Role of stem cells in repair of liver injury: Experimental and clinical benefit of transferred stem cells on liver failure

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Abstract
Although the liver has a high regenerative capacity, as a result of massive hepatocyte death, liver failure occurs. In recent years, there has been extensive experimental and clinical research in the field of cellular transplantation. Transplantation of cell lineages involved in liver regeneration, including mature and fetal hepatocytes, fetal liver progenitor and stem cells, hepatic progenitor and stem cells, mesenchymal stem cells, hematopoietic stem cells, and peripheral blood and umbilical cord blood stem cells, have been found to be beneficial for treating of liver failure. Herein, I review the results of experimental and clinical cell transplantation trials for liver failure.

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INTRODUCTION
The liver provides various vital functions, including protein synthesis, detoxification, bile excretion and storage of vitamins. It is necessary for survival that it should be regenerated following massive damage induced by environmental toxins, infections and alcohol, etc. Although in normal conditions, hepatocytes, the primary cell type of the liver, are in G0 phase of mitosis, following any injury they rapidly enter the G1 phase and undergo mitosis. S-phase hepatocytes can be located in all segments of the lobule in the normal adult liver. In the regenerating liver after partial hepatectomy (PH), portal cells replicate first, probably reflecting their shorter G1 phase. The peak of DNA synthesis is within 40-44 h after PH in mice. The average life span of the hepatocytes is relatively long, about 5 mo. These long-lived cells are capable of at least 69 cell divisions and can restore normal architecture and impaired function in the injured liver.
The liver is the only internal human organ capable of natural regeneration. Detailed studies of the mechanisms that regulate liver growth have been performed in animals subjected to PH or chemical injury. Livers from small animals enlarge after transplantation to reach a liver size in proportion to the size of the recipient animal (e.g., baboons to humans, small dogs to large dogs). In humans, previous studies have shown that the mean liver volume 6 mo after donor hepatectomy was 90.7% of the initial liver volume[7], and that the livers of the right lobe donor group regenerated faster than those of the left lobe donor group[8]. In fact, the growth of the liver is a restoration of function; the lobes that are removed do not regrow into their original form[9]. Nevertheless, functional restoration may be sufficient for survival of the organism.

The human liver is composed of mainly parenchymal cells, commonly referred to as “hepatocytes”, which are arranged in 1-2 cells-thick plates surrounded by hepatic sinusoids. They constitute 80% of the cell population of the liver. Sinusoidal endothelial cells, perisinusoidal macrophages (Kupffer cells), stellate cells (Ito cells) and liver-specific natural killer cells (pit cells) represent the non-parenchymal cells[10].

Hepatocytes are rich in membranous and non-membranous organelles and inclusions. Bile is secreted into the bile canaliculi, which are a part of the intercellular space isolated by junctional complexes from the rest of the intercellular compartment. Near the portal space, bile canaliculi transform into the canal of Hering, which is lined by both hepatocytes and cholangiocytes[11]. The canal of Hering is thought to serve a reservoir of liver progenitor cells. The cell compartment that resides in the canal of Hering is thought to serve a reservoir of liver progenitor cells. The cell compartment that resides in the canal of Hering has been called the progenitor (in humans) or the oval cell compartment (in rodents)[11]. In rodents, the canal barely extends beyond the limiting plate; in contrast, in humans, it extends to the proximate third of the lobule[12]. The epithelial cells of the canal, called “oval cells”, are oval in shape and can differentiate into both hepatocytes and cholangiocytes. Thus, it would appear that a name change from oval cells to “hepatic progenitor cells” (HPCs) is required[3]. The transdifferentiation of oval cells to hepatocytes may determine survival when it occurs during liver failure in humans.

Adult hepatic stem cells are scarcely detectable under physiological conditions and during the normal process of liver regeneration, presumably because of their small numbers. Analyses of oval cells have raised the possibility that adult hepatic stem cells are present in the canals of Herring, and that oval cells originate from the stem cells and differentiate into both the hepatic and cholangiocyte lineages[13]. Kuwahara et al.[13] enumerated four distinct stem cell niches: the canal of Hering (proximal biliary tree), the intralobular bile ducts, the peri-ductal “null” mononuclear cells and the peri-biliary hepatocytes.

Although the liver has a high regenerative capacity, as a result of massive hepatocyte death, liver failure occurs. Liver transplantation, sometimes the only option for patient survival, often leads to immunological complications. On the other hand, it is limited by the availability of donor organs. In addition to liver failure, for acute, chronic and hereditary diseases of the liver, cell transplantation therapies can stimulate regeneration or at least ensure sufficient function until liver transplantation can be performed. The lack of donor organs and risks of rejection have prompted extensive research in the field of cellular transplantation. In this article, I review hepatic cell types involved in liver regeneration and cell transplantation therapies for liver failure, with an emphasis on regeneration.

CATEGORIZATION OF STEM CELLS

Stem cells are the main cells of organisms from which the all of the mature body cells are derived. Their high proliferative capacity for self-renewal permit them to increase their numbers by symmetric division. They may remain in the undifferentiated state for long periods. When the morphological as well as functional, differentiation begins, these cells differentiate into a specialized cell lineage. Stem cells are the source of progenitor cells committed to one or several lineages. The committed progenitor cells exhibit a capacity for active proliferation and supply abundant daughter cells, which in turn give rise to terminally differentiated cells[14].

Stem cells are classified depending on the potential for differentiation into specialized cell types. The most talented stem cells, totipotent cells of the zygote within first 4 d of the intrauterine life, are able to form a full organism in an appropriate microenvironment. However, pluripotent cells, known as “embryonic stem cells” (ESCs), derived from the inner cell mass of the embryo, can form virtually any cell type derived from any of three embryonic germ layers; ectoderm, mesoderm or endoderm. Thus, an embryonic stem cell can form hepatocytes (endodermal in origin), cardiomyocytes (mesodermal in origin), and neurons (ectodermal in origin). Surplus embryos obtained from in-vitro fertilization laboratories are the main sources of the ESCs. However, some disadvantages including, high immune reaction risk and ethical concerns, limit their applications. Multipotent stem cells, known as “adult stem cells”, with a relatively limited differentiation potential, can form different cell types of the tissue. These cells reside together with the specialized cell types of the adult tissues and are thought to be responsible for the tissue maintenance and repair. The exact mechanisms that force them to differentiate into a specialized cell type are not fully known. The two major populations of adult stem cells are bone marrow mesenchymal and hematopoietic stem cells (HSCs). Hematopoietic stem cells have a predetermined fate to form all types of mature blood cells. Mesenchymal stem cells
can differentiate into multiple cell lineages, including tendon cells, muscle cells, osteocytes and fat cells. The term “multipotent stromal cell” implies the multipotent stem cells of both bone marrow and of non-marrow tissue, such as umbilical cord blood, adipose tissue, muscle tissue and dental pulp. In laboratory conditions, multipotent cells show plasticity. “Plasticity” or “transdifferentiation” means that the stem cells of an adult tissue can generate differentiated cell types of a different tissue. For instance, HSCs can transform into hepatocytes or brain stem cells or form skeletal muscle fibers. It is not clear if this occurs in the body. Multipotent cells do not cause any immune reaction, because they are genetically identical to their hosts. However, these cells are restricted in their ability to form different cell types. Moreover, they have some disadvantages, including slow rate of cell division and difficulties in isolating sufficient numbers for application because of their scarcity within tissues. The last type of stem cells is unipotent stem cells, which have very limited capacity for differentiation and can give rise to only one type of cell under normal conditions. For example, unipotent stem cells of colony forming unit of erythrocytes (CFU-E) can only give rise to mature blood erythrocytes.

In recent years, stem cells have been widely studied for their potential therapeutic use. However, some of studies were not successful. Researchers agree that as well as isolation of adequate numbers of healthy stem cells, selection of the most convenient transportation route, regulation of stem cell differentiation into a special cell type and obtaining the normal functions of the differentiated cells are very important regarding the benefit of stem cell applications. The most important risk of the transplanted stem cells is generation of tumors if cell division occurs in an uncontrolled manner. Unfortunately, stem cell transplantation therapy may be considered as a double-edged sword.

HEPATIC CELLS INVOLVED IN REGENERATION

The liver can regenerate itself by increasing the rate of hepatocyte mitosis and differentiation of stem cells into hepatocytes or cholangiocytes. Stem cells are the main cell lineage for liver regeneration. Several studies suggest the existence of one or more population of cells (e.g., stem cells, progenitor cells and extrahepatic stem cells) that are able to differentiate into hepatocytes and biliary epithelial cells. However, the exact location of these cells is not yet clear. In humans and rodents, potential liver stem cells may exist within the biliary tree. Both rodent and human ESCs, bone marrow HSCs, mesenchymal stem cells (MSCs), umbilical cord stem cells, fetal and adult liver progenitor cells, and mature hepatocytes have been reported to be capable of self-renewal, giving rise to daughter hepatocytes both in vivo and in vitro. Although the factors controlling proliferation, differentiation and secretion processes are not well defined, recent studies emphasize the role of several local (microenvironment) and systemic factors. However, the exact triggering mechanisms for differentiation of these cells into mature hepatocytes are not fully understood.

During embryonic development, hepatoblasts generate the two epithelial cell lineages: hepatocytes and biliary cells. The area connecting the terminal segment of the biliary ductal system with parenchymal hepatocytes persists in the adult liver and is known as the canals of Hering. The primitive intrahepatic bile ducts expressing both hepatocyte proteins and biliary epithelial markers have consequently been referred to as “transitional cells”. Transitional cells have properties intermediate between those of oval cells and hepatocytes. These cells are believed to remain in the adult liver as bipotential progenitors for both hepatocytes and biliary cells.

Many investigators favor the view that the liver harbors facultative stem cells that are located throughout the biliary epithelium. The activation of these cells for transformation into mature hepatocytes is a conditional process that occurs only when the regenerative capacity of hepatocytes is overwhelmed. Hepatocyte differentiation within bile ducts in the human liver has been noted, which has led to the belief that small biliary cells, hepatocyte-like cells expressing both markers of bile duct cells and hepatocytes, which repopulate severely damaged liver parenchyma, can function as a progenitor cell population for new hepatocytes. In rodents, early reactive bile ductules do not generally resemble hepatocytes, but later acquire features of hepatocytes. By contrast, direct evidence for the transformation of hepatocytes into biliary cells provided in cell culture had raised a possibility that hepatocytes themselves may be precursor cells for the biliary epithelium if the latter’s ability to proliferate and repair themselves is compromised for some reason.

The oval cells represent the progeny of liver stem cells and function as an amplification compartment for the generation of “new” hepatocytes. The oval cell compartment, consisting of small ovoid cells with scant, lightly basophilic cytoplasm and pale blue staining oval nuclei, is widely used to describe liver progenitors. It is generally accepted that oval cells are bipotential transit-amplified cells derived from normally quiescent “true stem cells”, which reside in the biliary tree and are absent in the healthy liver. In fact, to date, whether oval cells pre-exist in the tissue or develop from other adult cell types (e.g., bile duct cells) after injury, is unknown. The restricted potential to differentiate into hepatocytes and cholangiocytes qualifies oval cells more as progenitor cells than as true stem cells. The oval cells compartment can probably not to be attributed to a single cell type. A primitive oval cell population that do not express alpha-fetoprotein (AFP), cytokeratin 19 (CK-19), OV-6; a hepatocyte-like oval cell population that express AFP, but not OV-6; and a ductular-like oval cell population that not express AFP, but express CK 19 and OV-6 have been isolated. It is presently unclear if antigenically distinct subpopulations of oval cells are derived from different
precursor cells or if their phenotype merely reflects the commitment of an oval cell to a specific lineage\textsuperscript{[50]}.

Oval cells form ductular structures that communicate with the biliary system at one end and terminate at a hepatocyte-forming blind end\textsuperscript{[31]}. Markers commonly used to assess differentiation and to trace lineages of oval cells include expressed antigenic markers for hepatocytes, biliary ducts and oval cells (BSD7, OC2, OC3, OV-1, and OV-6), intermediate filaments, extracellular matrix proteins (CK8, 18, 19), enzymes and secreted proteins (alpha-fetoprotein and gamma-glutamyl transferase)\textsuperscript{[32,33]}. Oval cells also express some markers considered characteristic of stem cells, including stem cell factor\textsuperscript{[34]}, bel-2\textsuperscript{[35]} and cytokeratin 14\textsuperscript{[36]}. They are also immunoreactive to antibodies generally associated with hematopoietic lineages, such as CD34, and c-kit\textsuperscript{[37,38]}; therefore, there may be a common lineage between hematopoietic and liver cell precursors. In a recent study, a population of cells (beta-2-microglobulin-ve, Thy-1+ve) in rat and human bone marrow was identified that also expressed hepatocyte specific functions, suggesting that these cells may be hepatic stem cells. After intraportal infusion into rat livers, rat-derived bone marrow cells integrated with hepatic cell plates and differentiated into mature hepatocytes\textsuperscript{[39]}. Moreover, Crosby \textit{et al}\textsuperscript{[37]} have shown that c-kit and CD34 positive cells isolated from human liver are able to differentiate into biliary epithelial cells and endothelial cells. Thus, biliary cells and endothelial cells may also share some common precursors. It has been postulated that oval cells arise either from cells lining the canals of Hering\textsuperscript{[31,36]}, from mature biliary cells\textsuperscript{[35]}, liver epithelial or stromal cells\textsuperscript{[40]}, or from circulating hematopoietic stem cells\textsuperscript{[39,41]}. Additionally, some antigens traditionally associated with hematopoietic cells (c-kit and CD34) can also be expressed by oval cells, leading to the notion that at least some hepatic oval cells are directly derived from a precursor of bone marrow origin\textsuperscript{[39,42]}. Fausto \textit{et al}\textsuperscript{[38]} suggested that bone marrow stem cells can generate oval cells and hepatocytes; however, differentiation is very rare and inefficient. Bone marrow derived hepatocytes constituted from 0.008% to 0.8% of total parenchymal cells; therefore, differentiation of bone marrow cells into mature hepatocytes is very inefficient under physiological conditions\textsuperscript{[43]}. Additionally, the repopulation process is not complete and is relatively slow\textsuperscript{[3,7]}.

Studies have demonstrated that HSCs have the capacity to fuse with other cell types\textsuperscript{[46]}. Several publications subsequently emerged to demonstrate that the appearance of new hepatocytes from bone marrow precursors in liver repopulation models was not caused by transdifferentiation of the marrow stem cells to hepatocytes, but to fusion of the marrow cells with the hepatocytes of the recipient\textsuperscript{[46,49]}. While fusion with hepatocytes in whole animal experiments may have a role, it cannot explain the appearance of hepatocyte-like cells in cell cultures of bone marrow\textsuperscript{[50]}.

The periductular stem cells are one of the other cell types related to liver regeneration in some types of liver injury. These cells are rare in the liver, have a very long proliferation potential, and may be multipotent; however, their full potential has yet to be defined. These cells may be hematopoietic stem cell types that either reside in liver or bone marrow\textsuperscript{[50]}.

Another cell type related to the regeneration of rat liver has been identified, referred to as “small hepatocytes” (small hepatocyte-like progenitor cells)\textsuperscript{[51,52]}. This cell population is phenotypically different from fully differentiated hepatocytes, cholangiocytes and oval cells. They represent a unique parenchymal (less differentiated) progenitor cell population\textsuperscript{[53]}. These cells have an extensive proliferative capacity and may represent a novel progenitor cell population that responds to liver deficit when the replicative capacity of differentiated hepatocytes is impaired, and can restore tissue mass\textsuperscript{[53]}. However, there is still controversy as to whether these cells represent an intermediate state in oval cell differentiation or are derived from hepatocytes resistant to stem cells. Best \textit{et al}\textsuperscript{[44]} suggested that small hepatocytes are not the progeny of oval cell precursors, but represent an independent liver progenitor cell population. By contrast, Vig \textit{et al}\textsuperscript{[55]} showed that oval cells can form small hepatocyte-like progenitor cell nodules during the regeneration stage after chronic hepatocellular liver injury.

A number of studies have been published demonstrating that stem/progenitor cells can be differentiated toward “hepatocyte-like cells”, a term that has been used to describe cells generated in \textit{vitro} that show some characteristics of mature hepatocytes, but are still not fully mature and/or characterized\textsuperscript{[46]}. Classic studies by Evarts \textit{et al}\textsuperscript{[50]} demonstrated that oval cells gradually transform themselves into small basophilic hepatocytes, which then become fully mature hepatocytes and replace the lost liver mass. They also showed the transfer of radiolabeled thymidine from oval cells to newly formed hepatocytes in \textit{vitro}. Thus, the precursor-product relationship between oval cells and basophilic hepatocytes has been suggested\textsuperscript{[29]}.

Recently, a unique population of liver-derived bipotential liver progenitors was isolated from unmanipulated rat liver\textsuperscript{[58]}. These bipotential liver cells express both hematopoietic stem cell markers, such as CD45, CD34 and thy-1, similar to oval cells\textsuperscript{[58,61]}, and endodermal/hepatic markers. In contrast to oval cells, these liver progenitors are negative for OV-6, cytokeratin 7 and CK 19, and express very little or no AFP\textsuperscript{[58,62]}. Their capacity for hepatic differentiation makes them a valuable resource for important applications such as cell therapies for a variety of liver diseases\textsuperscript{[62]}.

Although mature hepatocytes and cholangiocytes represent the first and most important resource for tissue repair, experimental data support the hypothesis that the liver also contains or activates a stem cell compartment\textsuperscript{[53,54]}. Herrera \textit{et al}\textsuperscript{[56]} isolated a pluripotent population similar to rodent oval cells from adult liver and may be more mesenchymal in lineage. These cells expressed mesenchymal stem cell markers, but not the hematopoietic...
etic stem cell markers. The absence of staining for cytokeratin-19, CD117, and CD34 indicated that these cells were not oval stem cells.

Castorina et al.\textsuperscript{[46]} reported that human liver stem cells express several mesenchymal markers, such as CD 44, but not hematopoietic stem cell markers. Additionally these multipotent cells express AFP, albumin, CK7 and CK19, indicating a partial commitment to hepatic and biliary lineages. Schmelzer et al.\textsuperscript{[60-67]} isolated two pluripotent hepatic progenitors: hepatic stem cells and progenitors. The gene expression profile of hepatic stem cells throughout life consists of high levels of expression of cytokeratin 19 (CK19), neuronal cell adhesion molecule (NCAM), epithelial cell adhesion molecule (EpCAM), and claudin-3 (CLDN-3); low levels of albumin; and a complete absence of expression of AFP. By contrast, hepatoblasts, found as < 0.1% of normal adult livers, express high levels of AFP, elevated levels of albumin, low levels of CK19 and a loss of NCAM and CLDN-3.

Notably, both hepatocytes and hepatic progenitor cells may differentiate into hepatocytes and biliary cells, as well indicating their bipotent differentiation capacity. Hence, both cell types meet the minimal definition criteria of a stem cell, i.e., the potential of self-renewal to maintain the stem cell reserve, and a multiple differentiation potential giving rise to progeny of at least two different lineages\textsuperscript{[48]}.

### FACTORS RELATED TO HEPATIC REGENERATION

Studies of liver injury have led the identification of several factors that are involved in the regulation of cell activation related to liver regeneration. It is not clear whether the same factors known to be involved in normal hepatic regeneration are also involved in regeneration via the stem cell compartment.

As mentioned before, the hepatic progenitor cell niche is located at the level of the canals of Hering. The ductular and periductular area is composed of numerous different cells, such as portal myofibroblasts, stellate cells, endothelial cells, hepatocytes, cholangiocytes, Kupffer cells, pit cells and inflammatory cells. All these cells could interact and crosstalk with hepatic parenchymal cells, influencing their proliferative and differentiative processes through the provision of numerous signals within the niche\textsuperscript{[5]}. The local environments of endogenous and transplanted cells mainly affect their proliferation, differentiation, secretion, and other functions\textsuperscript{[40,70]}. Hepatocyte growth factor (HGF), epidermal growth factor (EGF), and transforming growth factor-α (TGF-α), as potent mitogens, are primarily associated with normal hepatic regeneration\textsuperscript{[71-73]}. In cultures, the mouse liver progenitor cells differentiated into hepatocytes upon treatment with EGF or differentiated into biliary lineages upon treatment with HGF\textsuperscript{[74]}. In their quiescent state, hepatocytes do not fully respond to growth factors such as HGF, TGF and EGF, which are potent stimulators of DNA replication for hepatocytes in primary culture\textsuperscript{[75-77]}. In the intact liver, hepatocytes need to be “primed” to enter the cell cycle and respond to growth factors\textsuperscript{[73]}. The results show that TNF acts as a primer to sensitize hepatocytes to the proliferative effects of growth factors, and offers a mechanism to explain the initiation and progression phases of liver regeneration after PH\textsuperscript{[77]}.

In addition to hepatocyte-autonomous signals, endocrine and paracrine factors are critical to normal regeneration, and extensive work has focused on the role of the liver microenvironment, i.e., non-parenchymal cells and the extra-cellular matrix (ECM), in liver homeostasis and regeneration\textsuperscript{[71-73]}. Non-parenchymal cells, such as endothelial cells, Kupffer cells, stellate cell and intrahepatic lymphocytes provide critical signals to hepatocytes during regeneration\textsuperscript{[78-80]}. Intercellular interaction seems to be crucial during liver regeneration. Indeed, the initiation of liver regeneration involves the rapid and simultaneous activation of multiple signaling pathways in both hepatocytes and non-parenchymal cells, which are the main sources of tumor necrosis factor, interleukin-6, and heparin binding EGF\textsuperscript{[75,76,81]}. Following acute liver injury, release of IL-6 from Kupffer cells and neutrophils and the growth factors including HGF, EGF, TGF-α, and fibroblast growth factor-α released from hepatic stellate cells, stimulate hepatocytes to enter mitosis\textsuperscript{[76,82]}. Stellate cells are regarded as the principal source of extracellular matrix proteins during hepatic regeneration\textsuperscript{[83]}. A recent study demonstrated that HSCs act as a positive regulator at the early phase and a negative regulator at the terminal phase of liver regeneration through cell-cell interaction and cytokine networks\textsuperscript{[80]}. The authors reported that high levels of HGF at early phase of liver regeneration stimulated oval cell proliferation via extracellular signal-regulated kinase and p38 pathway, whereas high levels of TGF-β1 at the terminal phase of liver regeneration suppressed DNA synthesis of oval cells. The shift between these two distinct effects depended on the balance between HGF and TGF-β1 secreted by HSCs. Paku et al.\textsuperscript{[81]} demonstrated that proliferating oval cells are closely associated with stellate cells, suggesting that non-parenchymal cells nurture oval cell growth and differentiation through secretion of growth factors and cytokines, and also by direct cell-to-cell interactions. The factors involved in the regulation of oval cell activation include TGF, HGF and its receptor c-met, IL-6 and peroxisome proliferators/peroxisome proliferator activated receptor alpha\textsuperscript{[84,85]}. It is clear that from the first stem/progenitor activation phase to the final differentiation phase of the oval cell cycle, several growth factors and other factors are effective.

More recent studies have emphasized the involvement of TNF-like weak inducer of apoptosis (TWEAK), a member of the TNF family, in the proliferation of oval cells. TWEAK expressed by T cells can stimulate hepatic progenitor cell proliferation. It appears that TWEAK selectively promotes proliferation of oval cells without having an effect on hepatocytes\textsuperscript{[86]}.

Some of the other key molecules in the liver microen-
environment that determine regenerative behavior include the pro-inflammatory cytokines and angiogenic factors, such as vascular endothelial growth factor (VEGF)\[^{[89,90]}\].

Changes in microenvironments may have contributed to the positive outcomes of many liver cell transplantation studies, and might be initiated by the strong outputs (e.g., signaling, secretion) from the transplanted hepatocytes that drastically affect the environments to stimulate endogenous hepatocyte regeneration\[^{[90]}\]. Improvement of liver microenvironments related to liver regeneration is one of the goals of cell transplantation therapies. Recently, numerous experimental and clinical studies have been performed investigating the factors that increase the benefit of cell transplantation therapies and survival of the patients with liver damage or failure.

### CELL TYPES TRANSPLANTED FOR LIVER FAILURE

Cell transplantation therapy is a promising alternative approach that leads to donor cell-mediated repopulation of the liver and improved survival rates in experimental models of liver disease. It may serve to alleviate the symptoms while the patients are waiting for liver transplantation. However, significant challenges remain before these cells can be used in humans, such as the lack of consensus about the immunophenotype of liver progenitor cells, uncertainty of the physiological role of reported candidate stem/progenitor cells, practicality of obtaining sufficient quantity of cells for clinical use, and concerns over ethics, long-term efficacy, and safety\[^{[10]}\]. A registered clinical application based on stem cell technology will take at least an additional 5-10 years because of certain limitations; e.g., the lack of suitable cell sources and risk of teratoma formation\[^{[90]}\].

Stem cell therapy exerts its beneficial effect through a number of mechanisms, not necessarily transdifferentiation. Paracrine factors also have an important role in the improvement mechanism. Mature hepatocytes, stem/progenitor cells (ESCs, adipose-derived stem cells, umbilical stem cells, bone marrow-derived stem cells and oval cells), and hepatocyte-like cells are the main cell types used for cell transplantation in experimental and/or clinical studies. Transplanted hepatocytes have high function, but short survival time, whereas transplanted stem/progenitor cells have weak function, but high proliferative capacity. Hepatocyte-like cells accumulate over time \(via\) differentiation and proliferation\[^{[91]}\]. However, the numbers of hepatocytes needed for transplantation in humans can be quite large\[^{[92]}\], cells that can differentiate into mature hepatocytes have been great interest. Additionally, since hepatocytes are large in diameter, up to 70% of transplanted hepatocytes get trapped in the hepatic sinusoids, which leads to temporary obstruction with subsequent portal hypertension\[^{[93]}\], and they have a poor engraftment rate\[^{[94]}\].

### MATURe HEPATOCYTES

Hepatocyte transplantation has been performed for more than 10 years in humans, meeting with varied degrees of success\[^{[95]}\]. Data published for almost 70 years have unequivocally shown that hepatocytes are the replicating cells responsible for liver regeneration and that progenitor cell activation leading to lineage generation is not observed during this process\[^{[31,96]}\]. Although the other cell types of the liver are necessary to support hepatocyte replication and hepatic growth, it has now been established that the hepatocyte has a remarkable capacity for cell proliferation and is the most efficient cell for liver repopulation after injury\[^{[105,106]}\]. Therefore, transplantation of mature hepatocytes into an injured liver seems to be helpful to support recovery process. However, transplanted hepatocytes have a low liver-engraftment rate and survival\[^{[77]}\], and hepatocytes are only available from cadaveric donor livers, which mean that the cells largely lack transplantation quality and quantity. Moreover, cryopreservation of mature hepatocytes before use leads to an additional substantial loss of viability and function. Thus, research is aiming to obtain transplantable cells from embryonic and adult stem cells, or liver progenitor cells that can be expanded \(in vitro\). One attractive alternative source of transplantable hepatocytes is cells derived from an immortalized hepatocyte cell line that provides an unlimited supply of transplantable cells\[^{[98]}\]. Immortalized hepatocytes could then grow in tissue culture and subsequently function as differentiated, non transformed hepatocytes following transplantation\[^{[98,99]}\].

### Experimental results

Rhim et al\[^{[100,101]}\] showed that a small number of transplanted hepatocytes could repopulate the liver of newborn urokinase-type plasminogen activator (uPA) transgenic mice. Transplantation of rat liver cells into these mice resulted in the complete reconstitution of a mouse liver with rat hepatocytes. The transplanted liver cell populations replaced up to 80 % of the diseased recipient liver. Overturf et al\[^{[102]}\] found evidence that short-term therapeutic liver repopulation does not require progenitor or stem cells. The majority of the transplanted cells apparently participated in the repopulation process and intermediate-size hepatocytes appeared to have a better replicative capacity than small hepatocytes. Recently, transplanted hepatocytes were shown to engraft in the liver of animals with acute liver failure (ALF)\[^{[103]}\]. However, only 20%-30% of the transplanted hepatocytes survive and engraft in the liver of rats\[^{[104]}\]. In fact, several studies using rat models of primary hepatocyte transplantation revealed that transplantation leads to efficacious donor chimerism\[^{[105-107]}\]. When hepatocytes were transplanted \(via\) the spleen, cells were distributed immediately in periportal areas, fibrous septa and regenerative nodules of the cirrhotic liver\[^{[107]}\]. However, transplanted cell proliferation in the liver was limited, and animals did not show any dif-
Hepatic progenitor/stem cells, constituting approximately 0.5%-2.5% of liver parenchyma, can be isolated by immunoselection for epithelial cell adhesion molecule-positive cells (EpCAM+). Isolation of hepatic progenitor cells from human material has proven to be very difficult. In fact, although hepatic progenitor cells express several markers, their unequivocal isolation as a pure fraction has been a major obstacle in liver progenitor cell research. Novel cell surface markers in adult progenitor cells include tight junction proteins, integrins, cadherins, cell adhesion molecules, receptors, membrane channels and other transmembrane proteins. Cell surface markers, CD133, Claudin-7, cadherin 22, mucin-1, ros-1 and Gabrp9 are overexpressed and are unique for the adult progenitors. Thymus cell antigen 1 (Thy-1) is a marker for sorting bipotential progenitor cells from human livers. None of the described markers are completely specific; therefore, isolation of viable cells is limited.

Clinical results

In an early study, in 10 Japanese patients with cirrhosis, hepatocytes (1-60 × 10⁷) isolated from a piece of their own liver were transplanted into various sites, including the spleen. In one of these patients, transplanted hepatocytes were detected in the spleen 11 mo following transplantation. One of these patients recovered. In another trial, five patients with hepatic encephalopathy and multiple organ failure were transplanted with allogeneic hepatocytes (2.8 × 10⁹-2.9 × 10⁸) through the splenic artery. Biochemical evidence of liver injury improved significantly and blood ammonia levels decreased significantly to normal levels in the hepatocyte-treated patients. Three of these patients bridged to liver transplantation and were normal with more than 20 mo of follow-up. Transplantation of hepatocytes via the abdominal cavity has also been found beneficial. Seven patients with fulminant hepatic failure (FHF) were transplanted (6 × 10⁹/kgBW) via the abdominal cavity resulting in survival and improved encephalopathy.

Cryopreserved hepatocyte transplantation is a bridging method while patients with chronic liver failure await liver transplantation. Three of five patients with ALF who received transplantation of 1.3 × 10⁹-3.9 × 10⁹ cryopreserved hepatocytes through intrasplenic and intraportal infusion improved afterwards. A patient with ALF infused intraportally with 8 × 10⁹ cryopreserved human hepatocytes fully recovered 12 wk after transplantation. Repeated application of primary human hepatocytes seems to be safe and results in measurable benefits for patients with ALF.

Fetal human hepatocytes exhibit unique properties, including the capacity for extensive proliferation and excellent recovery following partial liver resection. However, experimental studies have predominantly focused on transplantation of fetal hepatic progenitor cells. Oertel et al. purified hepatic stem/progenitor cells from fetal livers that are fully capable of repopulating the normal adult liver. This represents a major advance toward developing
protocols that will be essential for clinical application of liver cell transplantation therapy.

**Experimental results**

After transplantation of mouse fetal liver progenitor cells into 14 to 20 d-old uPA-mice with subacute liver failure, donor-derived regeneration nodules were detectable. Fetal liver cells showed a mature hepatic phenotype, as established by gene expression profiling and a functional integration within in the first 4 wk after transplantation. Transplanted rat fetal liver epithelial progenitor cells were able to repopulate a recipient liver subjected to PH, alone or with retorsine, in syngeneic dipeptidyl peptidase IV (DPPIV) mutant rats. Progenitor cells were able to differentiate into both hepatocytes and bile epithelial cells, unlike mature hepatocytes that are not able to differentiate to bile epithelial cells. Moreover, progenitor cells continued to proliferate for longer than hepatocytes after transplantation. Likewise, Dlk+ hepatic stem/progenitor cells purified from rat midgestational fetal livers were able to extensively repopulate the host liver in syngeneic DPPIV mutant rats subjected to PH alone. In the CCl4 rat model of FHF with 2/3 hepatectomy, fetal liver stem/progenitor cells were found to be effective to repair the damaged liver. Thus, fetal hepatic stem/progenitor cells exhibit potency for reconstitution of the adult liver under a particular set of conditions.

**Clinical results**

As far as I know, to date, no clinical application has been performed.

**EMBRYONIC STEM CELLS**

**Experimental results**

The first report of hepatic differentiation of mouse embryonic cells was in 2001 by Hanazaki et al., who produced an embryoid body from an ES cell and subsequently added fibroblast growth factor, HGF, oncostatin M (Osm) and dexamethasone (Dex) to induce the differentiation of cells exhibiting hepatocyte-like properties. The results of Heo et al. are particularly noteworthy, as they report that liver precursor cells induced from ES cells in the absence of exogenous growth factors or feeder cell layers also have the ability to differentiate into biliary epithelial cells. In 2003, Yamamoto et al. demonstrated hepatic cells with a high level of liver function by transplanting ES cells into mice livers 24 h after CCl4 intoxication. In terms of ultrastructural analysis, these ES-derived hepatocytes were generally similar to normal hepatocytes. Additionally, no teratoma formation was observed in the transplant recipients. In the study of Hu et al., ES-derived hepatocytes could improve the life quality and lengthen the survival time of CCl4-induced FHF. Sprague-Dawley rats with surgically induced liver failure via 90% hepatectomy, receiving 10^6-10^8 ESCs as splenectomy transplantation, showed 100% survival rate up to 3 mo. Similarly, hepatocytes derived from ES cells in a bioartificial liver device were able to improve survival in rats with liver failure induced by galactosamine after 10 h of extracorporeal liver dialysis. Additionally, embryonic derived hepatocytes, implanted subcutaneously as a bioartificial liver device into mice subjected to 90% hepatectomy, reversed the liver failure. Transplantation of ES cell-derived hepatic cells significantly suppressed the onset of fibrosis in mice.

**Clinical results**

Embryonic stem cell studies remain at the preclinical stage because of the risk of teratomas. Despite these successful animal studies, there have been no clinical trials using human ES cells to treat liver diseases in human patients, because utilization of human ES cells raises serious ethical questions in many countries.

**MESENCHYMAL STEM CELLS**

Mesenchymal stem cells (MSCs) are an adult stem cell population found in numerous living tissues. It has been reported that among MSCs obtained from bone marrow, adipose tissue, umbilical cord blood and placenta, several hepatocyte-like cells have the ability to differentiate. Besides, MSCs, immune-privileged cells with low MHC I and no MHC II expression have low rejection risk and, as such, are a particularly promising source of cells for the treatment of acute and degenerative liver diseases. Chamberlain et al. transplanted clonal human MSCs into severe fetal sheep by intrahepatic and intraperitoneal routes in their study. The intrahepatic injection of human MSCs was safe and resulted in more efficient generation of hepatocytes throughout the liver parenchyma at days 56-70. Human MSCs cells accumulated in the injured liver. The injected liver may produce regulatory factors for homing of stem cells to the injury site.

**Bone marrow-derived mesenchymal stem cells**

The most important source of MSCs is bone marrow. The injured liver may produce regulatory factors for homing of stem cells to the injury site.

**Experimental results**

A recent study by Carvalho et al. demonstrated that MSCs injection into the portal vein of mice or rats with liver cirrhosis induced by CCl4 and ethanol did not reduce hepatic fibrosis or promote any improvement in parameters of liver function. However, Oyagi et al. demonstrated benefits in transplantation of bone marrow-derived mesenchymal stem cells (BMMCs) cultured with HGF in CCl4-induced rats. Transplantation of the BMMCs into liver-injured rats restored their serum albumin level and significantly suppressed transaminase activity and liver fibrosis. These effects were not seen when the BMMCs were cultured without HGF. Similar results of Fang et al. supported the beneficial effects of BMMCs on reducing collagen deposition.

**Clinical results**

Autologous BMMC transplantation to 53 patients with liver failure caused by hepatitis B had fa-
vorab short-term efficacy with improved levels total bilirubin, prothrombin time and Model for End-Stage Liver Disease score of patients 2-3 wk after transplantation. Patients who received 120 mL of autologous bone marrow fluid via a hepatic artery showed improved hepatic function in the early period (1-48 wk). Analysis showed no adverse effects from bone marrow administration a long observation period. Additionally, data obtained from eight patients with liver cirrhosis showed that MSCs injection through peripheral or portal vein under ultrasound guidance could be used for the treatment of end-stage liver disease with satisfactory tolerability. The study of Amer et al. reported the safety and short-term efficacy of autologous bone marrow-derived hepatocyte-like cell transplantation in the treatment of patients with end-stage liver cell failure. Comparing hepatic and splenic routes of injection, there was no significant difference, except in the first month. The splenic route was technically easier, although it was associated with a higher incidence of mild complications (fever and transient shivering).

Placenta-derived mesenchymal stem cells

Another promising source of MSCs is the placenta. Human placental MSCs are free of ethical concerns, are non-invasively accessible, abundant and strongly immunosuppressive. Placenta derived MSCs can be differentiated into hepatocyte-like cells in vitro.

Experimental results: The experimental study of Cao et al. revealed that human placental MSCs could not only differentiate into hepatocyte-like cells in vitro and in vivo, but also could prolong the survival time of pigs with ALF. The survival rate was significantly higher in the transplantation group than in the control group (66.7% vs 0%).

Clinical results: Despite the several positive results gained from experimental studies, the therapeutic role of MSCs in liver regeneration must be further investigated, as the clinical evidence is still limited. As far as I know, to date, no clinical application has been performed.

Adipose tissue-derived mesenchymal stem cells

Adipose tissue is a source of MSCs that can be easily isolated, selected and induced into mature, transplantable hepatocytes. The fact that they are easy to procure ex vivo in large numbers makes them an attractive tool for clinical studies in the context of establishing an alternative therapy for liver dysfunction. Adipose tissue-derived MSCs have immunomodulation, differentiation (plasticity), homing, revascularization, anti-apoptotic and tissue regenerating abilities.

Experimental results: Transplanted adipose-derived MSCs through tail vein injection were able to differentiate into hepatocytes in BALB/c nude mice with CCl4-induced liver injury, and were able to function like human mature hepatocytes. Adipose-derived MSCs could be differentiated into hepatocytes within 13 d. When approximately 10^6 of adipose-derived human MSCs (0.2 mL of the cell suspension via tail vein) transplanted by injection into mice with liver failure, the ammonia concentration fell to near normal levels within 24 h. Of the various transplantation routes (tail vein, portal vein, and direct liver parenchymal injections), transplantation via the tail vein was found to be the most effective in reducing biochemical parameters in CCl4-induced liver failure in mice.

Clinical results: In the study of Zhang et al. 30 chronic hepatitis B patients with decompensated livers received umbilical cord-derived MSC transfusion. No significant side effects or complications were observed. Liver function improved and the volume of ascites significantly decreased. Umbilical cord-derived MSC have also been found to be safe and beneficial in the treatment of the patients with acute-on chronic liver failure associated with hepatitis B virus infection. The cell transusions significantly increased the survival rates in ACLF patients.

Bone marrow-derived hematopoietic stem cells

In 1999 Petersen et al. and in 2000 Lagesaas et al. described the contribution of bone marrow-derived stem cells (BMSs) to liver regeneration. Data in the literature increasingly suggest bone marrow as a transplantable source of hepatic progenitors. Initial reports of the hepatic potential of HSCs were later shown to have resulted from fusion between transplanted donor cells and resident recipient hepatocytes. The authors analyzed sex-mismatched bone marrow and liver transplantations in rats, mice and humans, and were able to show Y-chromosome-positive hepatocytes as single cells or small clusters in the recipients. Adjusted Y-positive hepatocyte and cholangiocyte engraftment ranged from 4% to 43%, and from 4% to 38%, respectively.
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**Experimental results:** Cantz et al\(^\text{[162]}\) have investigated the contribution of intrasplenic bone marrow transplants or *in vivo* mobilized HSCs to the formation of hepatocytes in normal and injured liver by CCl\(_4\). They concluded that there is little or no contribution of BMSs to the regeneration of normal and injured livers in the animal models used. Kanazawa et al\(^\text{[163]}\) also demonstrated that there is little or no contribution of BMCs to the replacement of injured livers (both acute and chronic) in three different models, as follows: CCl\(_4\)-treatment, albumin-urokine transgenic mouse, hepatitis B transgenic mouse. By contrast, Jang et al\(^\text{[164]}\) reported that transplantation of a population of bone marrow purified stem cells promoted functional improvement in mice with CCl\(_4\)-induced acute liver injury. Moreover, liver function was restored 2-7 d after transplantation. Fibrosis reduction was also reported in rats with CCl\(_4\)-induced acute liver injury after bone marrow mononuclear cells transplantation *via* the portal vein. The general condition of the rats in the treatment group also improved markedly\(^\text{[165]}\).

In the study of Shizhu et al\(^\text{[166]}\) transplanted bone marrow mononuclear cells *via* tail veins of mice were found to populate the damaged liver around the portal and centrallobular regions, and they appeared to differentiate into albumin-producing hepatocyte-like cells. Animals that received bone marrow mononuclear cells also showed a trend toward improved liver enzymes, as well enhanced survival rates, relative to controls.

**Clinical results:** Although the results of experiments on rodents are conflicting, several clinical trials found that BMSCs were beneficial in the treatment of the patients with liver failure. Autologous BMSCs transplantation *via* the portal vein, peripheral vein or hepatic artery into patients with cirrhosis, resulted in improvement of liver function tests\(^\text{[167-171]}\). Clinical studies by Lyra et al\(^\text{[172,173]}\) suggested the safety of autologous bone marrow-derived cells through a hepatic artery for chronic liver disease patients. In nine patients with alcohol-related cirrhosis, the reinfusion of CD34+ HSCs into the hepatic artery was well tolerated and beneficial to liver function\(^\text{[174]}\). However, in the study of Cauto et al\(^\text{[171]}\), one case of dissection of the hepatic artery and one case of Takotsubo syndrome occurred as early complications. A patient developed a cutaneous immunological disorder and another patient developed hepatocellular carcinoma 12 mo after infusion *via* the hepatic artery. A phase 1 trial using BMSCs injected *via* the hepatic artery after portal embolization was prematurely terminated when a patient with decompensated cirrhosis died from radio contrast nephropathy and hepatorenal syndrome\(^\text{[175]}\).

A recent case report described the use of autologous unsorted BMSCs as rescue treatment for hepatic failure in a 67-year-old man ineligible for liver transplantation\(^\text{[176]}\). Apparent rapid improvement in hepatic synthetic function was obtained after the portal venous infusion of the cells. A liver biopsy performed 20 d after cell transplant was reported to show increased hepatocyte replication around necrotic foci. Salama et al\(^\text{[177]}\) reported that near normalization of liver enzymes was observed in 54% of 90 patients with end-stage liver disease received GSF for five days followed by autologous CD34+ and CD133+ stem cell infusion in the portal vein. Similarly, in a phase I clinical trial of five patients with acute on chronic liver failure, administering G-CSF and then reinfusing the CD34+ cells improved liver function in more than 50% of cases during a 60-d follow-up\(^\text{[167]}\). The patients receiving autologous infusion of mobilized adult bone marrow derived CD34+ cells without G-CSF were monitored for up to 18 mo, which confirmed the safety of the procedure, with beneficial effects lasting around 12 mo\(^\text{[170]}\). Terai et al\(^\text{[166]}\) implemented a clinical trial on nine patients with decompensated liver cirrhosis. These patients were infused with 5.2 ± 0.63 × 10\(^3\) autologous bone marrow cells from the peripheral vein. At 24 wk after transplantation, significant improvements were observed.

**Peripheral and umbilical blood stem cells**

Stem cells derived from cord blood of human origin exhibit higher plasticity than the respective mouse or rat cells\(^\text{[178]}\). Like the BMSCs, cell fusion has been implicated as the mechanism by which human cells are seen in the recipient’s liver. Some researchers observed cell fusion in most cells\(^\text{[179]}\) and some claim no evidence of cell fusion\(^\text{[180]}\). Newsome et al\(^\text{[160]}\) demonstrated that human umbilical cord-blood (huUCB)-derived cells could differentiate into hepatocytes after transplantation into immunodeficient mice. The percentage of human, compared with mouse, hepatocytes reached an average of 0.011% after 16 wk. Kögler et al\(^\text{[181]}\) reported that these somatic multipotent stem cells could differentiate into hepatocytes after transplantation into a pre-immune fetal sheep model. Human hepatocytes constituted as much as 20% of the liver 11 mo after transplantation\(^\text{[182]}\).

**Experimental results:** Intraperitoneal administration resulted in a rapid liver engraftment using a model of hepatic damage induced by allyl alcohol in nonobese diabetic-severe combined immunodeficient (NOD/SCID) mice\(^\text{[179]}\). Hepatocyte-like cells, known as NeoHeps, which are derived from terminally differentiated peripheral blood monocytes, also seem to be very effective in treating experimental ALF in Wistar rats\(^\text{[183]}\).

**Clinical results:** In a clinical trial, 40 patients with HBV-related cirrhosis were randomized to receive G-CSF alone or in combination with the reinfusion of peripheral blood monocytes in the hepatic artery. Over a 6-mo follow-up, significant biochemical and clinical improvement was seen in both groups\(^\text{[184]}\). In a different setting, Gasbarini et al\(^\text{[176]}\) transplanted peripheral blood stem cells into a single patient with ALF and showed improvement of liver function over 30 d, although the patient eventually succumbed to sepsis.
CONCLUSION

Although several cell transplantation trials concerning different types of mature or progenitor/stem cells in rodents succeeded in improving liver failure, cell transplantation therapies for human liver disorders are still in the early stages of development. Animal models of small animals may not reproduce the clinical syndrome of LF adequately, and trials in large animal models are required. Also mechanisms concerning transplanted cell engraftment and proliferation in LF need further analysis. Most of these clinical trials have limitations, being performed on small groups of patients, with no controls and using outcome parameters that are easily biased. The current inability to track transplanted or infused cells in human subjects represents a major challenge in further developing and understanding stem cell therapies. Clinical trials should be planned, with the development of standardized protocols for standardized procedures to define the nature of cells, the patients enrolled, the transplantation procedure and pre-treatment of the liver, as well as standard data collection regarding efficacy, and possible side effects. The results of the experiments are promising; therefore, cell transplantation therapies should be the first choice in the treatment of acute or end-stage liver failure in the near future.

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Liver regeneration after partial hepatectomy involves the proliferation of hepatic progenitor cells that differentiate into mature hepatocytes. The process is complex and involves the activation of progenitor cells, which then proliferate and differentiate to repopulate the liver. The role of growth factors and cytokines in hepatic regeneration is well studied, with studies showing that factors such as hepatocyte growth factor and TWEAK can induce liver regeneration.

The liver's regenerative capacity is a result of the presence of hepatocyte progenitor cells (HPCs) that are capable of proliferation and differentiation. These cells are found in the liver's perisinusoidal space of Disse, a region rich in sinusoidal endothelium, which is critical for liver regeneration.

Mechanisms of liver regeneration include the activation of progenitor cells, which then proliferate and differentiate to repopulate the liver. The role of growth factors and cytokines in hepatic regeneration is well studied, with studies showing that factors such as hepatocyte growth factor and TWEAK can induce liver regeneration. Additionally, the presence of stem cells, including pluripotent human hepatic progenitors, has been implicated in the regeneration process.

The use of liver-derived stem cells in the treatment of liver failure, such as in the treatment of non-alcoholic steatohepatitis (NASH), is a promising area of research. The use of these cells could potentially provide a non-invasive and effective treatment option for liver failure.

Furthermore, the role of progenitor cells in repair of liver injury and in liver transplantation is also a critical area of research. The characterization of these cells and their role in liver regeneration is essential for the development of novel therapeutic strategies for liver failure.
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