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Review

Arouse potential stemness: Intrinsic and acquired stem cell therapeutic strategies for advanced liver diseases

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ABSTRACT

Liver diseases are a major health issue, and prolonged liver injury always progresses. Advanced liver disorders impair liver regeneration. Millions of patients die yearly worldwide, even with the available treatments of liver transplantation and artificial liver support system. With its abundant cell resources and significant differentiative potential, stem cell therapy is a viable treatment for various disorders and offers hope to patients waiting for orthotopic liver transplantation. Considering such plight, stem cell therapeutic strategies deliver hope to the patients. Moreover, we conclude intrinsic and acquired perspectives based on stem cell sources. The properties and therapeutic uses of these stem cells' specific types or sources were then reviewed. Owing to the recent investigations of the above cells, a safe and effective therapy will emerge for advanced liver diseases soon.

1. Background

Liver illnesses caused by alcohol abuse, viral infection, and inborn metabolic abnormalities account for many global health issues and impose huge economic loads on sufferers (Asrani et al., 2019). Due to the limitations of current therapeutic methods, advanced liver diseases (ALD), defined as cirrhosis of any cause with one or more liver-related complications, is an inevitable end, and it is responsible for 560.4 age-standardized disability-adjusted life years per 100,000 population globally (Jepsen & Younossi, 2021; Naik et al., 2020). Due to the inconvenience and expensive cost of traditional artificial liver support systems, most patients view orthotopic liver transplantation (OLT) as the best approach to prolong their lives. As for the cell-based bio-artificial liver, primary porcine liver cells have been used to construct an extracorporeal hybrid liver support system clinically (Sauer et al., 2003). Another extracorporeal supporting system using human fibroblast-induced hepatocytes has been shown to benefit acute liver failure in pigs and humans (Wang et al., 2023; Shi et al., 2016). Yet, it has not been proven to rescue patients with chronic liver diseases once and for all. American liver transplantation has steadily increased to 8906 in 2020 (Jepsen & Younossi, 2021). However, owing to high-risk operations, possible utilization of lifelong immunosuppressants and specifically the scarcity of suitable deceased-donor, its clinical application is hindered from benefiting all. Split liver transplantation (SLT) and living donor liver transplantation (LDLT) have reduced mortality by narrowing the gap between patients on the waiting list and accessible livers. Still, they have not eliminated it (Fisher, 2017; Hackl et al., 2018). Hepatocyte transplantation (HT) and stem cell therapy, which are less invasive, have shown promise in reconstituting the functional parenchyma with fewer grafts, prolonging the bridging period to OLT, and boosting liver regeneration to reduce the need for organ transplantation (Dwyer et al., 2021). Stem cells' potential for self-renewal and differentiation can be described as a Taoist saying goes, "One produced two, two produced three, three produced all" (Fig. 1). Stem cells are also more likely to solve the

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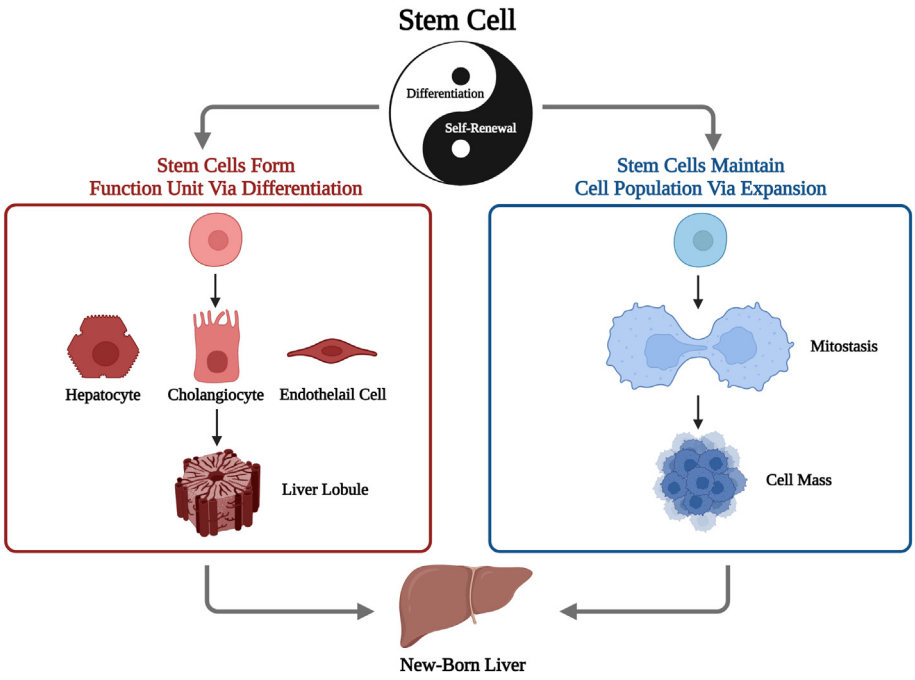

Fig. 1. One produced two, two produced three, and three produced all things. Stem cells harbor self-renewal and differentiation abilities, which enable such cells to maintain the cell population and form functional units, thus leading to the future of providing all patients with appropriate newborn livers.

difficulties than hepatocyte transplantation due to their wider range of origins and ability to survive cryogenic preservation (Zhang et al., 2021a). Initially, stem cell therapy was applied clinically to hematopathology. Then, to broaden its application range, it was investigated to have a profound prospect in neurology and ophthalmology as the immune privilege of brains and eyes simplified the trials. As for other solid organs with their more intricate niche, such as the liver, stem cell therapy still has a long way to go. The types of stem cells concerning the

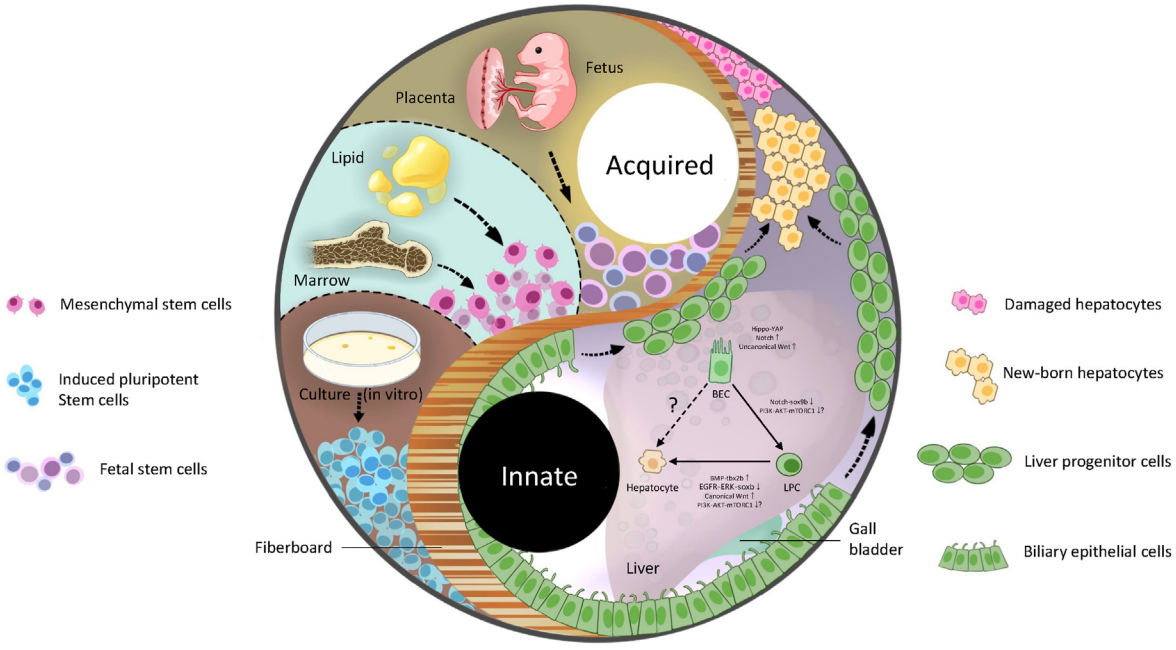

Fig. 2. Potential intrinsic and acquired stem cell therapy. There are two stem cell therapies for advanced liver diseases, intrinsic and acquired, to treat the patients possibly. As for the former, the upregulation of Hippo-YAP, Notch and uncanonical Wnt pathways promote the expansion of BECs, then the downregulation of Notch-Sox9b pathways proceeds dedifferentiation of BEC, and at last, upregulation of BMP-tbx2b and canonical Wnt pathways and downregulation of EGFR-ERK-sox9 pathway assist the process of LPC-to-hepatocytes. In contrast, the role of the PI3K-AKT-mTORC1 pathway remains unclear. Cell sources for acquired stem cell therapy in advanced liver diseases include fetal-related tissue and adult tissue, from which mesenchymal and fetal stem cells can be isolated and induced pluripotent stem cells can be reprogrammed. For their application, there are indirect and direct approaches.
On the one hand, these cells are cultured into hepatocyte-like cells consequent to the differentiation *in vitro*. Contrarily, MSC and FSC can use in the patient directly since they could differentiate *in vivo* with relatively low risk. iPSC, induced pluripotent stem cell; MSC, mesenchymal stem cell; FLSC, fetal liver stem cell; BEC, biliary epithelial cell; LPC, liver progenitor cell.

potential treatments of ALD can be roughly classified into 2 categories, intrinsic stem cells and acquired stem cells (Fig. 2). The "facultative stem cells" liver progenitor cells (LPCs) and biliary epithelial cells (BECs) can transdifferentiate into hepatocytes. However, the existence of preexisting hepatic tissue-specific stem cells is contested (Michalopoulos & Khan, 2015; Raven et al., 2017). The latter continues to be divided into three groups, including fetal stem cells (FSCs), mesenchymal stem cells (MSCs) and pluripotent stem cells (PSCs), which harbor the capability to replenish the liver parenchyma and simultaneously modulate the microenvironment of liver regeneration at some extent.

This review presents numerous information regarding the main types of stem cells and their effects on ALD from innate and acquired perspectives. Simultaneously, we discuss the current progress of clinical research with its bottlenecks and prospects.

2. Intrinsic stem cell therapy

The liver's parenchymal and nonparenchymal cells are all involved in hepatocyte regeneration, making it a highly regenerative organ (Fausto, 2004). To seek the cellular source of liver regeneration, it is reported that a group of telomerase high-expressing hepatocytes distribute throughout the liver lobule, repopulating the liver mass in homeostasis or injury (Lin et al., 2018). However, persistent liver injury, specifically in ALD with a loss of native hepatocytes and severe pathological alterations like cirrhosis, can decrease hepatocyte proliferating ability (Choi et al., 2014). Then targeting the intrinsic stem cells from non-hepatocytes residing in the liver seems to be a natural idea facing ALD. However, the existence of adult liver tissue-specific stem cells cannot be ascertained yet.

2.1. Liver progenitor cells and biliary epithelial cells

2.1.1. Controversial types of intrinsic stem cells

LPCs in the peribiliary glands and Canals of Hering, a population of quiescent liver cells, increase and differentiate when hepatocyte-driven regeneration is inhibited (Carpino et al., 2016; Kohn-Gaone et al., 2016). Moreover, with the single-cell RNA sequencing, a human liver cell atlas was provided to reveal a gradient expression of TROP2 that used to be identified as LPC markers among the liver cells, and a TROP2 intermediate expression subpopulation of bile duct cells strongly confirms the derivation of putative liver progenitor population after in situ location (Aizarani et al., 2019). Contrarily, LPCs activation was inhibited due to the implication of methylenedianiline that damages the bile duct; it is controversial whether LPCs exist in liver as an individual cell type (Ko et al., 2020). In various animals, BECs were also shown to supplement hepatocytes. BEC transdifferentiation replaces liver parenchyma in NTR/MTZ-induced zebrafish hepatocyte ablation models (He et al., 2014). A recent study observed that BECs converse into proliferative hepatocytes after short-term injury when blocking primary hepatocyte regeneration in hepatocyte-target p21 overexpressing or ltgb1 elimination mouse models (Raven et al., 2017). However, the mechanism how BECs sense the proliferation ability of hepatocytes is still not understood, and the triggering mechanism for such cells to play a stem-like role needs further exploration.

Moreover, in a mouse model induced by long-term thioacetamide (TAA) or 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) treatment without genetic manipulations, a study implicated that up to 55.7% hepatocytes could be repopulated from the BECs by an HNF4α^{+}CK19^{+} biphenotypic status without forming cancer nodules, which mimics the real progress in chronic liver injuries. Such phenotypic cells were also discovered in cirrhotic human livers (Deng et al., 2018). A study revealed that there was a transformation from K19^{+}/GS^{+}/EpCAM^{+}/Heppar1^{-} to K19^{-}/GS^{-}/EpCAM^{-}/Heppar1^{+} of hepatocyte bud, a potential anatomic structure referring to the stem cell-based regeneration of the liver, in human cirrhosis specimens. In contrast, such buds are reduced in biliary diseases with bile duct loss; thus, it ensures the potential contribution of BECs in ALD (Stueck & Wanless, 2015). Cholangiocytes lose their transcriptional differences during organoid culture but retain their adaptability and *in vivo* signatures, which is appealing when transplanting the cholangiocytes organoid into the human liver to repair bile ducts (Sampaziotis et al., 2021), indicating that BECs harbor the potential stemness and their fate seems to be controlled by the specific types of liver injury.

2.1.2. Possible mechanisms of intrinsic stem cell-derived hepatocyte regeneration

Scientists are fascinated by the conceivable process which underpins potential therapeutic techniques, as the initiative events and inherent stem cell fate remain unknown. With the zebrafish model, Ko et al. revealed that all the preexisting BECs dedifferentiate into LPCs during the BEC-derived liver regeneration, indicating that it may contain two major steps, including BEC-to-LPC and LPC-to-hepatocyte in BECs-based liver regeneration. Unlike zebrafish, TAA-treated mouse models may regenerate biliary-to-hepatocytes directly based on new LPC markers (Deng et al., 2018). However, the process in mouse models is controversial since small *Lgr5*$^{+}$ cells were still observed near bile ducts after the server liver damage (Huch et al., 2013). Thus, it seems that an indirect process is temporarily more conceivable, of which the potential molecular mechanisms are described below.

During biliary-to-hepatocyte differentiation, Notch signaling boosts the IGF1R to make BECs more sensitive to IGF1 and increase their quantity. However, persistent BEC proliferation prevents hepatocellular development, demonstrating that proliferation alone is insufficient (Minnis-Lyons et al., 2021). Remarkably, Ko et al. uncovered that Notch inhibition impels the conversion of LPCs to hepatocytes *in vivo* by *sox9b* (Russell et al., 2019). According to Ko et al., the Notch signaling pathway is transiently activated in the early stage of biliary-mediated differentiation and then intervenes before the following step (He et al., 2014). With the single-cell analysis, dynamic activation of YAP was uncovered among the BECs population, which was induced by the bile acid exposure level to maintain BECs' homeostatic (Pepe-Mooney et al., 2019). Considering that gut microbiota is involved in the progression of bile acid metabolism, it could also have a crucial role in the transdifferentiation of BECs via the liver-gut axis.

Moreover, the Hippo/YAP pathway was currently validated to promote the BECs expansion during the ductular reaction (DR) (Planas-Paz et al., 2019), which not only contains the BECs expansion and differentiation but also promotes intrahepatic angiogenesis (Coll et al., 2022). LPC-to-hepatocyte differentiation controls liver function restoration. BMP4 induces LPC mid- and late-phase hepatic markers (Fan et al., 2009; Wang, Yuan, & Shen, 2015), and BMP9 functions as a negative regulator of LPC expansion by decreasing cell expansion and increasing apoptosis (Addante et al., 2018). Then, Choi et al. certified that BMP signaling suppression did not hinder the dedifferentiation of BECs, but governs the LPCs differentiation into hepatocytes by *tbx2b* in a hepatocyte ablation model (Choi et al., 2017), which further validated the BMP role in LPC-to-hepatocytes differentiation. EGFR signaling not only regulates hepatocyte proliferation (Gonzalez et al., 2021), but is regarded as among cores of the regenerative process after the liver injury and involves cellular transformation associated with chronic damage (Gonzalez et al., 2021). In a zebrafish model, EGFR governs LPC-to-hepatocyte differentiation through the ERK-Sox9 axis, and EGFR inhibitors are more effective than Notch inhibitors (So et al., 2021), which further concludes a more promising target for regenerative medicine and reprogramming *in vitro*. Besides the above signaling, Hdac1 regulates LPC-to-hepatocyte differentiation by repressing *sox9b* expression (Ko et al., 2019). mTOR and Wnt signaling is thought to be involved in biliary-to-hepatocyte differentiation. Though experiments associated with the influence of mTOR on biliary-mediated regeneration are still limited, it is proven to take different effects in the thorough process during biliary-to-hepatocyte regeneration. In an NTR/MTZ-treated zebrafish model, mTORC1 inhibition suppresses BEC dedifferentiation partially through Urb2-mediated protein synthesis, which is vital for

mTORC1 downstream effectors and LPC duplication. However, it only represses the proliferation of LPC-derived hepatocytes in the late stage (He et al., 2019).

Consequently, such evidence indicates that mTORC1 is truly involved in the BEC-driven regeneration, but the actual effects of mTORC1 urge further investigation. As for Wnt signaling, its uncanonical and canonical pathways are involved in BEC-driven regeneration, contributing to different processes. Contrarily, non-canonical Wnt signaling is considered significant merely for initiating DR (Okabe et al., 2016). However, Wnt3a-induced canonical Wnt/β-catenin signaling causes LPCs to become hepatocytes (Boulter et al., 2012). Canonical Wnt signaling may have contributed to other BEC-driven hepatocyte regeneration mechanisms. Recently, LGR4/5-mediated Wnt/β-catenin signaling is neither active nor necessary for DR (Planas-Paz et al., 2019). It is provided to assure further that the canonical Wnt/β-catenin signaling pathway mainly participates in the LPC redifferentiation into hepatocytes. DNA methylation at the p53 locus activates the dedifferentiation by inhibiting mTORC1 signaling and induces hepatocyte redifferentiation by repressing BMP signaling, which suggests that epigenetic modification also regulates the whole process (He et al., 2022). The degree of transdifferentiation determines whether intrinsic stem cells cause cancer, hence finding the essential regulator will lead to further research.

Besides, the stem cell niche has a tight relationship with cell plasticity and fate (Chacon-Martinez, Koester, & Wickstrom, 2018). Physically, the proliferation and liver organoid formation of BECs was reported to be negatively correlated with dynamical cell-cell contacts between them and $PDGFRa^{+}SCA1^{+}$ periportal mesenchymal cells (Cordero-Espinoza et al., 2021). Despite this, proliferating BECs recruit part of immune cells, myofibroblasts and endothelial cells by secreting the chemoattractant at the DR initiation. Macrophages help trigger the DR and promote biliary-mediated regeneration by the Wnt signaling pathway. (Boulter et al., 2012). Additionally, ECM, a complicated network composed of fibrous proteins and proteoglycans, can regulate the regeneration with matrix metalloproteinases (MMPs) which modulate collagenolytic activity (Roderfeld, 2018). Studies in humans and animals have shown that BECs can develop into hepatocytes after leaving a laminin-rich environment (Dubuquoy et al., 2015; Lorenzini et al., 2010). Due to complicated cellular or non-cellular components, the new understanding of the extracellular niche and BEC-driven regeneration cannot harness intrinsic cell plasticity and proliferative ability for ALD therapy.

In conclusion, LPC, or BEC-driven hepatocyte regeneration, is an exceedingly complex process with intricate networks of multiple signaling and factors inside the cells. Moreover, the regenerative niche around BECs also influences cell fate. The findings enable the invention of precise transdifferentiation-regulating regenerative therapies. Given their positive and negative effects, balancing the safety and effectiveness of intrinsic repair cautiously is still a challenge that urges us to address, and the more precise mechanism of biliary-to-hepatocyte transdifferentiation in humans must be further certified by a more appropriate and efficient model and other brand technologies to mine deep data.

2.1.3. Therapeutic applications

With the above data, researchers could not yet paint the picture of BEC-to-hepatocyte regeneration, much alone the proper dose and delivery techniques. Therefore, employing these cells in clinical stem cell therapy for ALD is not yet safe, which is still at the proof-of-concept stage.

For cell transplantation, research regarded CD45(−)/CD11b(−)/CD31(−)/MIC1-1C3(+)/CD133(+)/CD26(−) subpopulation as a prospective isolation strategy for adult hepatic stem cells (Dorrell et al., 2011). Later, Huch et al. designed a culture medium with the Wnt agonist RSPO1 to expand the mouse-derived single $Lgr5^{+}$ liver stem cells. Then they certified that Wnt signals, cAMP activation, and *Tgf-β* inhibition were crucial for stable long-term expansion of human bile duct-derived stem cells (Huch et al., 2013, 2015). By precoating BECs with hyaluronic acid before transplantation, 11% of the liver parenchyma was restored, and ALB levels increased significantly, improving BEC engraftment (Nevi et al., 2017). Furthermore, with the progressing isolation, ex vivo expansion and long-term culture technologies, BECs have been successfully acquired from discarded human livers with excessive steatosis or fibrosis to transplant to rescue a mouse model of biliary diseases. It is also proved that transplantation of hBECs ameliorates the level of bilirubin, fibrosis and survival rate (Hallett et al., 2022), whereas it is unclear whether BECs repopulate the parenchyma. In addition, BECs regulate bile acid levels to enable remaining intact hepatocyte cell cycle progression because FXR and TGR5 preserve bile acids (Merlen et al., 2017). Nonetheless, scant evidence exists to support the direct interaction between BECs and the remaining healthy hepatocytes. This may be due to the fact that they are spatially distant from each other.

Moreover, for regenerative medicine, which is a non-invasive therapeutic strategy compared to cell transplantation, a recent study showed that farnesoid X receptor (FXR) activation inhibited the BEC-driven regeneration by suppressing PI3K-AKT-mTORC1 signaling and, therefore, downregulating LPC-to-hepatocyte differentiation rather than BEC-to-LPC dedifferentiation (Jung et al., 2021). In another work, FXR impaired BEC-driven regeneration by accumulating LPCs and preventing Notch-controlled hepatocyte production (Cai et al., 2021). Consequently, FXR blockers can function *in vivo* to impel the BEC-driven regeneration. Further, since FXR contributes to regulating the homeostasis of bile acid, whether metabolic homeostasis plays a pivotal role in such liver regeneration arouses huge interests and may lead to the development of medicines or therapies concerning metabolism. However, few regenerative medicine research targets BECs in situ to promote the biliary-to-hepatocyte transition without tumorigenicity.

3. Acquired stem cell therapy

Targeting intrinsic stem cells does not always improve liver function in all types of ALD because intrinsic stem cell-based healing happens step by step while some patients are on the brink of death. ALD patients with congenital aetiology, including inborn errors of metabolism (IEM), cannot undergo this type of correction since genetic mistakes persist after that. Thus, developing acquired cell-based treatment is considered a more promising method to deal with emergencies and correct these intrinsic conditions. Mature hepatocytes are obvious choices, and HT for IEM is currently regarded as a theoretical and practicable strategy. Though the HT clinical safety and short-term effectiveness were underpinned in a series of experiments with mouse models (Ambrosino et al., 2005; Celik et al., 2019; Overturf et al., 1997; Soltys et al., 2017; Stephenne et al., 2012), the clinical research elucidated that HT did not benefit as much as preclinical research (Iansante et al., 2018). Considering these drawbacks of HT, stem cell-based cell transplantation seems to be a more promising method.

3.1. Fetal stem cell

3.1.1. Sources and characteristics

Since the initial fetal tissue transplantation for diabetes mellitus, fetal stem cells have attracted significant research. Studies have shown that fetal stem cells are derived from the fetus and extra-embryonic tissues. The former includes cadaveric fetuses due to miscarriage, stillbirth, ectopic pregnancy and elective abortion (Ishii & Eto, 2014), and the latter includes amnion membrane, amniotic fluid, Wharton jelly and placenta (Marcus & Woodbury, 2008). Fetal stem cells derived from the two sources share the similar property of self-proliferation and reduced immunogenicity, but the differentiative potential of fetal stem cells is source dependent. Stem cells generated directly from the fetus are usually multipotent, meaning they can only differentiate into a few cell types. In contrast, those obtained from extra-embryonic tissues usually display pluripotency markers like Oct-4 and Sox2 (Bacakova et al., 2018). Therefore, extra-embryonic tissues derived stem cells seem to be more attractive.

Fetal liver stem cells (FLSCs), one type isolated from fetal livers, are regarded as the only choice in fetus-derived stem cells to effectively

regenerate the almost normal liver (Oertel, 2011), representing an attractive stem cell therapy for liver diseases. These cells were found to contain a long-term compartment of colony-forming cells with multipotency, powerful self-renewal, and proliferative ability under extracorporeal culture conditions. They can also form hepatic-like tissue morphologically and phenotypically at the selective location according to liver injury (Yasen et al., 2019). Additionally, it is speculated that FLSCs possess less immunogenicity since they are immature cells without HLA class II antigen expression (Shi et al., 2005). Even if under long-term cryopreservation, they maintain the ability of proliferation and differentiation without much apoptosis (Ikeda et al., 2002). FLSCs require fewer cells for cell transplantation than mature hepatocytes to cure liver disorders effectively (Yoshida et al., 1996). Notwithstanding their limited availability, preprepared FLSCs are a viable alternative for acquired stem cell treatment.

The extra-embryonic tissue-derived stem cells comprise amniotic epithelial cells (AECs), amniotic fluid-derived stem cells (AFSCs), and the MSCs derived from amnion, amniotic fluid and placenta. These cells all harbor a strong ability for differentiation and proliferation (Marcus & Woodbury, 2008). These cells also have immunomodulatory effects, less ethical problems, low immunogenicity, and low tumorigenicity. Despite the wide application of extra-embryonic tissue-derived MSCs on liver diseases, other subpopulations of these fetal stem cells are also involved in some clinical research.

3.1.2. Therapeutic application

Compared to other disorders like hematopathy, ALD clinical trials using fetal stem cells are rare. The efficiency of FLSC transplantation for liver diseases has been demonstrated in animals and humans. In a DPPIV-deficient rat model, $DPPIV^+$ HLCs occupied 60–80% of the primary liver after engraftment of $DPPIV^+$ FLSCs (Sandhu et al., 2001). Recently, in rat models of chronic liver injury, another study observed that the portal vein injection of fetal liver stem cell-derived liver buds led to a level of 70% reconstitution of primary parenchyma and decreased the DR intensity, in which liver organoids were revealed settling down inside the liver rather than residing in other places (Tsuchida et al., 2019). The 6-month clinical observation of 25 FLSC-infused patients with liver cirrhosis of various etiologies demonstrates a significant rise in ALB and a decrease in SGOT, ALP, bilirubin, and MELD scores (Khan et al., 2010). Some studies just utilized AECs as a vector to carry therapeutic genes for immunodeficient liver diseases but did not detect whether these cells replenished the parenchyma of the liver (Saha & Jaenisch, 2009; Touboul et al., 2010). In liver fibrosis, AECs may block the activation of hepatic stellate cells and macrophages, acting as immunomodulators (Kuk et al., 2019) rather than replenishing the liver's parenchyma (Cargnoni et al., 2018). These studies suggest fetal stem cells act *in vivo* in a complex way, and how to limit their use to predicted results is unknown.

3.2. Mesenchymal stem cells

3.2.1. Sources and characteristic

MSCs, a subtype of adult fibroblast-like cells, were initially described in 1968 by Friedenstein et al. (Friedenstein et al., 1968). The results of hitherto investigations verify that MSCs can move to injury sites, secrete regulatory factors, modulate immune response (Akker, de Jager, & Sluijter, 2013), differentiate into mesoderm (Pittenger et al., 1999), and self-renew. Various convenient sources are investigated to produce sufficient populations of MSCs like extra-embryonic, adipose and other adult tissues. Thus, MSCs are not scarce compared to the stem cell types mentioned above. Due to its widespread availability in adult tissues and low intrusive damage, adipose is the best MSC-based cell treatment candidate (Kolaparthy et al., 2015). These MSCs from various sources share similar properties on surface markers and morphological features (Mattar & Bieback, 2015). However, there are still discrepancies in differentiation potential, proliferative ability, clonality, tolerance for aging, and paracrine activity, among them underlying the sources (Jin et al., 2013). Several studies showed that umbilical cord-derived MSCs (UC-MSCs) expand more than MSCs derived from adult tissues (Baksh, Yao, & Tuan, 2007; Jin et al., 2013). As for the differentiation potential, UC-MSCs also seem to perform better than other types on multilineage potential, which have adipogenic, chondrogenic and osteogenic capacities and can differentiate into endothelial-like cells and neuron-like cells (Mushahary et al., 2018). Besides, even if the same source-derived MSCs are a constellation of heterogenous cells, each population has special advantages in the proliferative, differentiative and immunomodulatory activity of MSCs. Researchers sorted the $CD34^+$ population of MSC in a TAA-induced liver fibrosis model. They found that they reduce collagen levels and mute hepatic stellate cells to prevent fibrosis and maintain liver function (Lee et al., 2016). Given the above advantages, distinct properties of some subtypes and the ability to well survive under cryopreservation, allogenic UC-MCSs are appropriate to be 'off-the-shelf' therapeutic products in case of diseases that sufficient cell quantities must be administrated promptly such as acute-on-chronic liver failure and even a more precise therapeutic application for ALD based on individual demands is possible.

3.2.2. How can MSCs exert therapeutic effects on advanced liver diseases?

MSCs have been demonstrated to ameliorate various liver diseases, whereas the actual mechanism remains unclear. Due to the pluripotency of MSCs, it seems apparent that they can replenish the functional hepatocytes. Schwartz and colleagues found that bone marrow-derived MSCs (BM-MSCs) treated with FGF-4 and HGF can develop into hepatocyte-like cells *in vitro* with limited hepatic capabilities, including as urea and albumin synthesis, phenobarbital-inducible CYP activity, and Dil-acil-LDL absorption (Schwartz et al., 2002). *In vivo*, however, some studies investigated that the bone marrow-derived stem cells hardly transdifferentiate into other types of cells (Castro et al., 2002; Wagers et al., 2002), indicating that there possibly be another mechanism in the above facts. Wang et al. pointed out that cell fusion is the crucial procedure contributing to increased bone marrow-derived hepatocytes. Afterwards, supplementary experiments were implemented and the result that hepatocytes expanses with donor surface markers further validates that viewpoint (Camargo, Finegold, & Goodell, 2004; Willenbring et al., 2004). MSCs also have pro- and anti-inflammatory actions to maintain the immunological microenvironment (Jiang & Xu, 2020), promoting the proliferation of remaining healthy hepatocytes. When the immune niche changes, MSCs sense the dynamic level of inflammatory factors such as IFN-γ, TNF-α, IL-1α and IL-1β and regulate the behavior of the adaptive and intrinsic immune cells and the activity of hepatic stellate cells (Tsuchiya et al., 2019). Besides the direct cell-to-cell contact in situ, MSCs can influence the remote immunological environment through the paracrine effect even if they are passively halted at the non-target site, which is now thought to be their main function rather than differentiation into HLCs (Alfaifi et al., 2018), suggesting that the secretions rather than the cells themselves will benefit more patients.

3.2.3. Therapeutic application

MSCs have been extensively studied, although their clinical use in liver disorders is still limited. For direct applications, a review summarized 321 MSC-based complete clinical trials. However, there were only 16 cases concerning liver diseases, which is much fewer than bone diseases (n = 62) or brain diseases (n = 53) (Yang et al., 2020). Currently, some clinical research focuses on subpopulations of ALDs, with some attempting to examine the positive and negative effects of MSC-based therapy. Though the effectiveness of MSCs from multiple sources is different due to their distinct characteristics on differentiation and proliferation, the collected researches show that MSCs derived from the umbilical cord, bone marrow and adipose tissue improve liver function and increase the survival rate of liver cirrhosis or liver failure caused by different etiologies (Amer et al., 2011; El-Ansary et al., 2012; Huang et al., 2019; Lanthier et al., 2017; Lin et al., 2017; Salama et al., 2014; Schacher et al., 2021; Shi et al., 2012, 2021). However, one study

involved 58 patients with alcoholic liver cirrhosis, some of whom were administered BM-MSCs, and discovered that MSC-based therapy only has a limited effect on liver cirrhosis, activating the liver regenerative pathway but not expanding hepatocytes in liver biopsies (Zhang et al., 2012). Considering the powerful differentiation potential of MSCs, the chief problem of whether the application of MSCs is safe is crucial to be addressed. *In vivo*, tremendous research has revealed that MSC can be chemoattracted towards the tumor microenvironment and exert promotive and suppressive effects on tumor progression (Rosland et al., 2009; Yagi & Kitagawa, 2013).

Moreover, MSCs can multiply at the 15th passage *in vitro* and are stable in serum-free media without tumor transformation (Chen et al., 2014). Eventually, in collected clinical trials, the iatrogenic tumor formation was hardly observed after the infusion of MSCs, which did not simultaneously increase the risk of side effects. The MSCs' differentiation into HLC has also been reported in animals and humans (Banas et al., 2007). Thus, MSCs cultured *in vitro* can be an alternative source of hepatocyte transplantation in preclinical research, and the indirect application of MSCs attracts researchers. Both differentiated and undifferentiated BM-MSC transplantation helped cirrhosis patients, although statistical comparisons showed no meaningful difference (El-Ansary et al., 2012). Due to the complicated process of differentiating MSCs into HLC *in vitro*, infusing MSCs directly may be a better MSC-based therapy for ALD. More recently, evidence indicates that MSC-derived exosome emerges as a novel cell-free approach owing to the low risk of tumorigenicity and little toxicity of MSC-based cell therapy. The therapeutic effects of MSC-derived exosomes for liver fibrosis are confirmed in cirrhotic animal models, but the major mechanisms remain vague. UC-MSC exosomes suppressed the epithelial-mesenchymal transition and TGF-β/SMAD signaling pathway by lowering type I/III collagen in the CCl_4-induced liver cirrhosis model (Li et al., 2013). Additionally, these exosomes were found to mitigate the acute injury and liver fibrosis by antioxidant effects (Jiang et al., 2018). In Schistosoma japonicum-infected mice, MSC-derived exosomes suppressed HSC activation and downregulated type I/III collagen, reducing liver fibrosis. However, the clinical applications of extracellular vesicles have not been fully implemented, which is waiting for an optimal purification protocol without contamination and damage.

3.3. Pluripotent stem cell

3.3.1. Sources and characteristics

Pluripotent stem cells include embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). Human embryonic stem cells (hESCs) from the embryo's inner cell mass are used in regenerative medicine due to their pluripotency (Damdimopoulou et al., 2016). Recently, it was reported that hESC lines could be derived from single biopsied blastomeres of a human *in vitro* fertilization-embryo under utterly chemically defined and xeno-free conditions without destroying the embryo. Additionally, stable pig pregastrulation ESC lines have also been generated (Zhi et al., 2022), which provides a theoretical basis for regenerative medical research such as xenotransplantation. Takahashi and Yamanaka (Takahashi & Yamanaka, 2006) initially produced iPSCs from mouse fibroblasts in 2006 with infinite proliferation and differentiation capacity of three germ layers. Based on previous studies, they identified four reprogramming factors: Oct3/4, Sox2, Klf4, and c-Myc. Then, human iPSCs were generated from human dermal fibroblasts in the next year (Takahashi et al., 2007), which completely overcame the ethical plight of stem cell therapy and further underpinned the basis of iPSC clinical application in patients. Four other factors—OCT4, SOX2, NANOG, and LIN28—also transformed human somatic cells into iPSCs (Yu et al., 2007), therefore broadening the alternative sources of iPSCs. To properly apply the PSC in liver diseases, heterogeneity (Nishizawa et al., 2016), one of their characteristics, should be considered. A couple of studies suggest that genetic background and epigenetic changes explain the heterogeneity in differentiation capability across iPSC lines (Choi et al., 2015; Nishizawa et al., 2016), referring to the strong correlation between iPSCs and their original cell types. Despite maintaining the liver-specific transcriptional signature, iPSCs from human liver biopsies cannot develop into mature hepatocytes *in vitro* (Calabrese et al., 2019). These facts also suggest that the directed redifferentiation of intrinsic stem cells *in vivo* might undergo a more complex process.

Further, another study compared isogenic primary human hepatocyte and dermal fibroblast-derived iPSCs to assess their differentiation potential into hepatocytes, showing that there are no statistically significant differences in the liver-enriched HNF4α promotor region and the level of the HNF4α methylation was downregulated accompanied with the culture process (Heslop et al., 2017). Thus, personal genetics dominate iPSC differentiation (Kajiwara et al., 2012). The donor-dependent potential of iPSCs enlightens the possibility of aggregating a constellation of high-quality allogenic somatic cells as the reservation of effective iPSCs. Since iPSCs inherit the immunogenicity of the donors, patients may be at risk of immune rejection when utilizing these cells. And to overcome immune rejection issues, HLA-matched PSC lines were created by choosing common HLA types among diverse ethnicities (Yamanaka, 2020).

3.3.2. How can PSCs exert therapeutic effects on advanced liver diseases?

One of the PSCs' therapeutic strategies is to generate hepatocytes *in vitro*. To ensure liver disease treatment safety, it is important to avoid tumorigenicity, which may come from its tremendous differentiation potential and endless growth ability. Thus, unlike MSCs, iPSCs are rarely administrated directly without a differentiation process *in vitro*. For clinical application, ideal iPSC-induced hepatocytes are supposed to possess the surface markers and functions of mature human hepatocytes. Despite high hopes, hepatocytes produced from iPSCs express alpha-fetoprotein (AFP), a marker of immature hepatic cells, and exhibit immature cytochrome P450 enzyme function (Si-Tayeb et al., 2010). Thus, many researchers continue to improve differentiation strategies. Like ESCs, Actin A, Wnt 3a, and FGF2 signaling pathways also played a significant role in iPSC differentiation. Thus, ex vivo culture protocols emerge to influence these pathways with precise management of hormonal and chemokines, plating techniques, and transduction of key liver-specific transcription factors (Zhang et al., 2021b). The expression of albumin, CYP450 enzymes, and clotting factors V, VII, and IX shows that OSM and HGF play a key role in the ex vivo differentiation of iPSC-induced hepatocytes (Ang et al., 2018).

Moreover, recently, gene editing to overexpress microRNA and culturing with decellularized scaffolds were demonstrated to account for a higher-level expression of hepatic surface markers and more stable metabolic activities (Abazari et al., 2020; Jaafarpour et al., 2020; Mobarra et al., 2019, 2021). Though scientists have worked hard to enhance differentiation techniques, the impurity of iPSC-derived liver products limits clinical research and requires strict purification. With the development of good manufacturing practice-compatible cell sorting systems, a group of selective genes, such as CYP3A4 and CYP3A7, are committed to isolating the final mature hepatocytes from the mixed cells, mapping their specific traits during the differentiation process (Zabulica et al., 2019), thus lower the unexpected risk of tumorigenicity.

Liver organoids are another option. As indicated above, PSCs' ability to differentiate all three germ layers is their most desirable attribute. Wang et al. generated expandable hepatic organoids (hEHOs) from hESCs. hEHOs were demonstrated to differentiate into hepatic lineages restrictively *in vivo* and repopulated the damaged livers of mice (Wang et al., 2019). Sato and colleagues generated a crypt-villus organoid by a single $Lgr5^+$ stem cell, developing under long-term culture conditions with Matrigel and growth factors (EGF and R-spondin 1) (Noggin et al.) (Sato et al., 2009). Thus, iPSC-derived liver organoids with all types of hepatic parenchymal and nonparenchymal cells and a three-dimensional shape like human livers appear promising.

Moreover, in 2013, a study generated an iPSC-derived liver bud (iPSC-LB) *in vitro* by recapitulating multicellular interactions (Takebe et al., 2013, 2014). Despite these promising results, iPSC-LBs have not

shown human liver capabilities, specifically self-renewal, which is necessary for long-term use. A novel protocol was established with three specific mediums, including expansion, differentiation and hepatic medium, based on the expansion medium designed by Clevers' group and containing essential factors like Dexamethasone, OSM and insulin-transferrin-selenium (Huch et al., 2015). Consequently, the novel liver-like organoids exhibit self-renewal ability and maintain other physiological functions simultaneously (Mun et al., 2019). All evidence corroborates the belief that artificial organs can ultimately answer ALD.

3.3.3. *Therapeutic application*

Though PSC, a new stem cell therapy approach, lacks clinical data on direct application to liver illnesses, it nonetheless aids other therapeutic options. The hEHOs mentioned above were regarded as new models to mimic the pathophysiologic of alcoholic liver injury (Wang et al., 2019). It is essential to assess the efficiency of iPSC-derived HLCs in animal models before applying for clinical ALD. Indeed, a study showed that iPSC-derived HLC transplantation enhanced the secretion of total serum ALB and reduced LDH and bilirubin in the CCL_4-induced cirrhosis mice models (Asgari et al., 2013). However, the number of research on ALD treated by indirect iPSC therapy is also limited. Unfortunately, due to the complex human microenvironment *in vivo* and insufficient methodologies to enable their application in humans, all of these findings are limited to cell or animal models, urging future research and achievements.

Following the generation of liver organoids whose structure is akin to the human organs, scientists have further transplanted the 3D spherical tissue mass on the mesentery of immunodeficient mice, which was validated to produce liver-specific proteins and exert metabolic functions like human beings' independently as consequences of a further maturation by the host blood perfusion. Furthermore, such a possible therapeutic method was utilized to ganciclovir-induced lethal liver failure models to improve survival and outperform fetal liver cell-derived liver buds and human hepatocytes (Takebe et al., 2013). The above-mentioned studies were rarely based on ALD but suggested that organoids from iPSCs could replace the OLT for ALD. Currently, most of the application of liver organoids is used to mimic the real response to diseases and drugs *in vivo*. These include steatohepatitis, virus hepatitis, Alagille syndrome, polycystic liver disease and Wilson's disease et al. (Oliveira & Fiorotto, 2021), thereby assisting in understanding the latent mechanisms of liver diseases and evaluating new medicines' efficacy.

4. Conclusion

The liver self-regenerates and performs several metabolic tasks to maintain human homeostasis. Due to liver-damaged regenerative ability and restricted liver transplantation, ALD therapy is important. There has been promising progress in the intrinsic and acquired stem cell treatments for ALD since hepatocyte regeneration is curbed by harsh microenvironments (Table 1).

BEC are the best intrinsic liver stem cells for repair, while LPC may be a transition form that transdifferentiates to repopulate wounded hepatocytes. Understanding the specific signaling pathways during each process of BEC-to-hepatocytes transdifferentiation, including Notch, Hippo/YAP, BMP, EGFR, Sox9b, mTORC1 and Wnt pathway, and interactions of cellular or non-cellular components in microenvironments benefits the designation for targets of regenerative medicine to treat the ALD.

Fetal stem cells, MSC, and PSCs can develop into hepatocytes for acquired stem cell treatment *in vivo* or *in vitro*. Liver organoids from iPSCs can eliminate the need for OLT. Moreover, with a benign precondition, MSCs can exert typical immunomodulatory function directly to regulate the inflammation level in the injured liver niche and facilitate the progression of cirrhosis. Moreover, with the iPSC-derived liver disease models, the precision of current and future medicines will probably be further improved. In cellular dynamics, hepatocytes are the most proliferative adult cell type. Given that cellular crosstalk exists in the self-replication of hepatocytes under normal conditions (Shu et al., 2022), intrinsic and acquired stem cells may also play a pivotal role in motivating and stimulating the proliferation of residual, undamaged healthy hepatocytes. This contribution increases the hepatocyte pool during liver regeneration through direct cell-cell connections or indirect signal transmission.

These results have partly been demonstrated to narrow the gap between normal people and patients with ALD in some clinical trials.

Table 1
Application of intrinsic and acquired Stem cells in liver diseases.

Cell source	Types of liver diseases	Patients or models	Follow-up	Principal improvements	References
BEC	Biliary diseases	Mouse model	10 days	Bilirubin, survival rate, fibrosis	Hallett et al. (2022)
	Severely combined immunodeficient condition	Mouse models	4 weeks	Liver parenchyma, ALB	Nevi et al. (2017)
FLSC	Alcoholic cirrhosis, HBV/HCV-induced cirrhosis	25 treatments	6 months	ALB, bilirubin, SGOT, ALP, MELD score	Khan et al. (2010)
	Retrorsine/partial hepatectomy model	Rat models	180 days	Survival rate, decrease of precancerous lesion	Tsuchida et al. (2019)
UC-MSCs	HBV-induced decompensated liver failure	111 treatments; 108 controls	75 months	Survival rate, ALB, prothrombin activity, cholinesterase, total bilirubin	Shi et al. (2021)
	HBV-induced decompensated liver cirrhosis	30 treatments; 15 controls	1 year	Ascites, ALB, TB. MELD	Zhang et al. (2012)
	HBV-induced acute-on-chronic liver failure	24 treatments; 19 controls	48 or 72 weeks	ALB, prothrombin time, total bilirubin, ALT, survival rates and MELD score	Shi et al. (2012)
BM-MSCs	Alcoholic cirrhosis	28 treatments; 30 controls	4 weeks	Nothing but observation of macrophagic expansion	Lanthier et al. (2017)
	Alcoholic cirrhosis	34 treatments; 16 controls	12 months	Collagen proportionate area, Child-Pugh score, ALT, AST, GGT, bilirubin	Suk et al. (2016)
	HCV-induced end-stage liver disease	20 treatments; 20 controls	6 months	ALB, bilirubin, INR, prothrombin concentration, ALT	Salama et al. (2014)
	HCV-induced liver cirrhosis	15 treatments; 10 controls	6 months	Encephalopathy, jaundice, lower limb edema, tremors, hematemesis, ascites. Laboratory data: Albumin, prothrombin, bilirubin. MELD score	El-Ansary et al. (2012)
	HCV-induced liver cirrhosis	20 treatments; 20 controls	6 months	Child-Pugh score, MELD score, fatigue scale, and performance status	Amer et al. (2011)
iPSC	CCL4-induced cirrhosis	Mouse model	5 weeks	ALB, LDH, bilirubin	Asgari et al. (2013)
	Gancyclovir-induced liver failure	Mouse model	–	Survival rate	Takebe et al. (2013)

However, standard application techniques for these stem cell-related therapies are unclear, and their long-term effects and safety are unknown. Therefore, future comparative and quantitative experiments are needed to establish a timely, low-risk and high-return therapeutic strategy.

Declaration of competing interest

The authors declare no competing interests.

Authors' contributions

YS Song was the major contributor in reviewing the literature, writing the manuscript, and creating descriptive figures. ZY Lu was a major contributor to editing the manuscript and figures. All authors read and approved the final manuscript.

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