World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i40.6757

World J Gastroenterol 2013 October 28; 19(40): 6757-6773
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

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

Mukaddes Esrefoglu

Mukaddes Esrefoglu, Department of Histology and Embryology, Medical Faculty, Bezmialem Vakif University, 34093 Istanbul, Turkey

Author contributions: Esrefoglu M solely contributed to this paper.

Correspondence to: Mukaddes Esrefoglu, Professor, Department of Histology and Embryology, Medical Faculty, Bezmialem Vakif University, Adnan Menderes Bulvari, Vatan Cad, Istanbul 34093, Turkey. drmukaddes@hotmail.com
Telephone: +90-532-3465239 **Fax:** +90-212-6217580

Received: May 10, 2013 **Revised:** July 23, 2013
Accepted: August 17, 2013

Abstract

Although the liver has a high regenerative capacity, as a result of massive hepatocyte death, liver failure occurs. 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 the risks of rejection have prompted extensive experimental and clinical research in the field of cellular transplantation. Transplantation of cell lineages involved in liver regeneration, including mature hepatocytes, fetal hepatocytes, fetal liver progenitor cells, fetal stem cells, hepatic progenitor cells, hepatic stem cells, mesenchymal stem cells, hematopoietic stem cells, and peripheral blood and umbilical cord blood stem cells, have been found to be beneficial in the treatment of liver failure. In this article, the results of experimental and clinical cell transplantation trials for liver failure are reviewed, with an emphasis on regeneration.

Key words: Liver regeneration; Liver failure; Stem cell

Core tip: 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.

Esrefoglu M. Role of stem cells in repair of liver injury: Experimental and clinical benefit of transferred stem cells on liver failure. *World J Gastroenterol* 2013; 19(40): 6757-6773 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i40/6757.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i40.6757

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[1]. In the regenerating liver after partial hepatectomy (PH), periportal cells replicate first, probably reflecting their shorter G1 phase[2]. The peak of DNA synthesis is within 40-44 h after PH in mice[3]. 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[4]. Hepatocytes are the cells that normally shoulder the burden of regenerative growth after liver damage; therefore, they can be considered as the functional stem cells under most circumstances[5].

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)[6]. 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), stallate 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[10]. 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[13]. 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 cholangiocytic lineages[14]. Kuwahara *et al*[15] 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 multiple specialized cell lineages. 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 morrow 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 cells 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*[16]. 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[17]. The area connecting the terminal segment of the biliary ductular system with parenchymal hepatocytes persists in the adult liver and is known as the canals of Hering[18]. The primitive intrahepatic bile ducts expressing both hepatocyte proteins and biliary epithelial markers have consequently been referred to as "transitional cells"[19-21]. Transitional cells have properties intermediate between those of oval cells and hepatocytes[20]. These cells are believed to remain in the adult liver as bipotential progenitors for both hepatocytes and biliary cells[21].

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[22]. 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[23]. In rodents, early reactive bile ductules do not generally resemble hepatocytes, but later acquire features of hepatocytes[22]. 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[24,25].

The oval cells represent the progeny of liver stem cells and function as an amplification compartment for the generation of "new" hepatocytes[22]. The oval cell compartment, consisting of small ovoid cells with scant, lightly basophilic cytoplasm and pale blue staining oval nuclei[26], 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[27]. 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[28]. 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[29]. 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[30].

Oval cells form ductular structures that communicate with the biliary system at one end and terminate at a hepatocyte-forming blind end[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)[32,33]. Oval cells also express some markers considered characteristic of stem cells, including stem cell factor[34], bcl-2[35] and cytokeratin 14[36]. They are also immunoreactive to antibodies generally associated with hematopoietic lineages, such as CD34, and c-kit[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[39]. Moreover, Crosby *et al*[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[31,40], from mature biliary cells[12], liver epithelial or stromal cells[41], or from circulating hematopoietic stem cells[42,43]. 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[39,44]. Fausto *et al*[45] suggested that bone barrow stem cells can generate oval cells and hepatocytes; however, transdifferentiation 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[46]. Additionally, the repopulation process is not complete and is relatively slow[43,47].

Studies have demonstrated that HSCs have the capacity to fuse with other cell types[48]. 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[48,49]. 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[25].

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[50].

Another cell type related to the regeneration of rat liver has been identified, referred to as “small hepatocytes” (small hepatocyte-like progenitor cells)[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[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[52]. 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 *et al*[54] suggested that small hepatocytes are not the progeny of oval cell precursors, but represent an independent liver progenitor cell population. By contrast, Vig *et al*[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 vitro* that show some characteristics of mature hepatocytes, but are still not fully mature and/or characterized[56]. Classic studies by Evarts *et al*[57-59] 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 vivo*. Thus, the precursor-product relationship between oval cells and basophilic hepatocytes has been suggested[59].

Recently, a unique population of liver-derived bipotential liver progenitors was isolated from unmanipulated rat liver[60]. These bipotential liver cells express both hematopoietic stem cell markers, such as CD45, CD34 and thy-1, similar to oval cells[60,61], 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[60,62]. Their capacity for hepatic differentiation makes them a valuable resource for important applications such as cell therapies for a variety of liver diseases[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[63,64]. Herrera *et al*[65] 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 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*[64] 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*[66,67] 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[68].

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[5]. The local environments of endogenous and transplanted cells mainly affect their proliferation, differentiation, secretion, and other functions[69,70]. 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[71-73]. In cultures, the mouse liver progenitor cells differentiated into hepatocytes upon treatment with EGF or differentiated into biliary lineage cells upon treatment with HGF[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[75-77]. In the intact liver, hepatocytes need to be “primed” to enter the cell cycle and respond to growth factors[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[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[71,78]. Non-parenchymal cells, such as endothelial cells, Kupffer cells, stellate cell and intrahepatic lymphocytes provide critical signals to hepatocytes during regeneration[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[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[76,81]. Stellate cells are regarded as the principal source of extracellular matrix proteins during hepatic regeneration[82]. 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[83]. 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*[31] 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[84-87]. 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[87].

Some of the other key molecules in the liver microenvironment that determine regenerative behavior include the pro-inflammatory cytokines and angiogenic factors, such as vascular endothelial growth factor (VEGF)[80,88].

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[89]. 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[16]. 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[3,19,96]. 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[45,75]. 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[97], 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 differences in mortality over a 12-mo period. On the contrary, Kobayashi *et al*[108] found that intrasplenic cell transplantation in extremely sick cirrhotic rats was associated with improvement in liver tests, coagulation abnormality and outcomes. Additionally, cell transplantation has been shown to prevent the development of intracranial hypertension in pigs following acute ischemic liver failure[109].

Immortalized hepatocytes have also been shown to improve the survival rate in an ALF model[110]. Immortalized hepatocytes that can function as well as primary hepatocytes following transplantation were found to be effective in the treatment of liver failure in rats with end-stage cirrhosis with hepatic encephalopathy[98,111]. The immortalized hepatocytes may achieve a meaningful liver population using a clonal cell line; however, the malignant potential of these immortalized cell lines needs to be fully investigated before they could be applied in the clinic.

Clinical results

In an early study, in 10 Japanese patients with cirrhosis, hepatocytes (1-60 × 10^7) isolated from a piece of their own liver were transplanted into various sites, including the spleen[112]. 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 × 10^7-2.9 × 10^7) through the splenic artery[113]. 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 also has been found beneficial. Seven patients with fulminant hepatic failure (FHF) were transplanted (6 × 10^7/kgBW) *via* the abdominal cavity resulting in survival and improved encephalopathy[114].

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 × 10^9-3.9 × 10^{10} cryopreserved hepatocytes through intrasplenic and intraportal infusion improved afterwards[115]. A patient with ALF infused intraportally with 8 × 10^9 cryopreserved human hepatocytes fully recovered 12 wk after transplantation[116]. Repeated application of primary human hepatocytes seems to be safe and results in measurable benefits for patients with ALF.

HEPATIC PROGENITOR/STEM CELLS

Human hepatic stem cells, constituting approximately 0.5%-2.5% of liver parenchyma, can be isolated by immunoselection for epithelial cell adhesion molecule-positive cells (EpCAM+)[67]. 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 Gabrp 9 are overexpressed and are unique for the adult progenitors[117]. Thymus cell antigen 1 (Thy-1) is a marker for sorting bipotential progenitor cells from human livers[118]. None of the described markers are completely specific; therefore, isolation of viable cells is limited[119].

Much less is known about the mechanisms of oval cell replication and differentiation, although new information on these topics is rapidly accumulating. Regarding cellular aspects of liver growth and regeneration, it needs to be established what kind of signaling mechanisms may exist, direct and/or indirect, between hepatocytes and oval cells that determines whether one cell type or the other is the main or initial target for a growth stimulus[45].

Experimental results

Schmelzer *et al*[67] demonstrated that purified EpCAM+ cells from fetal or postnatal livers are able to engraft the livers of immunodeficient adult mice (with or without prior injury) and give rise to mature human liver parenchymal cells. Similar results were obtained by Weiss *et al*[118] through the isolation of Thy-1+ cells from adult human livers and their transplantation in immunodeficient Pfp/Rag2 mice. Analysis of *in situ* material revealed that transplanted cells express human hepatic markers HepPar1 and albumin, indicating functional engraftment.

Oval cell proliferation is prominent in many models of liver injury, including CCl4 treatment in combination with PH[120,121]. A recent study showed that transfer of oval cells to Wistar rats with FHF could significantly increase their survival rate[122]. In the study of Wang *et al*[123], 3,5-diethoxycarbonyl-1,4-dihydrocollidine induced oval cell proliferation. Transplantation of murine oval cells could repopulate the recipient liver in fumarylacetoacetate hydrolase-deficient mice, and rescue the phenotype.

Clinical results

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

FETAL HEPATOCYTES/FETAL LIVER PROGENITOR CELLS/FETAL STEM CELLS

Fetal human hepatocytes exhibit unique properties, including the capacity for extensive proliferation and excellent recovery following partial liver resection[124]. However, experimental studies have predominantly focused on transplantation of fetal hepatic progenitor cells. Oertel *et al*[125] 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[126]. Transplanted rat fetal liver epithelial progenitor cells were able to repopulate a recipient liver subjected to PH, alone or with retrorsine, in syngeneic dipeptidyl peptidase IV (DPPIV) mutant rats[127]. 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[125]. 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[89]. 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 Hamazaki *et al*[128], 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*[129] 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*[130] produced hepatic cells with a high level of liver function by transplanting ES cells into mice livers 24 h after CCl_4 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*[131], ES-derived hepatocytes could improve the life quality and lengthen the survival time of CCl_4-induced FHF. Sprague-Dawley rats with surgically induced liver failure *via* 90% hepatectomy, receiving 10^6-10^8 ESCs as splenic transplantation, showed 100% survival rate up to 3 mo[132]. Similarly, hepatocytes derived from ES cells in a bioartificial assisted liver device were able to improve survival in rats with liver failure induced by galactosamine after 10 h of extracorporeal liver dialysis[133]. Additionally, embryonic derived hepatocytes, implanted subcutaneously as a bioartificial liver device into mice subjected to 90% hepatectomy, reversed the liver failure[134]. Transplantation of ES cell-derived hepatic cells significantly suppressed the onset of fibrosis in mice[135].

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 cells 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[136-138]. 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[136]. Chamberlain *et al*[139] transplanted clonal human MSCs into preimmune 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 injured liver may produce regulatory factors for homing of stem cells to the injury site[135].

Bone marrow-derived mesenchymal stem cells

The most important source of MSCs is bone marrow.

Experimental results: A recent study by Carvalho *et al*[140] demonstrated that MSCs injection into the portal vein of mice or rats with liver cirrhosis induced by CCl_4 and ethanol did not reduce hepatic fibrosis or promote any improvement in parameters of liver function. However; Oyagi *et al*[141] demonstrated benefits in transplantation of bone marrow-derived mesenchymal stem cells (BMMCs) cultured with HGF in CCl_4-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*[142] 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 favorable 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[143]. 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[144]. The study of Amer *et al*[145] 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[146,147]. Placenta derived MSCs can be differentiated into hepatocyte-like cells *in vitro*[148].

Experimental results: The experimental study of Cao *et al*[149] 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%). Recently, van Poll *et al*[150] provided evidence that MSC-derived molecules directly inhibit hepatocellular death, enhance liver regeneration and ultimately improve survival in rats undergoing D-galactosamine-induced FHF. Systemic infusion of MSC-conditioned medium resulted in a 90% reduction of apoptotic hepatocellular death and a three-fold increment in the number of proliferating hepatocytes. Moreover, transplanted human placental MSCs ameliorate CCl_4- induced liver cirrhosis by their anti-fibrotic effect in a rat model[151]. Mohsin *et al*[152] reported that pretreated MSCs expressing high levels of albumin, cytokeratin 8, 18, TAT and HNF1α transplanted in the left lateral lobe of mice with liver fibrosis resulted in a significant reduction in the fibrotic area in the liver, concomitant with improved serum levels of bilirubin and alkaline phosphatase. Cao *et al*[149] compared the effects of transplantation of placental MSCs through the peripheral (jugular) and portal veins; their data suggested that both transplantation routes were safe, with no portal vein thrombosis. However, histological data revealed that transplantation of human placental MSCs *via* the portal vein reduced liver inflammation, decreased hepatic denaturation and necrosis, and promoted liver regeneration.

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[153]. Adipose tissue-derived MSCs have immunomodulation, differentiation (plasticity), homing, revascularization, anti-apoptotic and tissue regenerating abilities[136].

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[154]. When approximately 10^5 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[153]. 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 CCl_4-induced liver failure in mice[155].

Clinical results: In the study of Zhang *et al*[156] 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 transfusions significantly increased the survival rates in ACLF patients[157].

Bone marrow-derived hematopoietic stem cells

In 1999 Petersen *et al*[42] and in 2000 Lagesaa *et al*[43] 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[158,159]. Initial reports of the hepatic potential of HSCs were later shown to have resulted from fusion between transplanted donor cells and resident recipient hepatocytes[48,160]. The authors analyzed sex-mismatched bone marrow and liver transplantations in rats[42], mice[158] and humans[161], 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[160].

Experimental results: Cantz *et al*[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*[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-urokinase transgenic mouse, hepatitis B transgenic mouse. By contrast, Jang *et al*[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[165]. In the study of Shizhu *et al*[166] transplanted bone marrow mononuclear cells *via* tail veins of mice were found to populate the damaged liver around the portal and centrolobular 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[167-171]. Clinical studies by Lyra *et al*[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[174]. However, in the study of Cauto *et al*[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[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[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*[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[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[170]. Terai *et al*[169] implemented a clinical trial on nine patients with decompensated liver cirrhosis. These patients were infused with $5.2 \pm 0.63 \times 10^9$ 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[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[179] and some claim no evidence of cell fusion[180]. Newsome *et al*[180] demonstrated that human umbilical cord-blood (hUCB)-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*[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[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[178]. 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[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[184]. In a different setting, Gasbarini *et al*[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.

REFERENCES

1 **Wright N**, Alison M. The Biology of Epithelial Cell Populations. In: Wright N, Alison M. The Liver. Oxford: Clarendon Press, 1984: 880-908

2 **Rabes HM**. Kinetics of hepatocellular proliferation after partial resection of the liver. *Prog Liver Dis* 1976; **5**: 83-99 [PMID: 775564]

3 **Fausto N**. Liver regeneration. *J Hepatol* 2000; **32**: 19-31 [PMID: 10728791]

4 **Overturf K**, al-Dhalimy M, Ou CN, Finegold M, Grompe M. Serial transplantation reveals the stem-cell-like regenerative potential of adult mouse hepatocytes. *Am J Pathol* 1997; **151**: 1273-1280 [PMID: 9358753]

5 **Alison MR**, Islam S, Lim S. Stem cells in liver regeneration, fibrosis and cancer: the good, the bad and the ugly. *J Pathol* 2009; **217**: 282-298 [PMID: 18991329 DOI: 10.1002/path.2453]

6 **Starzl TE**, Fung J, Tzakis A, Todo S, Demetris AJ, Marino IR, Doyle H, Zeevi A, Warty V, Michaels M. Baboon-to-human liver transplantation. *Lancet* 1993; **341**: 65-71 [PMID: 8093402]

7 **Ibrahim S**, Chen CL, Wang CC, Wang SH, Lin CC, Liu YW, Yang CH, Yong CC, Concejero A, Cheng YF. Liver regeneration and splenic enlargement in donors after living-donor liver transplantation. *World J Surg* 2005; **29**: 1658-1666 [PMID: 16311869]

8 **Haga J**, Shimazu M, Wakabayashi G, Tanabe M, Kawachi S, Fuchimoto Y, Hoshino K, Morikawa Y, Kitajima M, Kitagawa Y. Liver regeneration in donors and adult recipients after living donor liver transplantation. *Liver Transpl* 2008; **14**: 1718-1724 [PMID: 19025926 DOI: 10.1002/lt.21622]

9 **Demetriou AA**, Brown RS, Busuttil RW, Fair J, McGuire BM, Rosenthal P, Am Esch JS, Lerut J, Nyberg SL, Salizzoni M, Fagan EA, de Hemptinne B, Broelsch CE, Muraca M, Salmeron JM, Rabkin JM, Metselaar HJ, Pratt D, De La Mata M, McChesney LP, Everson GT, Lavin PT, Stevens AC, Pitkin Z, Solomon BA. Prospective, randomized, multicenter, controlled trial of a bioartificial liver in treating acute liver failure. *Ann Surg* 2004; **239**: 660-667; discussion 660-667 [PMID: 15082970]

10 **Esrefoglu M**. Ozel Histoloji. 1st ed. Malatya: Medipres matbaacilik yayincilik, 2009: 108-113

11 **Gaudio E**, Carpino G, Cardinale V, Franchitto A, Onori P, Alvaro D. New insights into liver stem cells. *Dig Liver Dis* 2009; **41**: 455-462 [PMID: 19403350 DOI: 10.1016/j.dld.2009.03.009]

12 **Theise ND**, Saxena R, Portmann BC, Thung SN, Yee H, Chiriboga L, Kumar A, Crawford JM. The canals of Hering and hepatic stem cells in humans. *Hepatology* 1999; **30**: 1425-1433 [PMID: 10573521]

13 **Roskams TA**, Theise ND, Balabaud C, Bhagat G, Bhathal PS, Bioulac-Sage P, Brunt EM, Crawford JM, Crosby HA, Desmet V, Finegold MJ, Geller SA, Gouw AS, Hytiroglou P, Knisely AS, Kojiro M, Lefkowitch JH, Nakanuma Y, Olynyk JK, Park YN, Portmann B, Saxena R, Scheuer PJ, Strain AJ, Thung SN, Wanless IR, West AB. Nomenclature of the finer branches of the biliary tree: canals, ductules, and ductular reactions in human livers. *Hepatology* 2004; **39**: 1739-1745 [PMID: 15185318]

14 **Kakinuma S**, Nakauchi H, Watanabe M. Hepatic stem/progenitor cells and stem-cell transplantation for the treatment of liver disease. *J Gastroenterol* 2009; **44**: 167-172 [PMID: 19214659 DOI: 10.1007/s00535-008-2297-z]

15 **Kuwahara R**, Kofman AV, Landis CS, Swenson ES, Barendswaard E, Theise ND. The hepatic stem cell niche: identification by label-retaining cell assay. *Hepatology* 2008; **47**: 1994-2002 [PMID: 18454509 DOI: 10.1002/hep.22218]

16 **Bae SH**. [Clinical application of stem cells in liver diseases]. *Korean J Hepatol* 2008; **14**: 309-317 [PMID: 18815454 DOI: 10.3350/kjhep.2008.14.3.309]

17 **Sadler TW**. Langman's Medical Embryology. 10th ed. Philadelphia: Lippincott Williams and Wilkins, 2006: 214

18 **Saxena R**, Theise ND, Crawford JM. Microanatomy of the human liver-exploring the hidden interfaces. *Hepatology* 1999; **30**: 1339-1346 [PMID: 10573509]

19 **Fausto N**, Lemire JM, Shiojiri N. Cell lineages in hepatic development and the identification of progenitor cells in normal and injured liver. *Proc Soc Exp Biol Med* 1993; **204**: 237-241 [PMID: 7694302]

20 **Sells MA**, Katyal SL, Shinozuka H, Estes LW, Sell S, Lombardi B. Isolation of oval cells and transitional cells from the livers of rats fed the carcinogen DL-ethionine. *J Natl Cancer Inst* 1981; **66**: 355-362 [PMID: 7005506]

21 **Shiojiri N**, Lemire JM, Fausto N. Cell lineages and oval cell progenitors in rat liver development. *Cancer Res* 1991; **51**: 2611-2620 [PMID: 1708696]

22 **Golding M**, Sarraf C, Lalani EN, Alison MR. Reactive biliary epithelium: the product of a pluripotential stem cell compartment? *Hum Pathol* 1996; **27**: 872-884 [PMID: 8816880]

23 **Nomoto M**, Uchikosi Y, Kajikazawa N, Tanaka Y, Asakura H. Appearance of hepatocytelike cells in the interlobular bile ducts of human liver in various liver disease states. *Hepatology* 1992; **16**: 1199-1205 [PMID: 1385291]

24 **Nishikawa Y**, Doi Y, Watanabe H, Tokairin T, Omori Y, Su M, Yoshioka T, Enomoto K. Transdifferentiation of mature rat hepatocytes into bile duct-like cells in vitro. *Am J Pathol* 2005; **166**: 1077-1088 [PMID: 15793288]

25 **Michalopoulos GK**. Liver regeneration: alternative epithelial pathways. *Int J Biochem Cell Biol* 2011; **43**: 173-179 [PMID: 19788929 DOI: 10.1016/j.biocel.2009.09.01]

26 **Xiao JC**, Ruck P, Kaiserling E. Small epithelial cells in extrahepatic biliary atresia: electron microscopic and immunoelectron microscopic findings suggest a close relationship to liver progenitor cells. *Histopathology* 1999; **35**: 454-460 [PMID: 10583561]

27 **Shafritz DA**, Oertel M, Menthena A, Nierhoff D, Dabeva MD. Liver stem cells and prospects for liver reconstitution by transplanted cells. *Hepatology* 2006; **43**: S89-S98 [PMID:

16447292]

28 **Cantz T**, Manns MP, Ott M. Stem cells in liver regeneration and therapy. *Cell Tissue Res* 2008; **331**: 271-282 [PMID: 17901986]

29 **Lee JH**, Rim HJ, Sell S. Heterogeneity of the "oval-cell" response in the hamster liver during cholangiocarcinogenesis following Clonorchis sinensis infection and dimethylnitrosamine treatment. *J Hepatol* 1997; **26**: 1313-1323 [PMID: 9210619]

30 **Faris RA**, Konkin T, Halpert G. Liver stem cells: a potential source of hepatocytes for the treatment of human liver disease. *Artif Organs* 2001; **25**: 513-521 [PMID: 11493271]

31 **Paku S**, Schnur J, Nagy P, Thorgeirsson SS. Origin and structural evolution of the early proliferating oval cells in rat liver. *Am J Pathol* 2001; **158**: 1313-1323 [PMID: 11290549]

32 **Germain L**, Noël M, Gourdeau H, Marceau N. Promotion of growth and differentiation of rat ductular oval cells in primary culture. *Cancer Res* 1988; **48**: 368-378 [PMID: 2446746]

33 **Thorgeirsson SS**. Hepatic stem cells in liver regeneration. *FASEB J* 1996; **10**: 1249-1256 [PMID: 8836038]

34 **Fujio K**, Evarts RP, Hu Z, Marsden ER, Thorgeirsson SS. Expression of stem cell factor and its receptor, c-kit, during liver regeneration from putative stem cells in adult rat. *Lab Invest* 1994; **70**: 511-516 [PMID: 7513770]

35 **Burt AD**, MacSween RN. Bile duct proliferation--its true significance? *Histopathology* 1993; **23**: 599-602 [PMID: 8314252]

36 **Bisgaard HC**, Nagy P, Ton PT, Hu Z, Thorgeirsson SS. Modulation of keratin 14 and alpha-fetoprotein expression during hepatic oval cell proliferation and liver regeneration. *J Cell Physiol* 1994; **159**: 475-484 [PMID: 7514611]

37 **Crosby HA**, Kelly DA, Strain AJ. Human hepatic stem-like cells isolated using c-kit or CD34 can differentiate into biliary epithelium. *Gastroenterology* 2001; **120**: 534-544 [PMID: 11159894]

38 **Omori N**, Omori M, Evarts RP, Teramoto T, Miller MJ, Hoang TN, Thorgeirsson SS. Partial cloning of rat CD34 cDNA and expression during stem cell-dependent liver regeneration in the adult rat. *Hepatology* 1997; **26**: 720-727 [PMID: 9303503]

39 **Avital I**, Inderbitzin D, Aoki T, Tyan DB, Cohen AH, Ferraresso C, Rozga J, Arnaout WS, Demetriou AA. Isolation, characterization, and transplantation of bone marrow-derived hepatocyte stem cells. *Biochem Biophys Res Commun* 2001; **288**: 156-164 [PMID: 11594767]

40 **Demetris AJ**, Seaberg EC, Wennerberg A, Ionellie J, Michalopoulos G. Ductular reaction after submassive necrosis in humans. Special emphasis on analysis of ductular hepatocytes. *Am J Pathol* 1996; **149**: 439-448 [PMID: 8701983]

41 **Deng H**, Wang HF, Gao YB, Jin XL, Xiao JC. Hepatic progenitor cell represents a transitioning cell population between liver epithelium and stroma. *Med Hypotheses* 2011; **76**: 809-812 [PMID: 21382669 DOI: 10.1016/j.mehy.2011.02.024]

42 **Petersen BE**, Bowen WC, Patrene KD, Mars WM, Sullivan AK, Murase N, Boggs SS, Greenberger JS, Goff JP. Bone marrow as a potential source of hepatic oval cells. *Science* 1999; **284**: 1168-1170 [PMID: 10325227 DOI: 10.1126/science.284.5417.1168]

43 **Lagasse E**, Connors H, Al-Dhalimy M, Reitsma M, Dohse M, Osborne L, Wang X, Finegold M, Weissman IL, Grompe M. Purified hematopoietic stem cells can differentiate into hepatocytes in vivo. *Nat Med* 2000; **6**: 1229-1234 [PMID: 11062533 DOI: 10.1038/81326]

44 **Oh SH**, Witek RP, Bae SH, Zheng D, Jung Y, Piscaglia AC, Petersen BE. Bone marrow-derived hepatic oval cells differentiate into hepatocytes in 2-acetylaminofluorene/partial hepatectomy-induced liver regeneration. *Gastroenterology* 2007; **132**: 1077-1087 [PMID: 17383429 DOI: 10.1053/j.gastro.2007.01.001]

45 **Fausto N**, Campbell JS. The role of hepatocytes and oval cells in liver regeneration and repopulation. *Mech Dev* 2003; **120**: 117-130 [PMID: 12490302 DOI: 10.1016/S0925-4773(02)00338-6]

46 **Mallet VO**, Mitchell C, Mezey E, Fabre M, Guidotti JE, Renia L, Coulombel L, Kahn A, Gilgenkrantz H. Bone marrow transplantation in mice leads to a minor population of hepatocytes that can be selectively amplified in vivo. *Hepatology* 2002; **35**: 799-804 [PMID: 11915025 DOI: 10.1053/jhep.2002.32530]

47 **Wang X**, Montini E, Al-Dhalimy M, Lagasse E, Finegold M, Grompe M. Kinetics of liver repopulation after bone marrow transplantation. *Am J Pathol* 2002; **161**: 565-574 [PMID: 12163381 DOI: 10.1016/S0002-9440(10)64212-5]

48 **Terada N**, Hamazaki T, Oka M, Hoki M, Mastalerz DM, Nakano Y, Meyer EM, Morel L, Petersen BE, Scott EW. Bone marrow cells adopt the phenotype of other cells by spontaneous cell fusion. *Nature* 2002; **416**: 542-545 [PMID: 11932747 DOI: 10.1038/nature730]

49 **Wang X**, Willenbring H, Akkari Y, Torimaru Y, Foster M, Al-Dhalimy M, Lagasse E, Finegold M, Olson S, Grompe M. Cell fusion is the principal source of bone-marrow-derived hepatocytes. *Nature* 2003; **422**: 897-901 [PMID: 12665832 DOI: 10.1038/nature01531]

50 **Sell S**. Heterogeneity and plasticity of hepatocyte lineage cells. *Hepatology* 2001; **33**: 738-750 [PMID: 11230756 DOI: 10.1053/jhep.2001.21900]

51 **Dabeva MD**, Laconi E, Oren R, Petkov PM, Hurston E, Shafritz DA. Liver regeneration and alpha-fetoprotein messenger RNA expression in the retrorsine model for hepatocyte transplantation. *Cancer Res* 1998; **58**: 5825-5834 [PMID: 9865742]

52 **Gordon GJ**, Coleman WB, Hixson DC, Grisham JW. Liver regeneration in rats with retrorsine-induced hepatocellular injury proceeds through a novel cellular response. *Am J Pathol* 2000; **156**: 607-619 [PMID: 10666390]

53 **Gordon GJ**, Coleman WB, Grisham JW. Temporal analysis of hepatocyte differentiation by small hepatocyte-like progenitor cells during liver regeneration in retrorsine-exposed rats. *Am J Pathol* 2000; **157**: 771-786 [PMID: 10980117]

54 **Best DH**, Coleman WB. Treatment with 2-AAF blocks the small hepatocyte-like progenitor cell response in retrorsine-exposed rats. *J Hepatol* 2007; **46**: 1055-1063 [PMID: 17434228]

55 **Vig P**, Russo FP, Edwards RJ, Tadrous PJ, Wright NA, Thomas HC, Alison MR, Forbes SJ. The sources of parenchymal regeneration after chronic hepatocellular liver injury in mice. *Hepatology* 2006; **43**: 316-324 [PMID: 16440343]

56 **Soto-Gutierrez A**, Navarro-Alvarez N, Yagi H, Yarmush ML. Stem cells for liver repopulation. *Curr Opin Organ Transplant* 2009; **14**: 667-673 [PMID: 19779345 DOI: 10.1097/MOT.0b013e3283328070]

57 **Evarts RP**, Hu Z, Omori N, Omori M, Marsden ER, Thorgeirsson SS. Precursor-product relationship between oval cells and hepatocytes: comparison between tritiated thymidine and bromodeoxyuridine as tracers. *Carcinogenesis* 1996; **17**: 2143-2151 [PMID: 8895481]

58 **Evarts RP**, Nagy P, Nakatsukasa H, Marsden E, Thorgeirsson SS. In vivo differentiation of rat liver oval cells into hepatocytes. *Cancer Res* 1989; **49**: 1541-1547 [PMID: 2466557]

59 **Evarts RP**, Nagy P, Marsden E, Thorgeirsson SS. A precursor-product relationship exists between oval cells and hepatocytes in rat liver. *Carcinogenesis* 1987; **8**: 1737-1740 [PMID: 3664968]

60 **Sahin MB**, Schwartz RE, Buckley SM, Heremans Y, Chase L, Hu WS, Verfaillie CM. Isolation and characterization of a novel population of progenitor cells from unmanipulated rat liver. *Liver Transpl* 2008; **14**: 333-345 [PMID: 18306374 DOI: 10.1002/lt.21380]

61 **Petersen BE**, Grossbard B, Hatch H, Pi L, Deng J, Scott EW. Mouse A6-positive hepatic oval cells also express several hematopoietic stem cell markers. *Hepatology* 2003; **37**: 632-640 [PMID: 12601361]

62 **Chen Y**, Zhou H, Sarver AL, Zeng Y, Roy-Chowdhury J, Steer CJ, Sahin MB. Hepatic differentiation of liver-derived progenitor cells and their characterization by microRNA analysis. *Liver Transpl* 2010; **16**: 1086-1097 [PMID: 20818747 DOI: 10.1002/lt.22111]

63 **Suzuki A**, Zheng YW, Kaneko S, Onodera M, Fukao K, Nakauchi H, Taniguchi H. Clonal identification and characterization of self-renewing pluripotent stem cells in the developing liver. *J Cell Biol* 2002; **156**: 173-184 [PMID: 11781341]

64 **Castorina S**, Luca T, Torrisi A, Privitera G, Panebianco M. Isolation of epithelial cells with hepatobiliary phenotype. *Ital J Anat Embryol* 2008; **113**: 199-207 [PMID: 19507460]

65 **Herrera MB**, Bruno S, Buttiglieri S, Tetta C, Gatti S, Deregibus MC, Bussolati B, Camussi G. Isolation and characterization of a stem cell population from adult human liver. *Stem Cells* 2006; **24**: 2840-2850 [PMID: 16945998]

66 **Schmelzer E**, Wauthier E, Reid LM. The phenotypes of pluripotent human hepatic progenitors. *Stem Cells* 2006; **24**: 1852-1858 [PMID: 16627685]

67 **Schmelzer E**, Zhang L, Bruce A, Wauthier E, Ludlow J, Yao HL, Moss N, Melhem A, McClelland R, Turner W, Kulik M, Sherwood S, Tallheden T, Cheng N, Furth ME, Reid LM. Human hepatic stem cells from fetal and postnatal donors. *J Exp Med* 2007; **204**: 1973-1987 [PMID: 17664288]

68 **Christ B**, Brückner S. Rodent animal models for surrogate analysis of cell therapy in acute liver failure. *Front Physiol* 2012; **3**: 78 [PMID: 22485094 DOI: 10.3389/fphys.2012.00078]

69 **Liu L**, Yannam GR, Nishikawa T, Yamamoto T, Basma H, Ito R, Nagaya M, Dutta-Moscato J, Stolz DB, Duan F, Kaestner KH, Vodovotz Y, Soto-Gutierrez A, Fox IJ. The microenvironment in hepatocyte regeneration and function in rats with advanced cirrhosis. *Hepatology* 2012; **55**: 1529-1539 [PMID: 22109844 DOI: 10.1002/hep.24815]

70 **Sell S**. The role of progenitor cells in repair of liver injury and in liver transplantation. *Wound Repair Regen* 2001; **9**: 467-482 [PMID: 11896989]

71 **Michalopoulos GK**. Liver regeneration after partial hepatectomy: critical analysis of mechanistic dilemmas. *Am J Pathol* 2010; **176**: 2-13 [PMID: 20019184 DOI: 10.2353/ajpath.2010.090675]

72 **Marsden ER**, Hu Z, Fujio K, Nakatsukasa H, Thorgeirsson SS, Evarts RP. Expression of acidic fibroblast growth factor in regenerating liver and during hepatic differentiation. *Lab Invest* 1992; **67**: 427-433 [PMID: 1279268]

73 **Webber EM**, Godowski PJ, Fausto N. In vivo response of hepatocytes to growth factors requires an initial priming stimulus. *Hepatology* 1994; **19**: 489-497 [PMID: 8294105]

74 **Li WL**, Su J, Yao YC, Tao XR, Yan YB, Yu HY, Wang XM, Li JX, Yang YJ, Lau JT, Hu YP. Isolation and characterization of bipotent liver progenitor cells from adult mouse. *Stem Cells* 2006; **24**: 322-332 [PMID: 16109753]

75 **Fausto N**, Laird AD, Webber EM. Liver regeneration. 2. Role of growth factors and cytokines in hepatic regeneration. *FASEB J* 1995; **9**: 1527-1536 [PMID: 8529831]

76 **Fausto N**, Riehle KJ. Mechanisms of liver regeneration and their clinical implications. *J Hepatobiliary Pancreat Surg* 2005; **12**: 181-189 [PMID: 15995805]

77 **Webber EM**, Bruix J, Pierce RH, Fausto N. Tumor necrosis factor primes hepatocytes for DNA replication in the rat. *Hepatology* 1998; **28**: 1226-1234 [PMID: 9794905]

78 **Fausto N**, Campbell JS, Riehle KJ. Liver regeneration. *Hepatology* 2006; **43**: S45-S53 [PMID: 16447274]

79 **Greenbaum LE**, Wells RG. The role of stem cells in liver repair and fibrosis. *Int J Biochem Cell Biol* 2011; **43**: 222-229 [PMID: 19914396]

80 **Ding BS**, Nolan DJ, Butler JM, James D, Babazadeh AO, Rosenwaks Z, Mittal V, Kobayashi H, Shido K, Lyden D, Sato TN, Rabbany SY, Rafii S. Inductive angiocrine signals from sinusoidal endothelium are required for liver regeneration. *Nature* 2010; **468**: 310-315 [PMID: 21068842]

81 **Cressman DE**, Greenbaum LE, DeAngelis RA, Ciliberto G, Furth EE, Poli V, Taub R. Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice. *Science* 1996; **274**: 1379-1383 [PMID: 8910279]

82 **Lemoinne S**, Cadoret A, El Mourabit H, Thabut D, Housset C. Origins and functions of liver myofibroblasts. *Biochim Biophys Acta* 2013; **1832**: 948-954 [PMID: 23470555 DOI: 10.1016/j.bbadis]

83 **Chen L**, Zhang W, Zhou QD, Yang HQ, Liang HF, Zhang BX, Long X, Chen XP. HSCs play a distinct role in different phases of oval cell-mediated liver regeneration. *Cell Biochem Funct* 2012; **30**: 588-596 [PMID: 22535704]

84 **Okano J**, Shiota G, Matsumoto K, Yasui S, Kurimasa A, Hisatome I, Steinberg P, Murawaki Y. Hepatocyte growth factor exerts a proliferative effect on oval cells through the PI3K/AKT signaling pathway. *Biochem Biophys Res Commun* 2003; **309**: 298-304 [PMID: 12951049]

85 **Matthews VB**, Klinken E, Yeoh GC. Direct effects of interleukin-6 on liver progenitor oval cells in culture. *Wound Repair Regen* 2004; **12**: 650-656 [PMID: 15555057]

86 **Kaplanski C**, Pauley CJ, Griffiths TG, Kawabata TT, Ledwith BJ. Differentiation of rat oval cells after activation of peroxisome proliferator-activated receptor alpha43. *Cancer Res* 2000; **60**: 580-587 [PMID: 10676640]

87 **Jakubowski A**, Ambrose C, Parr M, Lincecum JM, Wang MZ, Zheng TS, Browning B, Michaelson JS, Baetscher M, Wang B, Bissell DM, Burkly LC. TWEAK induces liver progenitor cell proliferation. *J Clin Invest* 2005; **115**: 2330-2340 [PMID: 16110324]

88 **Taub R**. Liver regeneration: from myth to mechanism. *Nat Rev Mol Cell Biol* 2004; **5**: 836-847 [PMID: 15459664]

89 **Zhang H**, Liu Z, Li R, Wang D, Liu W, Li J, Yu H, Zhang F, Dou K. Transplantation of embryonic small hepatocytes induces regeneration of injured liver in adult rat. *Transplant Proc* 2009; **41**: 3887-3892 [PMID: 19917406 DOI: 10.1016/j.transproceed.2009.06.205]

90 **Szidonya J**, Farkas T, Pali T. The fatty acid constitution and ordering state of membranes in dominant temperature-sensitive lethal mutation and wild-type Drosophila melanogaster larvae. *Biochem Genet* 1990; **28**: 233-246 [PMID: 2168167 DOI: 10.1007/s11684-011-0107-0]

91 **Zhang W**, Tucker-Kellogg L, Narmada BC, Venkatraman L, Chang S, Lu Y, Tan N, White JK, Jia R, Bhowmick SS, Shen S, Dewey CF, Yu H. Cell-delivery therapeutics for liver regeneration. *Adv Drug Deliv Rev* 2010; **62**: 814-826 [PMID: 20193722 DOI: 10.1016/j.addr.2010.02.005]

92 **Sgroi A**, Serre-Beinier V, Morel P, Bühler L. What clinical alternatives to whole liver transplantation? Current status of artificial devices and hepatocyte transplantation. *Transplantation* 2009; **87**: 457-466 [PMID: 19307780 DOI: 10.1097/TP.0b013e3181963ad3]

93 **Weber A**, Groyer-Picard MT, Franco D, Dagher I. Hepatocyte transplantation in animal models. *Liver Transpl* 2009; **15**: 7-14 [PMID: 19109838 DOI: 10.1002/lt.21670]

94 **Allen KJ**, Soriano HE. Liver cell transplantation: the road to clinical application. *J Lab Clin Med* 2001; **138**: 298-312 [PMID: 11709654]

95 **Fisher RA**, Strom SC. Human hepatocyte transplantation: worldwide results. *Transplantation* 2006; **82**: 441-449 [PMID: 16926585]

96 **Michalopoulos GK**, DeFrances MC. Liver regeneration. *Science* 1997; **276**: 60-66 [PMID: 9082986]

97 **Wang N**, Wang Z, Sun H, Shi X, Zhang Y, Liu Q. Augmenter of liver regeneration improves therapeutic effect of hepatocyte homotransplantation in acute liver failure rats. *Int Immunopharmacol* 2013; **15**: 325-332 [PMID: 23337881 DOI: 10.1016/j.intimp.2013.01.002]

98 **Cai J**, Ito M, Nagata H, Westerman KA, Lafleur D, Chowdhury JR, Leboulch P, Fox IJ. Treatment of liver failure in rats with end-stage cirrhosis by transplantation of immortalized

hepatocytes. *Hepatology* 2002; **36**: 386-394 [PMID: 12143047]

99 **Cai J**, Ito M, Westerman KA, Kobayashi N, Leboulch P, Fox IJ. Construction of a non-tumorigenic rat hepatocyte cell line for transplantation: reversal of hepatocyte immortalization by site-specific excision of the SV40 T antigen. *J Hepatol* 2000; **33**: 701-708 [PMID: 11097476]

100 **Rhim JA**, Sandgren EP, Palmiter RD, Brinster RL. Complete reconstitution of mouse liver with xenogeneic hepatocytes. *Proc Natl Acad Sci USA* 1995; **92**: 4942-4946 [PMID: 7761429]

101 **Rhim JA**, Sandgren EP, Degen JL, Palmiter RD, Brinster RL. Replacement of diseased mouse liver by hepatic cell transplantation. *Science* 1994; **263**: 1149-1152 [PMID: 8108734]

102 **Overturf K**, Al-Dhalimy M, Finegold M, Grompe M. The repopulation potential of hepatocyte populations differing in size and prior mitotic expansion. *Am J Pathol* 1999; **155**: 2135-2143 [PMID: 10595942]

103 **Gupta S**, Rajvanshi P, Irani AN, Palestro CJ, Bhargava KK. Integration and proliferation of transplanted cells in hepatic parenchyma following D-galactosamine-induced acute injury in F344 rats. *J Pathol* 2000; **190**: 203-210 [PMID: 10657020]

104 **Gupta S**, Rajvanshi P, Sokhi R, Slehria S, Yam A, Kerr A, Novikoff PM. Entry and integration of transplanted hepatocytes in rat liver plates occur by disruption of hepatic sinusoidal endothelium. *Hepatology* 1999; **29**: 509-519 [PMID: 9918929]

105 **Makowka L**, Rotstein LE, Falk RE, Falk JA, Nossal NA, Langer B, Blendis LM, Phillips MJ. Allogeneic and xenogeneic hepatocyte transplantation in experimental hepatic failure. *Transplantation* 1980; **30**: 429-435 [PMID: 7008291]

106 **Rajvanshi P**, Kerr A, Bhargava KK, Burk RD, Gupta S. Studies of liver repopulation using the dipeptidyl peptidase IV-deficient rat and other rodent recipients: cell size and structure relationships regulate capacity for increased transplanted hepatocyte mass in the liver lobule. *Hepatology* 1996; **23**: 482-496 [PMID: 8617428]

107 **Gagandeep S**, Rajvanshi P, Sokhi RP, Slehria S, Palestro CJ, Bhargava KK, Gupta S. Transplanted hepatocytes engraft, survive, and proliferate in the liver of rats with carbon tetrachloride-induced cirrhosis. *J Pathol* 2000; **191**: 78-85 [PMID: 10767723]

108 **Kobayashi N**, Ito M, Nakamura J, Cai J, Gao C, Hammel JM, Fox IJ. Hepatocyte transplantation in rats with decompensated cirrhosis. *Hepatology* 2000; **31**: 851-857 [PMID: 10733539]

109 **Arkadopoulos N**, Chen SC, Khalili TM, Detry O, Hewitt WR, Lilja H, Kamachi H, Petrovic L, Mullon CJ, Demetriou AA, Rozga J. Transplantation of hepatocytes for prevention of intracranial hypertension in pigs with ischemic liver failure. *Cell Transplant* 1998; **7**: 357-363 [PMID: 9710304]

110 **Kobayashi N**, Fujiwara T, Westerman KA, Inoue Y, Sakaguchi M, Noguchi H, Miyazaki M, Cai J, Tanaka N, Fox IJ, Leboulch P. Prevention of acute liver failure in rats with reversibly immortalized human hepatocytes. *Science* 2000; **287**: 1258-1262 [PMID: 10678831]

111 **Schumacher IK**, Okamoto T, Kim BH, Chowdhury NR, Chowdhury JR, Fox IJ. Transplantation of conditionally immortalized hepatocytes to treat hepatic encephalopathy. *Hepatology* 1996; **24**: 337-343 [PMID: 8690402]

112 **Mito M**, Kusano M, Kawaura Y. Hepatocyte transplantation in man. *Transplant Proc* 1992; **24**: 3052-3053 [PMID: 1466053]

113 **Strom SC**, Fisher RA, Thompson MT, Sanyal AJ, Cole PE, Ham JM, Posner MP. Hepatocyte transplantation as a bridge to orthotopic liver transplantation in terminal liver failure. *Transplantation* 1997; **63**: 559-569 [PMID: 9047152]

114 **Habibullah CM**, Syed IH, Qamar A, Taher-Uz Z. Human fetal hepatocyte transplantation in patients with fulminant hepatic failure. *Transplantation* 1994; **58**: 951-952 [PMID: 7940741]

115 **Bilir BM**, Guinette D, Karrer F, Kumpe DA, Krysl J, Stephens J, McGavran L, Ostrowska A, Durham J. Hepatocyte transplantation in acute liver failure. *Liver Transpl* 2000; **6**: 32-40 [PMID: 10648575]

116 **Schneider A**, Attaran M, Meier PN, Strassburg C, Manns MP, Ott M, Barthold M, Arseniev L, Becker T, Panning B. Hepatocyte transplantation in an acute liver failure due to mushroom poisoning. *Transplantation* 2006; **82**: 1115-1116 [PMID: 17060866]

117 **Yovchev MI**, Grozdanov PN, Joseph B, Gupta S, Dabeva MD. Novel hepatic progenitor cell surface markers in the adult rat liver. *Hepatology* 2007; **45**: 139-149 [PMID: 17187413]

118 **Weiss TS**, Lichtenauer M, Kirchner S, Stock P, Aurich H, Christ B, Brockhoff G, Kunz-Schughart LA, Jauch KW, Schlitt HJ, Thasler WE. Hepatic progenitor cells from adult human livers for cell transplantation. *Gut* 2008; **57**: 1129-1138 [PMID: 18417531 DOI: 10.1136/gut.2007.143321]

119 **Roskams T**. Different types of liver progenitor cells and their niches. *J Hepatol* 2006; **45**: 1-4 [PMID: 16723168]

120 **Petersen BE**, Zajac VF, Michalopoulos GK. Hepatic oval cell activation in response to injury following chemically induced periportal or pericentral damage in rats. *Hepatology* 1998; **27**: 1030-1038 [PMID: 9537443]

121 **Chiu CC**, Huang GT, Chou SH, Chien CT, Chiou LL, Chang MH, Lee HS, Chen DS. Characterization of cytokeratin 19-positive hepatocyte foci in the regenerating rat liver after 2-AAF/CCl4 injury. *Histochem Cell Biol* 2007; **128**: 217-226 [PMID: 17661067]

122 **Wu CX**, Zou Q, Zhu ZY, Gao YT, Wang YJ. Intrahepatic transplantation of hepatic oval cells for fulminant hepatic failure in rats. *World J Gastroenterol* 2009; **15**: 1506-1511 [PMID: 19322926]

123 **Wang X**, Foster M, Al-Dhalimy M, Lagasse E, Finegold M, Grompe M. The origin and liver repopulating capacity of murine oval cells. *Proc Natl Acad Sci USA* 2003; **100** Suppl 1: 11881-11888 [PMID: 12902545]

124 **Elchaninov AV**, Bolshakova GB. Dynamics of hepatocyte proliferation in regenerating fetal rat liver. *Bull Exp Biol Med* 2011; **151**: 374-377 [PMID: 22451891]

125 **Oertel M**, Menthena A, Chen YQ, Teisner B, Jensen CH, Shafritz DA. Purification of fetal liver stem/progenitor cells containing all the repopulation potential for normal adult rat liver. *Gastroenterology* 2008; **134**: 823-832 [PMID: 18262526 DOI: 10.1053/j.gastro.2008.01.007]

126 **Cantz T**, Zuckerman DM, Burda MR, Dandri M, Göricke B, Thalhammer S, Heckl WM, Manns MP, Petersen J, Ott M. Quantitative gene expression analysis reveals transition of fetal liver progenitor cells to mature hepatocytes after transplantation in uPA/RAG-2 mice. *Am J Pathol* 2003; **162**: 37-45 [PMID: 12507888]

127 **Sandhu JS**, Petkov PM, Dabeva MD, Shafritz DA. Stem cell properties and repopulation of the rat liver by fetal liver epithelial progenitor cells. *Am J Pathol* 2001; **159**: 1323-1334 [PMID: 11583960]

128 **Hamazaki T**, Iiboshi Y, Oka M, Papst PJ, Meacham AM, Zon LI, Terada N. Hepatic maturation in differentiating embryonic stem cells in vitro. *FEBS Lett* 2001; **497**: 15-19 [PMID: 11376655]

129 **Heo J**, Factor VM, Uren T, Takahama Y, Lee JS, Major M, Feinstone SM, Thorgeirsson SS. Hepatic precursors derived from murine embryonic stem cells contribute to regeneration of injured liver. *Hepatology* 2006; **44**: 1478-1486 [PMID: 17133486]

130 **Yamamoto H**, Quinn G, Asari A, Yamanokuchi H, Teratani T, Terada M, Ochiya T. Differentiation of embryonic stem cells into hepatocytes: biological functions and therapeutic application. *Hepatology* 2003; **37**: 983-993 [PMID: 12717379]

131 **Hu AB**, He XS, Zheng QC, Cai JY. [Curative effects of transplantation of hepatocytes differentiated from embryonic stem cells on treatment of fulminant hepatic failure: experiment with mice]. *Zhonghua Yi Xue Zazhi* 2006; **86**: 3280-3284 [PMID: 17313811]

132 **Tabei I**, Hashimoto H, Ishiwata I, Tachibana T, Akahori M,

Ohi S, Kubo H, Satou K, Yamazaki Y, Yanaga K, Ishikawa H. Characteristics of hepatocytes derived from early ES cells and treatment of surgically induced liver failure rats by transplantation. *Transplant Proc* 2005; **37**: 262-264 [PMID: 15808614]

133 **Cho CH**, Parashurama N, Park EY, Suganuma K, Nahmias Y, Park J, Tilles AW, Berthiaume F, Yarmush ML. Homogeneous differentiation of hepatocyte-like cells from embryonic stem cells: applications for the treatment of liver failure. *FASEB J* 2008; **22**: 898-909 [PMID: 17942827]

134 **Soto-Gutiérrez A**, Kobayashi N, Rivas-Carrillo JD, Navarro-Alvarez N, Zhao D, Okitsu T, Noguchi H, Basma H, Tabata Y, Chen Y, Tanaka K, Narushima M, Miki A, Ueda T, Jun HS, Yoon JW, Lebkowski J, Tanaka N, Fox IJ. Reversal of mouse hepatic failure using an implanted liver-assist device containing ES cell-derived hepatocytes. *Nat Biotechnol* 2006; **24**: 1412-1419 [PMID: 17086173]

135 **Teratani T**, Yamamoto H, Aoyagi K, Sasaki H, Asari A, Quinn G, Sasaki H, Terada M, Ochiya T. Direct hepatic fate specification from mouse embryonic stem cells. *Hepatology* 2005; **41**: 836-846 [PMID: 15742390]

136 **Ochiya T**, Yamamoto Y, Banas A. Commitment of stem cells into functional hepatocytes. *Differentiation* 2010; **79**: 65-73 [PMID: 19883970]

137 **Seo MJ**, Suh SY, Bae YC, Jung JS. Differentiation of human adipose stromal cells into hepatic lineage in vitro and in vivo. *Biochem Biophys Res Commun* 2005; **328**: 258-264 [PMID: 15670778]

138 **Hong SH**, Gang EJ, Jeong JA, Ahn C, Hwang SH, Yang IH, Park HK, Han H, Kim H. In vitro differentiation of human umbilical cord blood-derived mesenchymal stem cells into hepatocyte-like cells. *Biochem Biophys Res Commun* 2005; **330**: 1153-1161 [PMID: 15823564]

139 **Chamberlain J**, Yamagami T, Colletti E, Theise ND, Desai J, Frias A, Pixley J, Zanjani ED, Porada CD, Almeida-Porada G. Efficient generation of human hepatocytes by the intrahepatic delivery of clonal human mesenchymal stem cells in fetal sheep. *Hepatology* 2007; **46**: 1935-1945 [PMID: 17705296]

140 **Carvalho AB**, Quintanilha LF, Dias JV, Paredes BD, Mannheimer EG, Carvalho FG, Asensi KD, Gutfilen B, Fonseca LM, Resende CM, Rezende GF, Takiya CM, de Carvalho AC, Goldenberg RC. Bone marrow multipotent mesenchymal stromal cells do not reduce fibrosis or improve function in a rat model of severe chronic liver injury. *Stem Cells* 2008; **26**: 1307-1314 [PMID: 18308943 DOI: 10.1634/stemcells.2007-0941]

141 **Oyagi S**, Hirose M, Kojima M, Okuyama M, Kawase M, Nakamura T, Ohgushi H, Yagi K. Therapeutic effect of transplanting HGF-treated bone marrow mesenchymal cells into CCl4-injured rats. *J Hepatol* 2006; **44**: 742-748 [PMID: 16469408]

142 **Fang B**, Shi M, Liao L, Yang S, Liu Y, Zhao RC. Systemic infusion of FLK1(+) mesenchymal stem cells ameliorate carbon tetrachloride-induced liver fibrosis in mice. *Transplantation* 2004; **78**: 83-88 [PMID: 15257043]

143 **Peng L**, Xie DY, Lin BL, Liu J, Zhu HP, Xie C, Zheng YB, Gao ZL. Autologous bone marrow mesenchymal stem cell transplantation in liver failure patients caused by hepatitis B: short-term and long-term outcomes. *Hepatology* 2011; **54**: 820-828 [PMID: 21608000 DOI: 10.1002/hep.24434]

144 **Kharaziha P**, Hellström PM, Noorinayer B, Farzaneh F, Aghajani K, Jafari F, Telkabadi M, Atashi A, Honardoost M, Zali MR, Soleimani M. Improvement of liver function in liver cirrhosis patients after autologous mesenchymal stem cell injection: a phase I-II clinical trial. *Eur J Gastroenterol Hepatol* 2009; **21**: 1199-1205 [PMID: 19455046 DOI: 10.1097/MEG.0b013e32832a1f6c]

145 **Amer ME**, El-Sayed SZ, El-Kheir WA, Gabr H, Gomaa AA, El-Noomani N, Hegazy M. Clinical and laboratory evaluation of patients with end-stage liver cell failure injected with bone marrow-derived hepatocyte-like cells. *Eur J Gastroenterol Hepatol* 2011; **23**: 936-941 [PMID: 21900788 DOI: 10.1097/MEG.0b013e3283488b00]

146 **Wulf GG**, Viereck V, Hemmerlein B, Haase D, Vehmeyer K, Pukrop T, Glass B, Emons G, Trümper L. Mesengenic progenitor cells derived from human placenta. *Tissue Eng* 2004; **10**: 1136-1147 [PMID: 15363170]

147 **Semenov OV**, Koestenbauer S, Riegel M, Zech N, Zimmermann R, Zisch AH, Malek A. Multipotent mesenchymal stem cells from human placenta: critical parameters for isolation and maintenance of stemness after isolation. *Am J Obstet Gynecol* 2010; **202**: 193.e1-193.e13 [PMID: 20035913 DOI: 10.1016/j.ajog.2009.10.869]

148 **Chien CC**, Yen BL, Lee FK, Lai TH, Chen YC, Chan SH, Huang HI. In vitro differentiation of human placenta-derived multipotent cells into hepatocyte-like cells. *Stem Cells* 2006; **24**: 1759-1768 [PMID: 16822884]

149 **Cao H**, Yang J, Yu J, Pan Q, Li J, Zhou P, Li Y, Pan X, Li J, Wang Y, Li L. Therapeutic potential of transplanted placental mesenchymal stem cells in treating Chinese miniature pigs with acute liver failure. *BMC Med* 2012; **10**: 56 [PMID: 22673529 DOI: 10.1186/1741-7015-10-56]

150 **van Poll D**, Parekkadan B, Cho CH, Berthiaume F, Nahmias Y, Tilles AW, Yarmush ML. Mesenchymal stem cell-derived molecules directly modulate hepatocellular death and regeneration in vitro and in vivo. *Hepatology* 2008; **47**: 1634-1643 [PMID: 18395843 DOI: 10.1002/hep.22236]

151 **Lee MJ**, Jung J, Na KH, Moon JS, Lee HJ, Kim JH, Kim GI, Kwon SW, Hwang SG, Kim GJ. Anti-fibrotic effect of chorionic plate-derived mesenchymal stem cells isolated from human placenta in a rat model of CCl(4)-injured liver: potential application to the treatment of hepatic diseases. *J Cell Biochem* 2010; **111**: 1453-1463 [PMID: 20830742 DOI: 10.1002/jcb.22873]

152 **Mohsin S**, Shams S, Ali Nasir G, Khan M, Javaid Awan S, Khan SN, Riazuddin S. Enhanced hepatic differentiation of mesenchymal stem cells after pretreatment with injured liver tissue. *Differentiation* 2011; **81**: 42-48 [PMID: 20943307]

153 **Banas A**, Teratani T, Yamamoto Y, Tokuhara M, Takeshita F, Quinn G, Okochi H, Ochiya T. Adipose tissue-derived mesenchymal stem cells as a source of human hepatocytes. *Hepatology* 2007; **46**: 219-228 [PMID: 17596885]

154 **Banas A**, Teratani T, Yamamoto Y, Tokuhara M, Takeshita F, Osaki M, Kato T, Okochi H, Ochiya T. Rapid hepatic fate specification of adipose-derived stem cells and their therapeutic potential for liver failure. *J Gastroenterol Hepatol* 2009; **24**: 70-77 [PMID: 18624899 DOI: 10.1111/j.1440-1746.2008.05496.x]

155 **Kim SJ**, Park KC, Lee JU, Kim KJ, Kim DG. Therapeutic potential of adipose tissue-derived stem cells for liver failure according to the transplantation routes. *J Korean Surg Soc* 2011; **81**: 176-186 [PMID: 22066119 DOI: 10.4174/jkss.2011.81.3.176]

156 **Zhang Z**, Lin H, Shi M, Xu R, Fu J, Lv J, Chen L, Lv S, Li Y, Yu S, Geng H, Jin L, Lau GK, Wang FS. Human umbilical cord mesenchymal stem cells improve liver function and ascites in decompensated liver cirrhosis patients. *J Gastroenterol Hepatol* 2012; **27** Suppl 2: 112-120 [PMID: 22320928 DOI: 10.1111/j.1440-1746.2011.07024.x]

157 **Shi M**, Zhang Z, Xu R, Lin H, Fu J, Zou Z, Zhang A, Shi J, Chen L, Lv S, He W, Geng H, Jin L, Liu Z, Wang FS. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. *Stem Cells Transl Med* 2012; **1**: 725-731 [PMID: 23197664 DOI: 10.5966/sctm.2012-0034]

158 **Theise ND**, Badve S, Saxena R, Henegariu O, Sell S, Crawford JM, Krause DS. Derivation of hepatocytes from bone marrow cells in mice after radiation-induced myeloablation. *Hepatology* 2000; **31**: 235-240 [PMID: 10613752]

159 **Alison MR**, Poulsom R, Jeffery R, Dhillon AP, Quaglia A,

Jacob J, Novelli M, Prentice G, Williamson J, Wright NA. Hepatocytes from non-hepatic adult stem cells. *Nature* 2000; **406**: 257 [PMID: 10917519 DOI: 10.1038/35018642]

160 **Quintana-Bustamante O**, Alvarez-Barrientos A, Kofman AV, Fabregat I, Bueren JA, Theise ND, Segovia JC. Hematopoietic mobilization in mice increases the presence of bone marrow-derived hepatocytes via in vivo cell fusion. *Hepatology* 2006; **43**: 108-116 [PMID: 16374873 DOI: 10.1002/hep.21005]

161 **Theise ND**, Nimmakayalu M, Gardner R, Illei PB, Morgan G, Teperman L, Henegariu O, Krause DS. Liver from bone marrow in humans. *Hepatology* 2000; **32**: 11-16 [PMID: 10869283 DOI: 10.1053/jhep.2000.9124]

162 **Cantz T**, Sharma AD, Jochheim-Richter A, Arseniev L, Klein C, Manns MP, Ott M. Reevaluation of bone marrow-derived cells as a source for hepatocyte regeneration. *Cell Transplant* 2004; **13**: 659-666 [PMID: 15648736 DOI: 10.3727/000000004783983521]

163 **Kanazawa Y**, Verma IM. Little evidence of bone marrow-derived hepatocytes in the replacement of injured liver. *Proc Natl Acad Sci USA* 2003; **100** Suppl 1: 11850-11853 [PMID: 12920184 DOI: 10.1073/pnas.1834198100]

164 **Jang YY**, Collector MI, Baylin SB, Diehl AM, Sharkis SJ. Hematopoietic stem cells convert into liver cells within days without fusion. *Nat Cell Biol* 2004; **6**: 532-539 [PMID: 15133469 DOI: 10.1038/ncb1132]

165 **Cao BQ**, Lin JZ, Zhong YS, Huang SB, Lin N, Tang ZF, Chen R, Xiang P, Xu RY. Contribution of mononuclear bone marrow cells to carbon tetrachloride-induced liver fibrosis in rats. *World J Gastroenterol* 2007; **13**: 1851-184; discussion 1851-184; [PMID: 17465480]

166 **Shizhu J**, Xiangwei M, Xun S, Mingzi H, Bingrong L, Dexia K, Xinghong W, Fenghua P. Bone marrow mononuclear cell transplant therapy in mice with CCl4-induced acute liver failure. *Turk J Gastroenterol* 2012; **23**: 344-352 [PMID: 22965505]

167 **Gordon MY**, Levicar N, Pai M, Bachellier P, Dimarakis I, Al-Allaf F, M'Hamdi H, Thalji T, Welsh JP, Marley SB, Davies J, Dazzi F, Marelli-Berg F, Tait P, Playford R, Jiao L, Jensen S, Nicholls JP, Ayav A, Nohandani M, Farzaneh F, Gaken J, Dodge R, Alison M, Apperley JF, Lechler R, Habib NA. Characterization and clinical application of human CD34+ stem/progenitor cell populations mobilized into the blood by granulocyte colony-stimulating factor. *Stem Cells* 2006; **24**: 1822-1830 [PMID: 16556705 DOI: 10.1016/j.bpg.2012.01.001]

168 **Salama H**, Zekri AR, Zern M, Bahnassy A, Loutfy S, Shalaby S, Vigen C, Burke W, Mostafa M, Medhat E, Alfi O, Huttinger E. Autologous hematopoietic stem cell transplantation in 48 patients with end-stage chronic liver diseases. *Cell Transplant* 2010; **19**: 1475-1486 [PMID: 20587151 DOI: 10.3727/096368910X514314]

169 **Terai S**, Ishikawa T, Omori K, Aoyama K, Marumoto Y, Urata Y, Yokoyama Y, Uchida K, Yamasaki T, Fujii Y, Okita K, Sakaida I. Improved liver function in patients with liver cirrhosis after autologous bone marrow cell infusion therapy. *Stem Cells* 2006; **24**: 2292-2298 [PMID: 16778155]

170 **Levicar N**, Pai M, Habib NA, Tait P, Jiao LR, Marley SB, Davis J, Dazzi F, Smadja C, Jensen SL, Nicholls JP, Apperley JF, Gordon MY. Long-term clinical results of autologous infusion of mobilized adult bone marrow derived CD34+ cells in patients with chronic liver disease. *Cell Prolif* 2008; **41** Suppl 1: 115-125 [PMID: 18181952]

171 **Couto BG**, Goldenberg RC, da Fonseca LM, Thomas J, Gutfilen B, Resende CM, Azevedo F, Mercante DR, Torres AL, Coelho HS, Maiolino A, Alves AL, Dias JV, Moreira MC, Sampaio AL, Sousa MA, Kasai-Brunswick TH, Souza SA, Campos-de-Carvalho AC, Rezende GF. Bone marrow mononuclear cell therapy for patients with cirrhosis: a Phase 1 study. *Liver Int* 2011; **31**: 391-400 [PMID: 21281433 DOI: 10.1111/j.1478-3231.2010.02424.x]

172 **Lyra AC**, Soares MB, da Silva LF, Fortes MF, Silva AG, Mota AC, Oliveira SA, Braga EL, de Carvalho WA, Genser B, dos Santos RR, Lyra LG. Feasibility and safety of autologous bone marrow mononuclear cell transplantation in patients with advanced chronic liver disease. *World J Gastroenterol* 2007; **13**: 1067-1073 [PMID: 17373741]

173 **Lyra AC**, Soares MB, da Silva LF, Braga EL, Oliveira SA, Fortes MF, Silva AG, Brustolim D, Genser B, Dos Santos RR, Lyra LG. Infusion of autologous bone marrow mononuclear cells through hepatic artery results in a short-term improvement of liver function in patients with chronic liver disease: a pilot randomized controlled study. *Eur J Gastroenterol Hepatol* 2010; **22**: 33-42 [PMID: 19654548 DOI: 10.1097/MEG.0b013e32832eb69a]

174 **Pai M**, Zacharoulis D, Milicevic MN, Helmy S, Jiao LR, Levicar N, Tait P, Scott M, Marley SB, Jestice K, Glibetic M, Bansi D, Khan SA, Kyriakou D, Rountas C, Thillainayagam A, Nicholls JP, Jensen S, Apperley JF, Gordon MY, Habib NA. Autologous infusion of expanded mobilized adult bone marrow-derived CD34+ cells into patients with alcoholic liver cirrhosis. *Am J Gastroenterol* 2008; **103**: 1952-1958 [PMID: 18637092 DOI: 10.1111/j.1572-0241.2008.01993.x]

175 **Mohamadnejad M**, Namiri M, Bagheri M, Hashemi SM, Ghanaati H, Zare Mehrjardi N, Kazemi Ashtiani S, Malekzadeh R, Baharvand H. Phase 1 human trial of autologous bone marrow-hematopoietic stem cell transplantation in patients with decompensated cirrhosis. *World J Gastroenterol* 2007; **13**: 3359-3363 [PMID: 17659676]

176 **Gasbarrini A**, Rapaccini GL, Rutella S, Zocco MA, Tittoto P, Leone G, Pola P, Gasbarrini G, Di Campli C. Rescue therapy by portal infusion of autologous stem cells in a case of drug-induced hepatitis. *Dig Liver Dis* 2007; **39**: 878-882 [PMID: 16875890 DOI: 10.1016/j.dld.2006.06.037]

177 **Salama H**, Zekri AR, Bahnassy AA, Medhat E, Halim HA, Ahmed OS, Mohamed G, Al Alim SA, Sherif GM. Autologous CD34+ and CD133+ stem cells transplantation in patients with end stage liver disease. *World J Gastroenterol* 2010; **16**: 5297-5305 [PMID: 21072892 DOI: 10.3748/wjg.v16.i42.5297]

178 **Di Campli C**, Piscaglia AC, Pierelli L, Rutella S, Bonanno G, Alison MR, Mariotti A, Vecchio FM, Nestola M, Monego G, Michetti F, Mancuso S, Pola P, Leone G, Gasbarrini G, Gasbarrini A. A human umbilical cord stem cell rescue therapy in a murine model of toxic liver injury. *Dig Liver Dis* 2004; **36**: 603-613 [PMID: 15460845 DOI: 10.1016/j.dld.2004.03.017]

179 **Fujino H**, Hiramatsu H, Tsuchiya A, Niwa A, Noma H, Shiota M, Umeda K, Yoshimoto M, Ito M, Heike T, Nakahata T. Human cord blood CD34+ cells develop into hepatocytes in the livers of NOD/SCID/gamma(c)null mice through cell fusion. *FASEB J* 2007; **21**: 3499-3510 [PMID: 17576850 DOI: 10.1096/fj.06-6109com]

180 **Newsome PN**, Johannessen I, Boyle S, Dalakas E, McAulay KA, Samuel K, Rae F, Forrester L, Turner ML, Hayes PC, Harrison DJ, Bickmore WA, Plevris JN. Human cord blood-derived cells can differentiate into hepatocytes in the mouse liver with no evidence of cellular fusion. *Gastroenterology* 2003; **124**: 1891-1900 [PMID: 12806622 DOI: 10.1016/S0016-5085(03)00401-3]

181 **Kögler G**, Sensken S, Airey JA, Trapp T, Müschen M, Feldhahn N, Liedtke S, Sorg RV, Fischer J, Rosenbaum C, Greschat S, Knipper A, Bender J, Degistirici O, Gao J, Caplan AI, Colletti EJ, Almeida-Porada G, Müller HW, Zanjani E, Wernet P. A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. *J Exp Med* 2004; **200**: 123-135 [PMID: 15263023 DOI: 10.1084/jem.20040440]

182 **Almeida-Porada G**, Porada CD, Chamberlain J, Torabi A, Zanjani ED. Formation of human hepatocytes by human hematopoietic stem cells in sheep. *Blood* 2004; **104**: 2582-2590 [PMID: 15231580 DOI: 10.1182/blood-2004-01-0259]

183 **Glanemann M**, Gaebelein G, Nussler N, Hao L, Kronbach Z, Shi B, Neuhaus P, Nussler AK. Transplantation of monocyte-derived hepatocyte-like cells (NeoHeps) improves survival in a model of acute liver failure. *Ann Surg* 2009; **249**: 149-154 [PMID: 19106691 DOI: 10.1097/SLA.0b013e31818a1543]
184 **Han Y**, Yan L, Han G, Zhou X, Hong L, Yin Z, Zhang X, Wang S, Wang J, Sun A, Liu Z, Xie H, Wu K, Ding J, Fan D. Controlled trials in hepatitis B virus-related decompensate liver cirrhosis: peripheral blood monocyte transplant versus granulocyte-colony-stimulating factor mobilization therapy. *Cytotherapy* 2008; **10**: 390-396 [PMID: 18574771 DOI: 10.1080/14653240802129901]

P- Reviewers Asahina K, Qin JM, Yagi K **S- Editor** Zhai HH
L- Editor Stewart GJ **E- Editor** Zhang DN