Review Article

A review on the therapeutic potential of embryonic and induced pluripotent stem cells in hepatic repair

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Abstract

Despite the liver being proliferatively quiescent, it maintains balance between cell gain and cell loss, invokes a rapid regenerative response following hepatocyte loss, and restores liver mass. Human liver has immense regenerative capacity. Liver comprises many cell types with specialized functions. Of these cell types, hepatocytes play several key roles, but are most vulnerable to damage. Recent studies suggest that the extrahepatic stem cell pool contributes to liver regeneration. Stem cell therapies have the potential to enhance hepatic regeneration. Both embryonic and induced pluripotent stem cells could be a suitable source to regenerate hepatocytes. In the present review, we discuss the therapeutic potential of stem cells in hepatic repair and focus on the clinical applications of stem cells.

Key words: Embryonic stem cells, end-stage liver disease, hepatocytes, induced pluripotent stem cells, liver, stem cells

INTRODUCTION

End-stage liver disease is the final stage of acute or chronic liver damage, leading to irreversible liver failure. It is a healthcare burden and one of the major causes of terminal illness. Hepatitis B virus is the most common cause of chronic hepatitis and end-stage liver disease worldwide.[1] The prevalence of end-stage liver disease is increasing rapidly. In the US alone, end-stage liver disease is responsible for 8.8 deaths per 100,000 persons annually.[2]

Currently, liver transplantation is the preferred therapy for patients with end-stage liver disease. In the recent years, liver transplant has evolved and this medical procedure is currently the standard for treating end-stage liver disease; therefore, the donor liver has become a precious resource.

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Although liver transplantation is an effective therapy, the donor organ shortages remain a serious problem and other major hurdles include operative damage, post-transplant rejection, and high costs.[3] There is therefore a need for alternative therapies. Instead of liver transplantation, the alternative is the application of stem cells to repopulating the liver after injuries.[4,5] The first step toward this approach is to select stem cells that are good candidates for repopulating the liver.

Stem cell research is a cutting-edge area of science that uses stem cells to create specialized cells to treat myriad diseases. In 1963, two Canadian researchers, Ernest A. Mc Culloch and James E. Till, showed the existence of self-renewal stem cells in the mouse bone marrow and laid the foundation for stem cell research. Stem cells are of two types: (i) adult stem cells and (ii) embryonic stem cells. Adult stem cells (multipotent) (non-embryonic stem cells, regenetor stem cells, tissue stem cells) with long-term self-replicative potential and multilinage differentiation maintain and repair the tissue. However, the embryonic stem cells (pluripotent stem cells) have long-term self-replicative potential and are derived from the inner cell mass of the blastocyst-staged embryo. Stem cells

(undifferentiated cells) play a major role in regenerative medicine. These cells have the ability to self-replicate and transform into an array of specialized cells, including liver cells for patients with liver failure.[6]

Human liver has an immense regenerative capacity and, under physiological conditions, it does not need any external cell source to undergo repair. Despite the liver being proliferatively quiescent, it maintains balance between cell gain and cell loss, invokes a rapid regenerative response following hepatocyte loss, and restores liver mass. The hepatocytes that are resting have the ability to re-enter the cell cycle rapidly.[7] Liver comprises of many cell types with specialized functions, of which hepatocytes play several key roles. But, these cell types (hepatocytes) are most vulnerable to damage. Studies suggest that there exists an extrahepatic stem cell pool that contributes to liver regeneration.[8] Studies have also revealed that stem cells represent a potential resource for cell transplantation therapy. Human embryonic stem cells, somatic stem cells, hepatic stem cells, small hepatocytes, cord blood-derived hepatic progenitor cells, human hepatocyte cell lines, and bone marrow stem cells have the ability to differentiate into hepatocytes and these cells can be used in regenerative medicine in treating liver diseases.[9-11]

Stem cell therapies have the potential to enhance hepatic regeneration. Both embryonic and induced pluripotent stem cells could be a suitable source to regenerate hepatocytes. The application of embryonic stem cells however is associated with the ethical and legal issues, and the potential of adult stem cells and their regenerative capacity is therefore under intense investigation. To overcome limitations in cell number and tissue compatibility, embryonic stem cell-derived hepatic cells are also being investigated as for future therapeutic strategies. Induced pluripotent stem cells[12] are embryonic stem-like pluripotent cells that are artificially derived from non-pluripotent cells by a forced expression of specific transcription factors. These cells are molecularly and functionally indistinguishable from embryonic stem cells in many aspects. The hurdles associated with the embryonic stem cells can be overcome with the clinical application of induced pluripotent cells due to their generation from mature somatic cells and, therefore, considered increasingly important in cell therapy technology.[13] Recently, Liu *et al.*[14] have shown that cotransplantation of induced pluripotent stem cell-derived hepatocytes and mesenchymal stem cells may offer an alternative way to treat patients with end-stage liver disease. Sullivan *et al.*[15] were the first to demonstrate the efficient generation of hepatic endodermal lineage from human-induced pluripotent stem cells that exhibit key attributes of hepatocytes.

Currently, there is shortage of available livers for transplantation and new approaches for repairing the liver are therefore being developed. The need for transplantation of a partial/complete human liver to cure patients can be eliminated. Cell therapies represent one of the most promising alternatives to entire/partial liver transplantation. Studies, both *in vitro* and *in vivo*, investigate the ability of stem cells to give rise to hepatocytes. However, the application of stem cell transplantation in humans for liver diseases needs large efficacy and safety studies.

In the present paper, we discuss the therapeutic potential for stem cells in hepatic repair and focus on the clinical applications of stem cells.

STEM CELLS IN HEPATIC REPAIR: EMBRYONIC AND INDUCED PLURIPOTENT STEM CELLS

Human liver has a good regenerative capacity following damage. The liver invokes a rapid regenerative response following hepatocyte loss and restores liver mass. Stem cell therapies have the potential to enhance hepatic regeneration. Since the discovery of stem cell populations with the ability to differentiate into hepatocytes, the focus of intense investigation has been to use them in hepatic regeneration. A variety of cell types were tested both *in vitro* and *in vivo*, but a more suitable cell preparation for therapeutic use is yet to be determined. Bone marrow is the most promising stem cell candidate for liver regeneration/repair. However, the clinical use of bone marrow-derived cells for hepatic repair/regeneration is still in its infancy. In addition, both embryonic and induced pluripotent stem cells could be a suitable source to regenerate hepatocytes.

Human embryonic stem cells have the ability to differentiate into a variety of cell lineages. The hepatocytes derived from human embryonic stem cells are required to understand normal human hepatocyte development, cell replacement therapies, as well as screening of pharmacologic drugs.[16] Apart from these cells, somatic stem cells, hepatic stem cells, small hepatocytes, cord blood-derived hepatic progenitor cells, human hepatocyte cell lines, and bone marrow stem cells have the potential to differentiate into hepatocytes. These cells can also be used in regenerative medicine in treating liver diseases. The hepatic stem cells provide an alternative means to repopulate the liver after various injuries instead of liver transplant.[17-20] Recently, Esch *et al.*[21] reported the effect of infusing autologous bone marrow-derived CD133+ in patients undergoing partial hepatectomy for liver cancer to expand a remnant segment of the liver. Patients receiving the infusion of bone marrow cells showed a 2.5-fold higher mean proliferation

rate compared with those who did not receive bone marrow cells. Gordon *et al.*[22] determined the safety and tolerability of injecting autologous CD34(+) cells in patients (n = 5) with liver insufficiency. There were three of five and four of five patients who showed improvement in serum bilirubin and serum albumin, respectively. Terai *et al.*[23] showed that autologous bone marrow cell infusion therapy is a novel treatment in decompensated liver cirrhosis patients. In a phase 1 human trial of autologous bone marrow–hematopoietic stem cell transplantation in patients with decompensated cirrhosis, Mohamadnejad *et al.*[24] showed that infusion of CD34+ stem cells through the hepatic artery is not safe. This study does not preclude infusion of CD34+ stem cells through other routes. In another phase 1 trial of autologous bone marrow–mesenchymal stem cell transplantation in patients with decompensated liver cirrhosis, Mohamadnejad *et al.*[25] showed that mesenchymal stem cell transplant is feasible and safe. Adult bone marrow stem cells have the capacity to travel in the bloodstream and traffic into the liver and differentiate into cell types.[26-28] De Silvestro *et al.*[29] showed that hepatic injury caused by extensive liver resection may activate the bone marrow, thereby initiating the liver recovery process. Lee *et al.*[30] showed that mesenchymal stem cells *in vitro* differentiate into functional hepatocyte-like cells, serving as a cell source in hepatic regeneration. Götherström *et al.*[31] have suggested that fetal mesenchymal stem cells have a higher proliferative capacity and are less lineage-committed compared with the adult mesenchymal stem cells. Lemoli *et al.*[32] have showed that tissue damage following orthotopic liver transplantation and liver resection induces increased serum levels of multiple cytokines, but only ischemia/reperfusion injury associated with orthotopic liver transplantation results in the remarkable mobilization of bone marrow stem/progenitor cells. Adipose tissue may be a source of autologous stem cells. Taléns-Visconti *et al.*[33] demonstrated that *in vitro*, the adipose-derived stem cells can be induced to differentiate into hepatic lineage. Fürst *et al.*[34] evaluated the effectiveness of portal vein embolization and CD133(+) bone marrow stem cell administration to the liver versus portal vein embolization alone. The study showed that the combination of portal vein embolization with CD133(+) bone marrow stem cell administration substantially increased hepatic regeneration versus portal vein embolization alone in those with malignant liver lesions. Cai *et al.*[35] have developed an efficient way to direct the differentiation of human embryonic stem cells into hepatic cells in serum-free medium. Human umbilical cord matrix stem cells may have the differentiation potential to form hepatic lineage. Campard *et al.*[36] showed that human umbilical cord matrix stem cells have a newly demonstrated endodermic differentiation potential. These cells might be an alternative source for liver-directed cell therapies. Kuo *et al.*[37] showed that bone marrow-derived mesenchymal stem cells can effectively rescue experimental liver failure and contribute to liver regeneration, offering potentially alternative therapy to organ transplantation for treatment of liver diseases. Adipose tissue mesenchymal stem cells (adipose-derived stem cells) are an attractive cell source for future clinical applications due to high accessibility and minimal invasiveness during the procedure to obtain them. Banas *et al.*[38] showed that adipose tissue mesenchymal stem cells have the affinity for hepatocyte differentiation *in vitro* and liver regeneration *in vivo*.

Induced pluripotent stem cells are embryonic stem-like pluripotent cells. These cells are artificially derived from non-pluripotent cells by a forced expression of specific transcription factors. Induced pluripotent stem cells are molecularly and functionally indistinguishable from embryonic stem cells in many respects. These human somatic cells are reprogrammed to a pluripotent state. Yagi *et al.*[39] reviewed the existing technology to establish induced pluripotent stem cells. They discussed strategies to generate human liver disease modeling with the application of induced pluripotent stem cells. Recently, Chang *et al.*[40] investigated the potential for human bone marrow mesenchymal stem cells in recovery from liver damage, and the results suggest that these cells may facilitate recovery from chronic liver damage as well as decrease liver fibrosis. Song *et al.*[41] showed that human-induced pluripotent stem cells (similar to human embryonic stem cells) have the ability to differentiate into hepatocyte-like cells.

DISCUSSION

Worldwide, liver failure is one of the main causes of death, and organ transplantation is the definitive therapy for this life-threatening condition. New approaches for repairing the liver are being developed because of the shortage of available livers for transplantation. Cell therapies are one of the most promising alternatives to entire/partial liver transplantation. And, with the application of stem cell therapies, the need for transplantation of a partial/complete human liver to cure the patient can be eliminated. Stem cell therapies have the potential to enhance hepatic regeneration. At present, both *in vitro* and *in vivo* studies are investigating the ability of stem cells to give rise to hepatocytes. Somatic stem cells, hepatic stem cells, small hepatocytes, cord blood-derived hepatic progenitor cells, human hepatocyte cell lines, and bone marrow stem cells have the ability to differentiate into hepatocytes, and these cells can be used in regenerative medicine in treating liver diseases. In addition, embryonic and induced pluripotent stem cells could be used as a suitable source to regenerate hepatocytes. Although stem cells provide

a valuable resource for cell-based therapies for liver disease, the application of stem cell transplantation in humans for liver diseases need larger efficacy and safety studies. Standardization and optimization of methods and protocols for isolating specific cell types is required.

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