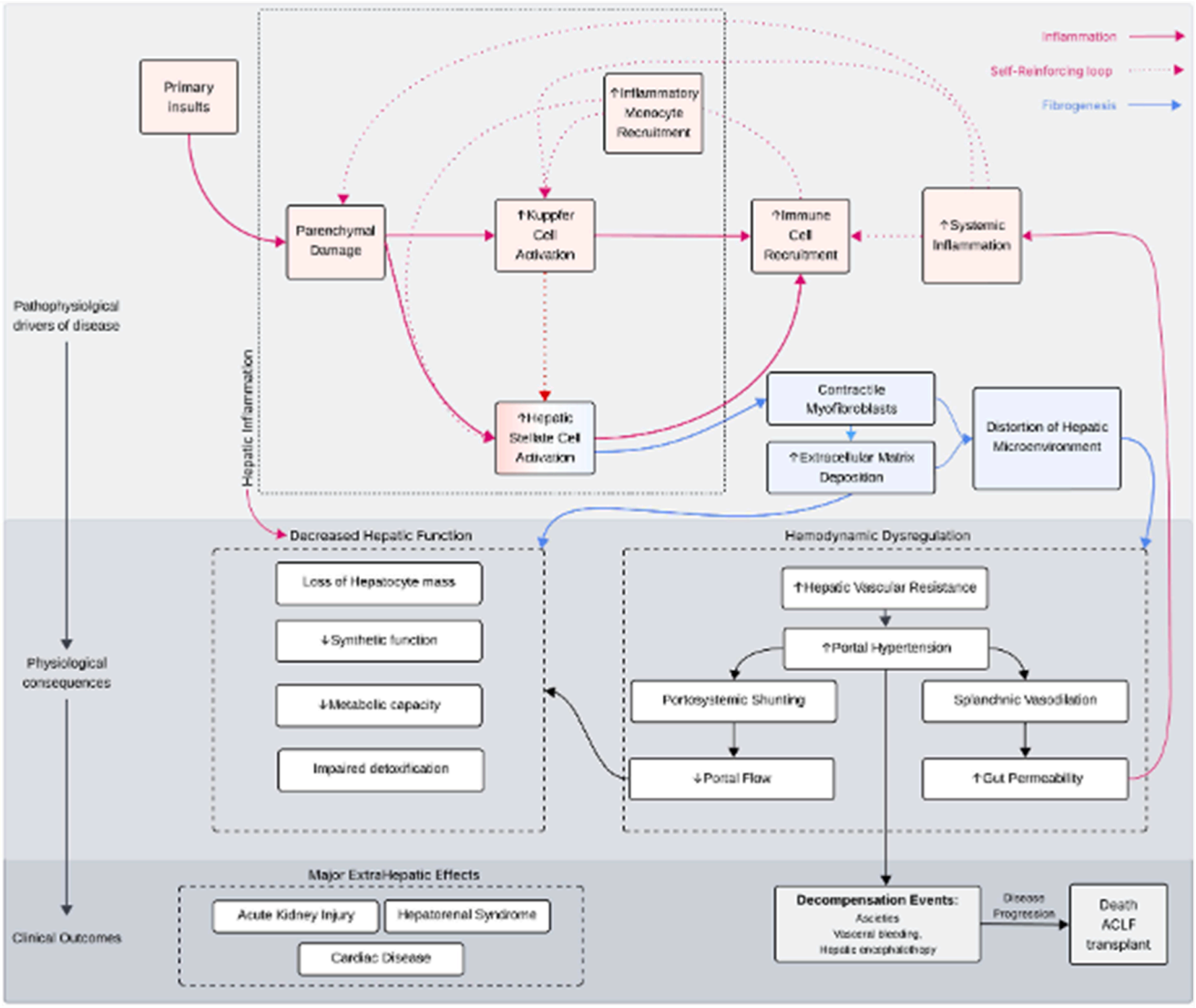


Figure. Pathophysiological drivers of end-stage liver disease. Regardless of etiology, progression to end-stage liver disease (ESLD) follows a conserved trajectory driven by persistent hepatic inflammation, activation of hepatic stellate cells, and progressive fibrogenesis. Chronic parenchymal damage leads to release of danger-associated molecular patterns (DAMPs) and activation of hepatic stellate cells and Kupffer cells, driving recruitment of inflammatory monocyte-derived macrophages, resulting in sustained production of proinflammatory and profibrogenic mediators. This continuous cycle promotes extracellular matrix deposition, sinusoidal capillarization, and architectural distortion, culminating in increased intrahepatic vascular resistance and portal hypertension. The resulting physiological consequences comprise 2 parallel and interrelated axes: (i) hemodynamic dysregulation, characterized by portal hypertension, splanchnic vasodilation, and hyperdynamic circulation with reduced effective arterial blood volume; and (ii) decreased hepatic function, reflecting loss of hepatocyte mass and impaired metabolic, synthetic, and detoxification capacity. Portal hypertension further promotes gut barrier dysfunction and bacterial translocation, amplifying hepatic and systemic inflammation through increased pathogen-associated molecular pattern (PAMP) and TNFα signaling. Together, these processes drive the development of clinical outcomes. The interplay between portal hypertension and systemic inflammation ultimately culminates in hepatic decompensation, progressive loss of functional reserve, and transition to ESLD.

once in culture, and have limited ability to expand ex vivo. Despite continuous improvements in cell isolation, cell culture, and cryopreservation, postthaw viability remains variable. Studies in both rodents and humans have shown that transplanted adult hepatocytes are rapidly cleared with limited long-term engraftment.[29–31]

To address the challenges of using adult hepatocytes for cell therapy, alternative sources of hepatocytes have been explored. These include neonatal/fetal hepatocytes, hepatocyte or biliary epithelial cell (BEC)-derived liver progenitor-like cells, and pluripotent stem cells. These cell sources all have high proliferative capacity and high potential for low

immunogenicity; however, they show immature hepatocyte functionality. Additionally, clinical trials carried out thus far have been small, and therefore clinical findings discussed below should be interpreted with caution.

Fetal/Neonatal Hepatocytes

Neonatal hepatocytes maintain high viability post-cryopreservation but show reduced cytochrome P450 (CYP450) activity, highlighting their immature metabolic phenotype. This may limit their use in transplantation and necessitate further research.[32] Clinical translation of fetal hepatocytes has been explored in a phase 1/2 matched case-control clinical study, which reported that fetal hepatocytes can be delivered safely to patients with hepatitis C and alcohol-related liver cirrhosis, and that they have the potential to deliver temporary disease stabilization, measured by Model for End-Stage Liver Disease (MELD) and Child–Pugh score and fewer episodes of portosystemic encephalopathy during the 1-year follow-up. However, at 1 year of follow-up, the treatment was considered a failure in 6/9 patients.[33] The lack of convincing clinical evidence, coupled with technical challenges around low cell numbers, and ethical restrictions on fetal tissue procurement make this option unsuitable for widespread therapeutic use.

Hepatocyte-Derived Liver Progenitor-Like Cells

An alternative source of hepatocytes is represented by hepatocyte-derived liver progenitor-like cells (HepLPCs). HepLPCs are obtained when adult hepatocytes are cultured in a specific medium containing growth factors, such as epidermal growth factor and hepatocyte growth factor, which promote reversion to a progenitor-like state.[34] HepLPCs remain functionally active (secrete albumin and express CYP450 activity) and successfully repopulate and reduce fibrosis in rat models. Therapeutic activity was shown to be driven by replacement of hepatocyte function and degradation of the ECM. Furthermore, these cells display immunomodulatory activity on T cells and do not express major histocompatibility class II antigens which may reduce the need for patients' immunosuppression. HepLPCs can be manufactured under good manufacturing practices (GMPs) conditions producing a stable off-the shelf product. An initial phase 1 study showed that HepLPCs were well-tolerated but failed to engraft, and there was no clear evidence of translatability of efficacy, as measured by lack of improvement in MELD and Child–Pugh scores.[35]

Biliary Epithelial Cells

BECs are specialized epithelial cells that line bile ducts and are responsible for regulating bile composition and transport. They are bipotent progenitor cells naturally able to differentiate into cholangiocyte or hepatocytes during liver regeneration, when hepatocyte-mediated regeneration is impaired.[36,37] BECs may be a therapeutically viable option as they can be isolated from discarded donor livers utilizing cell surface markers, such as epithelial cell adhesion molecule, and expanded under GMP-compliant conditions.[38] In preclinical models, transplanted BECs repopulate injured bile ducts and parenchyma, improve liver function, and enhance survival.[39] Clinical experience remains limited, but studies involving fetal-derived biliary cells show some promise in terms of short-term stabilization of liver cirrhosis.[40] As with hepatocytes, engraftment efficiency is a key issue, particularly in relation to the detrimental effect of the microenvironment. Finally, it has to be noted that despite the bipotential nature of these cells, it is the differentiation toward biliary cells that shows the best therapeutic promise in rodent models, therefore positioning BECs as potential therapy for cirrhosis of biliary origin (eg, primary biliary cholangitis) rather than of hepatocellular origin (ie, when most of the damage occurs in hepatocytes; eg, SLD).[36,37]

Pluripotent Stem Cell–Derived Hepatocytes

Pluripotent stem cells, including embryonic stem cells and induced pluripotent stem cells (iPSCs) offer another attractive source of hepatocytes for cell therapy. Because deriving pluripotent embryonic stem cells requires removal of the inner cell mass from the embryo, ethical considerations of the tissue source raise significant concerns.[41] To circumvent these concerns, focus has shifted toward differentiating iPSCs into hepatocyte-like cells (HLCs). iPSCs can be derived from patient-derived somatic cells thereby enabling the development of genetically personalized therapies with reduced risk of immunological rejection. iPSCs can be differentiated in vitro into HLCs that share similar function and phenotype with mature hepatocytes.[7,42–44] Despite advancements in culture and differentiation protocols, induced pluripotent stem cell hepatocyte-like cells (iPSC-HLCs) exhibit limited functionality, as in vivo hepatocyte maturation relies on complex interactions with multiple supporting cell types. Significant improvements of iPSC-HLC maturation and function have been achieved by leveraging developments in 3D culture systems, ECM scaffolds and coculture with nonparenchymal cells. iPSC-HLCs produced in scaffolds containing materials such as collagen, fibronectin, and vitronectin and defined laminins display improved function and show enhanced CYP450 activity.[45,46] Preclinical studies have demonstrated that transplanted hepatic organoids enhance survival, reduce fibrosis, and improve liver functionality in rodent models of liver fibrosis.[47] Additionally, transplantation of encapsulated, proliferating human hepatocyte organoids increased survival in posthepatectomy failure mice, with no reported tumorigenicity.[47]

Emerging 3D bioprinting technologies have been utilized to enhance precise spatial organization of hepatic cells within biometric scaffolds to promote hepatocyte survival, maturation and metabolic capacity. Transplantation of these scaffolds in mouse models of liver disease promoted liver regeneration through multiple mechanisms, including direct functional compensation with albumin synthesis and drug metabolism, antifibrotic effects by resolution of pathologic collagen deposition, stimulation of hepatocyte

proliferation and formation of functional vascular systems within 3–4 weeks of transplantation.[8–10,48,49]

Despite these advances, iPSC-HLCs generally resemble fetal rather than adult hepatocytes. They express fetal markers alpha-fetoprotein and cytochrome P450 3A7, and under-express adult-specific enzymes such as cytochrome P450 3A4 and functional markers such as urea secretion.[49] In addition, concern around the tumorigenicity of residual undifferentiated iPSCs remains. Currently, iPSC-HLCs, organoids and 3D-printed structures offer powerful disease modeling and drug testing platforms. However, their immature phenotype, limited scalability, safety, and manufacturing concerns, currently prevent their effective use as therapies for ESLD.[49–51]

Table summarizes cell therapy approaches aimed at restoring liver parenchymal cells discussed herein.

Limitations to Restoring the Parenchymal Mass

One of the major common hurdles to the success of approaches aimed at replacing parenchymal cells lies in the cirrhotic liver microenvironment, which is hostile to hepatocyte engraftment, expansion, and regeneration. This lack of stable engraftment is likely driven by low cell viability, blood-mediated inflammatory responses, and the elevated portal pressures characteristic of advanced cirrhosis.[26] Following infusion, transplanted hepatocytes encounter an instant blood-mediated inflammatory reaction, activating complement and coagulation cascades that can rapidly eliminate a large proportion of cells before they get a chance to integrate into the liver.[26,27] Once in the liver, the host parenchyma itself is also hostile, due to excess inflammation and senescence; hepatocyte senescence is an important feature of liver cirrhosis, and while hepatocyte senescence creates an essential noncompetitive environment needed for donor cells to engraft, high levels of senescence drive host-mediated paracrine senescence, which alongside the inflammatory response can impair engrafted hepatocyte function.[52] To address this hurdle, liver preconditioning to enhance transplanted cell survival and create a more receptive niche has been assessed preclinically with some degree of success.[27,53]

In conclusion, regardless of specific technical hurdles involving hepatocyte cell source utilized, the hostile microenvironment barrier is the major common obstacle to engraftment, durable and reproducible clinical efficacy. It could therefore be postulated that ESLD appears to be mostly a disease of the microenvironment, which prevents existing or transplanted parenchymal cells from regenerating. In the next section we will provide an overview of how cell therapy targeting the dysfunctional microenvironment could be the way forward toward durable clinical stabilization of ESLD patients.

Remodeling the Hepatic Microenvironment With Cell-Based Therapies

In the first section, we highlighted the key role that inflammation plays, both locally to the liver and systemically, in driving the establishment of fibrosis, progression of liver disease, and hemodynamic remodeling associated with liver decompensation events. An ideal therapy for decompensated cirrhosis would therefore need to act across multiple interconnected mechanisms: dampening pathologic inflammation to halt disease progression, exerting antifibrotic activity to inactivate or eliminate activated HSCs and promote matrix degradation, restoring endothelial function to reduce IHVR, and enhancing hepatocyte regeneration to rebuild functional parenchyma. By simultaneously reducing inflammatory drive, degrading scar tissue, and correcting the vascular abnormalities that sustain portal hypertension, such an approach could break the self-perpetuating portal hypertension–inflammation loop and shift the liver from progressive decompensation toward structural and functional recovery.

Key cell types that may control inflammation and are currently under preclinical or clinical investigation include Tregs, CAR-T cells, MSCs, and RMT.[11,54–60] Each is discussed in this section and summarized in Table.

Mesenchymal Stromal Cells

MSCs infusion is one of the most actively explored therapeutics for ESLD, with multiple worldwide early-phase clinical trials evaluating the safety and efficacy of these cells.[61–64] MSCs are multipotent adult stromal cells found in a plethora of tissues, with bone marrow, adipose tissue, and umbilical cord representing the most common sources. Their inherently low major histocompatibility expression makes them naturally hypoimmunogenic,[65] positioning them as a promising off-the-shelf allogeneic cell therapy for ESLD. Despite their ability to differentiate to HLCs, preclinical and clinical evidence suggest that they fail to engraft long-term. Therefore, their main therapeutic benefit may not lie in the "replacement" mechanism but instead in their ability to condition the microenvironment through immunomodulation and tissue remodeling.[66,67] Under appropriate conditions, MSCs can secrete hepatocyte growth factor to attenuate hepatocyte injury and promote liver regeneration.[68] Furthermore, in vitro evidence consistently showed that MSCs can exert strong antifibrotic effects by directly targeting activated HSCs, the principal mediators of liver fibrogenesis. They inhibit HSC proliferation and cell-cycle progression,[69,70] induce their apoptosis, and suppress profibrotic signaling pathways.[71,72] As documented in in vitro and in vivo studies, these actions collectively lead to a reduction in TGFβ signaling, decreased αSMA expression, and limited collagen deposition.[69–75] MSCs also display potent immunomodulatory properties. Coculture systems demonstrate that they suppress T cell activation, promote Treg development and inhibit T helper 1 and T helper 17 responses through the secretion of factors such as galectins, prostaglandin E2, interleukin-10 (IL-10) and indoleamine 2,3-dioxygenase.[54] Several in vitro and in vivo assessments demonstrate that MSCs also modulate B cells, natural killer cells, dendritic cells and macrophages via paracrine signaling. These effects promote anti-inflammatory immune phenotypes and limit

Table. Summary of Cell Therapies Being Evaluated for Liver Cirrhosis

Primary aim	Cell therapy	Mechanism of action	Clinical stage in ESLD	Clinical outcomes	Barriers to clinical translation
Parenchymal cell replacement	Mature hepatocytes	Increased hepatic function	Phase I/II	Safe but no clinical benefit to date	Consistency of product viability; engraftment efficiency
Parenchymal cell replacement	Immature hepatocyte (fetal/neonatal)	Increased hepatic function	Phase I/II	Safe but no clinical benefit to date	Ethical tissue sourcing; engraftment efficacy
Parenchymal cell replacement	Biliary epithelial cells	Increased hepatic function	Early clinical	Safe with short-term stabilization reported in 2 patients	Engraftment efficiency
Parenchymal cell replacement	Hepatic progenitors (HepLPCs)	Increased hepatic function; reduced ECM deposition; immune cell modulation (T cells)	Phase I	Safe but no clinical benefit to date	Engraftment efficiency
Parenchymal cell replacement	Induced pluripotent stem cell–derived products	Increased hepatic function; reduced ECM deposition; macrophage recruitment and polarization	Preclinical	No clinical data	Safety concerns; particularly tumorigenicity from residual undifferentiated cells
Microenvironment patterning/pathogenesis targeting	Mesenchymal stem cells	Increased hepatic function; reduced hepatic stellate cell activation; immune cell modulation (T, B, NK, dendritic cells, macrophages)	Phase I/II	Safe (isolated adverse events reported) with modest but inconsistent clinical benefits	Defining potency-related critical quality attributes, cell sourcing, tissue homing, and clarity of mechanism of action
Microenvironment patterning/pathogenesis targeting	CAR-T cells	Increased hepatic function; reduced hepatic stellate cell activation; modulation of inflammation	Preclinical	No clinical data	Ex vivo CAR-T products: Risk of cytokine release syndrome; variability of source material; transient/limited homing to tissue; cost of manufacturing In vivo CAR-T products: Transient nature of CAR-T cells in chronic disease; off-target safety concerns; risk of cytokine release syndrome
Microenvironment patterning/pathogenesis targeting	Regulatory T cells	Immune recruitment and macrophage polarization	Preclinical	No clinical data	Manufacturing scalability; achieving full dosing due to current limitations in critical quality attributes
Microenvironment patterning/pathogenesis targeting	Regenerative Macrophages	Reduced hepatic stellate cell activation; reduced ECM deposition; modulation of inflammation	Phase I/II	Safe, with clinical benefit observed Improved transplant-free survival (no death or liver transplant)	Defining potency-related critical quality attributes; cost of manufacturing

neutrophil infiltration and oxidative activity. Collectively, these mechanisms create a potent immunomodulatory environment that reduces chronic inflammation, slows tissue damage and supports repair processes in the liver, as suggested by clinical evidence of MSC therapy in ESLD patients.[62,64]

Overall, evidence from clinical studies indicates that MSC therapy is well-tolerated but modest in its efficacy, especially in patients with decompensated cirrhosis/ESLD.[62] Despite promising improvements in key liver parameters, including MELD scores, total bilirubin and albumin levels compared to conventional treatments, current evidence for MSC therapy remains limited by small, heterogeneous studies with short follow-ups, inconsistent effects on liver injury markers, and uncertain short-term survival benefits. Optimal treatment protocols are still unclear, and although major trials report good tolerability, isolated reports of adverse events highlight the need for larger and longer multicenter studies. Key translational challenges also persist, including improving MSC homing to the liver and sustaining long-term cell function post-infusion. In fact, heterogeneity of administration route (intravenous, portal venin and hepatic artery all utilized in clinical studies) may act as a confounding factor in these studies, as it is likely to result in distinct biodistribution and pharmacokinetic patterns.[62,64] Clarifying their mechanisms of action remains challenging because mechanistic insights from preclinical MSC studies often fail to align with observations in clinical settings.[61,62,76] In addition, manufacturing reproducibility and the inability to correlate critical quality attributes (CQAs) to the mechanism of action of MSCs form tightly interconnected chemistry, manufacturing, and controls bottlenecks for MSC therapeutics: variability of MSC sourcing and culture, and their unclear multimodal mechanism of action make it difficult to define robust potency assays that reliably predict therapeutic activity.[77,78] To bypass some of these mechanistic challenges, preclinical studies are increasingly focused on engineering MSCs with specific genes to improve their homing, survival and regenerative capacity in chronic liver disease models.[79] Despite various engineering approaches showing promise in preclinical models,[79] more comprehensive data package on long-term efficacy and safety are needed before clinical translation.

Recently, EVs have been recognized as key paracrine bioactive mediators of MSC. EVs are nanoscale vesicles of heterogeneous sizes that are secreted by parent cells through exocytic pathways to facilitate intercellular communication.[80] These vesicles carry a diverse cargo of proteins, lipids, metabolites, and nucleic acids that can alter the function of recipient cells, thereby influencing processes such as immune responses and tissue regeneration.[80,81] MSC-EVs represent a promising cell-free therapeutic approach for liver diseases due to their intrinsic hepatic tropism and engineering potential. Current preclinical evidence suggests that MSC-EVs can support liver regeneration by rebalancing the immune and stromal environment, reducing inflammation and limiting fibrogenesis.[82,83] They can also reprogram metabolic pathways by restoring redox balance and lipid metabolism. At a cellular level, they can modulate cell fate programs, including apoptosis, autophagy and ferroptosis, while promoting regeneration.[82,84] Despite their attractive characteristics as transformative cell-free therapeutic approaches, concerns regarding size heterogeneity, stability, cargo standardization, production scalability, and ability to establish reliable CQAs remain. These critical chemistry, manufacturing, and controls challenges are crucial to overcome to enable reliable and consistent manufacturing for clinical translation.[77,85]

Regulatory T Cells

Tregs are a small but important subset of cluster of differentiation 4 (CD4) T cells that actively maintain immune tolerance. In both humans and mice, they make up about 5%–10% of circulating $CD4^+$ T cells and prevent harmful autoimmune responses by suppressing self-reactive lymphocytes.[86] Tregs are defined by the expression of the transcription factor forkhead box P3 and by their characteristic $CD4^+CD25^{high}CD127^-$ phenotype. Due to their inherent tolerogenic potential, Treg therapies have been studied across multiple disease indications where immuno-regulation is required (eg, autoimmune disorders), primarily in early-phase clinical trials and preclinical models.[87,88]

In ESLD, Tregs play a critical protective role, and their dysfunction can worsen liver inflammation by allowing pro-inflammatory T cell, such as T helper 1, effector T and T helper 17, to further drive liver injury and contribute to disease progression.[55,89] In fact, depletion of Tregs during carbon tetrachloride–induced chronic inflammation in mice significantly exacerbated the severity of liver pathology by driving the activation and expansion of pro-fibrotic T helper 2 lymphocytes, as well as inflammatory monocytes/macrophages, in the already inflamed tissue.[90] Beyond the liver, the decline of visceral adipose tissue Tregs worsens systemic inflammation and indirectly contributes to hepatic disease progression.[91–93] These studies highlight that harnessing Treg functions may be a therapeutic strategy for ESLD. Adoptive transfer of ex vivo expanded Tregs in metabolic dysfunction–associated SLD rodent models showed that these cells can reduce intrahepatic tumor necrosis factor alpha signaling, lipopolysaccharide-induced hepatotoxicity and alleviate hepatic inflammation.[94,95]

Despite these encouraging findings, accumulating evidence indicates that Tregs may exert pathogenic effects under certain fibrotic conditions: paradoxically, during established fibrosis, Tregs in the liver can further drive fibrogenesis by activating HSCs through TGF-β, interleukin-8, and stress-responsive pathways, such as the activating transcription factor 4–integrin $\alpha v\beta 8$ axis, while simultaneously producing protective IL-10 to inhibit ECM production by HSCs.[96–100] In high fat diet mouse models, adoptive transfer of Tregs worsened hepatic steatosis and increased liver injury markers.[101,102] This paradox is supported by human studies reporting

inconsistent intrahepatic Treg frequencies in metabolic dysfunction–associated SLD, reflecting heterogeneity across disease stages.[102,103] Clinically, Treg-based therapy in liver transplantation has shown preliminary signs of tolerability, but its clinical efficacy remains unproven due to major logistical constraints: most patients in early stage studies cannot receive full infusions because manufacturing often fails to produce the required dose, and infused Tregs show only transient expansion with limited functional impact.[104,105] To fully harness the therapeutic potential of Tregs in ESLD, further understanding of the context-dependent effects of these cells on liver inflammation, fibrosis and regeneration is needed, alongside considerable improvement in GMP manufacturing processes and definition of reliable and reproducible CQAs.

Chimeric Antigen Receptor T Cells

CAR-T cell therapy is a well-recognized transformative modality in cancer treatment, with 6 Food and Drug Administration–approved products now used for hematologic malignancies. CAR-T cells are T cells genetically engineered with a class of synthetic receptors termed CARs that reprogram their specificity and function to eliminate tumor or dysfunctional immune cells.[106] CAR-T clinical success in hematology sparked growing interest in applying CAR-T technology beyond oncological conditions, including autoimmune, infectious, and fibrotic diseases.[107]

Early preclinical proof-of-concept studies in a bleomycin-induced model of systemic sclerosis offered one of the first hints of this potential, demonstrating that anti–cluster of differentiation 206 CAR-T cells were able to reduce dermal thickening and dampen inflammatory signaling.[108] Similar strategies were explored in cardiac fibrosis disease models. In these models, adoptive transfer of CAR-T cells engineered to target fibroblast activation protein (FAP) successfully reduced cardiac fibrosis and helped restore cardiac function, demonstrating that FAP-directed CAR-T cells could reverse structural cardiac damage in vivo.[109] Similar studies using CAR-Treg treatment in a bleomycin model of pulmonary fibrosis demonstrated a reversal of established fibrosis, while inducing negligible cytokine release syndrome (CRS), a key safety consideration of CAR-T therapies.[110]

Liver fibrosis has emerged as a particularly active area of investigation. Urokinase-type plasminogen activator receptor–specific CAR-T cells have been shown to restore tissue homeostasis in mice with fibrosis.[56] More recently, CAR-T cells directed against FAP, which is highly expressed in activated HSC, were able to alleviate fibrosis and even prevent progression into HCC, underscoring the therapeutic promise of targeting the fibrogenic machinery.[60]

Together, these studies outline an encouraging potential for ex vivo generated CAR-T cell therapy as a transformative approach to treat fibroinflammatory diseases. However, significant obstacles to clinical translation remain, such as reported CRS, poor quality of T cells derived from chronically ill patients, limited trafficking and persistence of CAR-T cells within dense fibrotic tissue, and high costs of manufacturing.[111,112]

To overcome the limitations of traditional ex vivo CAR-T manufacturing, in vivo CAR-T cell engineering is emerging as compelling alternative. Rather than manipulating T cells outside the body, this strategy delivers genetic instructions directly to the patient, enabling endogenous T cells to be reprogrammed in situ to exert their therapeutic activity. In vivo engineering offers the promise of streamlined manufacturing, reduced costs and improved scalability. Recent preclinical studies support this potential. In liver fibrosis models, anti–cluster of differentiation 5 targeted lipid nanoparticles delivering anti-FAP CAR messenger ribonucleic acid transiently produced activated anti-FAP CAR-T cells. These cells targeted profibrogenic HSC and modulated immune, endothelial, and parenchymal compartments, collectively reducing inflammation and promoting hepatic homeostasis.[57]

Overall, despite its exciting promise, in vivo CAR-T engineering still faces major hurdles. These include off-target gene delivery, unpredictable CAR-T expansion and increased risks of CRS. Because engineering happens inside the patient, it is difficult to regulate CAR expression and ensure T cell quality. Additionally, uncertain long-term effects remain as vectors may affect non–T cells and alter immune function over time. Moreover, adapting CAR-T therapies to multimodal fibroinflammatory diseases is more challenging than using them in malignancies. The main obstacles are identifying reliable antigens that can address the complex microenvironment typical of each disease, while also generating sustained CAR-T persistence to achieve lasting clinical impact rather than relying solely on direct tumor cell killing.[113] These concerns highlight the need for further development before in vivo CAR-T therapies can be translated into clinical settings requiring microenvironment modulation, such as ESLD.

Regenerative Macrophage Cell Therapy

In the mid-2000s, landmark studies highlighted that regenerative macrophages (RMs) are indispensable effectors of matrix remodeling and fibrosis resolution.[73,114,115] These studies highlighted the concept that inflammation, scar formation and remodeling are interlinked, and that fibrosis is a dynamic, immune-regulated process. The anti-inflammatory and antifibrotic nature of the RM uniquely positions them to drive coordinated tissue repair through targeting the key pathogenic pathways, as opposed to isolated pathway modulation in alternative therapeutic approaches such as anti-FAP therapies, which single out HSC pathways.[57]

Recent in vivo studies have enhanced our understanding of macrophage heterogeneity in chronic liver disease, demonstrating that triggering receptor expressed on myeloid cells 2 positive macrophages - also referred to as lipid-associated macrophages or scar-associated macrophages—comprise both resident KCs and recruited, monocyte-derived

macrophages, and are critical for orchestrating the transition from active fibrogenesis to fibrosis remodeling. Triggering receptor expressed on myeloid cells 2 expression is critical for fibrosis resolution, as it promotes a RM phenotype through efferocytosis, enhance lipid handling, and supports ECM remodeling.[116–118] Furthermore, in animal models of chronic liver injury, injection of bone marrow-derived macrophages with a regenerative phenotype promoted liver regeneration via coordinated immunomodulatory and matrix-remodeling pathways. Such pathways include enhanced endogenous macrophage recruitment, increased MMPs activity and IL-10 secretion, suppression of activated myofibroblasts, and stimulation of the hepatic progenitor niche.[11,119,120] By attenuating hepatic inflammation, thereby reducing HSC activation and contractility, RMs have the potential to decrease IHVR and disrupt the self-reinforcing inflammation-portal hypertension loop that underpins decompensation events. Interestingly, bone marrow precursors were tested side-by-side with macrophages in the same study, but did not fully recapitulate the beneficial effect of macrophage transfer on inflammation and fibrosis.[11] This was further confirmed when bone-marrow precursors were tested as therapeutics in an early-stage trial and failed to deliver meaningful therapeutic benefit (EudraCT 2009-010335-41).

This highlights that not all microenvironment-modifying therapy have equal chance of success, and clear understanding of the underpinning biology is key to translate research findings into clinical benefit: the clear mechanistic role of RMs in fibrosis resolution, coupled with the possibility of manufacturing them from the patient's own monocytes in a GMP-compliant fashion paved the way for the translation of RMT in chronic liver disease patients.[12,121]

Translation into human disease further supports regenerative macrophage therapy mechanistic framework. Autologous macrophage cell therapy has demonstrated safety in patients with stable cirrhosis in the MATCH Phase 1 study (ISRCTN 10368050), an open label, dose-escalation study, in which 3 doses were tested (n = 3/dose; 10^7, 10^8, and up to 10^9 cells). In this study, no acute toxicity and no increase in circulating cytokines postinfusion were detected, confirming the benign safety profile observed in rodent models. A trend toward reduction of various serum biomarkers, including MELD, was observed,[122] although no dose-response was detected. The positive outcomes of the Phase 1 study drove the design and execution of the randomized, multicenter, controlled MATCH phase 2 study. Twenty-six patients with ESLD received RM treatment, and were compared to 24 patients receiving standard of care.[122] The results in the first year showed no liver-related events in treated participants, compared with multiple liver-related events in the control group.[122] Furthermore, recent conference communications[123] support a long-term benefit of this treatment, with treated patients showing a statistically significant increase in overall survival and transplant-free survival, up to 3 years posttreatment. Treatment was associated with a transient systemic immunomodulatory signature, characterized by increased peripheral anti-inflammatory cytokines and reduced pro-inflammatory cytokines, persisting up to, but not beyond, 90 days postinfusion.

These findings highlight 3 important concepts as follows:

1) Macrophage-mediated effects work beyond the hepatic compartment, extending systemically, highlighting their potential to decrease portal hypertension and reduce further decompensation events.[58]
2) Alternative dosing strategies could be considered to enhance anti-inflammatory effects beyond 90 days, such as engineering for enhanced potency and/or a multiple dose regime, thereby enabling treatment of decompensated patients.
3) Preclinical data suggest that RMs recruit monocytes from the circulation, potentially expanding the pool of available monocyte-derived macrophage to then condition to a regenerative phenotype.[11] Given that a single dose triggers long-term benefit despite RM short half-life, it is reasonable to hypothesize that this mechanism translates from rodents to humans. An appropriate pharmacodynamic biomarker study should be deployed to interrogate this hypothesis further.

Currently, the use of RMT in advanced cirrhosis is being extended in the EMERALD phase 1/2 trial (NCT06823713), which uses autologous RM engineered with human IL-10 and matrix metalloproteinase-9 to improve the anti-inflammatory and antifibrotic mechanisms of action of RMs, and targets a more severe population as compared to the MATCH studies. In conclusion, RMs have the potential to address the core mechanistic drivers of portal hypertension; they suppress hepatic inflammation, halt fibrogenesis via the inactivation of the HSC population and promote fibrolysis through MMP secretion. Together, the anti-inflammatory and antifibrotic mechanism of action leads to liver regeneration via stimulation of hepatic progenitor cell proliferation and differentiation. The specific multimodal nature of this cell therapy, aimed at recapitulating the native role of RM in acute damage, is therefore well-suited to a disease with a complex pathogenesis such as ESLD. Further studies are needed to confirm RMT tolerability and efficacy profile.

Table provides a summary of all cell therapy approaches aiming at remodeling the hepatic microenvironment.

Conclusion

Liver decompensation is a pathologic mechanism rooted in a maladaptive response, characterized by chronic inflammation and fibrosis, which fuels a vicious cycle of endothelial dysregulations, portal hypertension, and severe clinical sequelae. No medical therapies currently exist for

this condition, with orthotopic liver transplantation being the only curative solution, hampered by limited access, shortage of suitable donors, complexity of the surgical procedure, and intensity of postoperative care.

In this context, cellular therapies are emerging as candidates to offer long-term clinical benefit. Despite promising preclinical results, the most obvious cell therapy approach, ie, replacement of the lost liver parenchyma with hepatocytes, has thus far yielded limited clinical success. Approaches aiming to correct the dysfunctional microenvironment have been significantly more successful; in particular, T cell therapies targeting myofibroblasts and RMs targeting inflammation and fibrosis thanks to their multimodal mechanism of action have shown great promise. RMT, thanks to a relative straightforward manufacturing, coupled with favorable tolerability profile, and supportive clinical data, place them at the forefront of the field as a future therapeutic option. Further studies on optimizing their dosing regime and potency profile are underway, to fully realize their therapeutic potential.

Finally, the success of microenvironment targeting therapies opens the door to the fascinating possibility to consider ESLD as a disease of the microenvironment rather than a disease driven by the loss of liver parenchyma, and therefore metabolic liver reserve. It is the dysfunctional microenvironment that creates a niche hostile to regeneration, preventing existing hepatocytes from proliferating and functioning properly. Transforming the microenvironment from hostile to permissive to regeneration may be the preferrable therapeutic strategy, addressing the underlying cause of diminished hepatic reserve, due to parenchymal cell loss, rather than simply adding new parenchymal cells to a dysfunctional niche.

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