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Review Article

Stem Cell Therapy in End Stage Liver Disease and Liver Failure

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Abstract

Liver cells have a tremendous capacity to multiply and regenerate the liver after any injury. However, this regenerative capacity of liver cells may be overwhelmed in acute liver failure and exhausted in cirrhosis with end stage liver disease. Currently liver transplantation is the only definitive treatment for these conditions of liver. However, due to the shortage of donor organs many patients are dying while on waitlist for liver transplantation. As a result it has become important to find an alternative strategy to keep these patients alive until their own livers regenerate or donor organs become available. Regenerative medicine and stem cell transplantation can help these patients. Adult stem cells and induced pluripotent stem cells showed good results when transplanted in experimental animals. Stem cells engineered from patients' own tissue proved to be safe, as well as non-immunogenic in clinical trials. Present review will discuss the current state of stem cell therapy, available stem cells and their application in different liver diseases.

Keywords: *Liver Failure; Cirrhosis; End Stage Liver Disease; LDLT; DDLT; Stem Cell; Regenerative Medicine; Embryonic Stem Cell; Adult Stem Cell; Mesenchymal Stem Cell; Haematopoietic Stem Cells; iPSCs; HLCs; iHeps*

Introduction

Liver is an organ with remarkable regenerative capacity. When a portion of parenchymal tissue or a part of a liver is injured, hepatocytes in the remaining portion of the liver can rapidly enter the cell cycle to replenish and regenerate the liver with all its previous function. However, when there is an acute and massive loss of liver tissue, the regenerative capacity of the liver fails to recover completely. Chronic destruction and fibrosis in chronic liver diseases and cirrhosis, on the other hand, can completely exhaust the regenerative capacity of the liver and impair the proliferative capacity of the liver cells, resulting in chronic liver failure and end stage liver disease [1].

At the present time, liver transplantation is the only definitive therapy for end stage liver diseases and also for most patients with liver failure. DDLT, the process of transplantation of cadaveric livers is more common in Western countries, whereas LDLT, or the process of transplanting a portion of the liver from a living donor to the recipient, is the most common type of liver transplantation in many Asian countries, as this procedure is more ethically compatible with most Asian cultures [2]. Currently, LDLT comprises more than 90% of liver transplant activity in Asia [3].

Advancement in surgical techniques and the addition of newer immunosuppressant medications have improved the survival of grafts and has brought tremendous success in the field of liver transplantation. The overall 1-year survival period for adult and pediatric orthotopic liver transplants is expected to be in excess of 85%, with 5 and 10-year survival periods in excess of 70 and 60%, respectively [4]. However, currently there is a long waiting list for liver transplantation. The existing mismatch between the great demand for liver transplants and the number of available donor organs highlights the urgent need for alternative therapeutic strategies in patients with acute and chronic liver failure. Rapid advancement in the field of regenerative medicine and stem cell therapy is opening new windows in the treatment of liver diseases.

The Role of Regenerative Medicine in acute and chronic liver diseases

Currently, scientists are trying to find ideal stem cells which will be able to regenerate the liver, reduce inflammatory changes in it, and will also be able to replace the damaged liver cells.

Stem cells are characterized by their capacity to grow into many different cell types in the body during early life and growth. Stem cells can divide limitlessly to replenish cells and repair any organ. Two important characteristics can distinguish a stem cell from other cells in the body. First, these cells are not specialized cells and they are capable of renewing themselves by the process of cell division, even after remaining inactive for a long time in the body. Second, stem cells can be induced to become tissue and organ specific cells and can carry out specialized functions when put in specific physiologic or experimental conditions. Originally stem cells were of two types: embryonic stem cells and non-embryonic "somatic" or "adult" stem cells. In 2006, scientists were able to identify specific conditions in which some specialized adults can be genetically "reprogrammed" to assume a stem cell like state. This new type of stem cell is known as an induced pluripotent stem cell (iPSCs) [5,6].

Embryonic stem cells are pluripotent and they can become all cell types of the body. Embryonic stem cells are grown from cells found in the embryo when it is just a few days old. Moreover, these stem cells can be grown relatively easily in culture. Adult stem cells are un-differentiated cells and they are usually found among differentiated cells in a tissue or organ. Adult stem cells have the capacity to renew themselves and they also have the potential to grow and differentiate into most of the major specialized cell types of the tissue or an organ. Adult stem cells take part in the repair and maintenance of the tissue in which they reside [5,6]. The main types of adult stem cells on which scientists are doing research include haematopoietic stem cells, mesenchymal stem cells, and induced pluripotent stem cells.

Haematopoietic stem cells

Adult stem cells can differentiate into cell types seen in mature organs and tissues other than those expected from the lineage which the cells usually follow. The process is considered as trans-differentiation and it is a characteristic of adult stem cells [5]. After receiving bone marrow cells (hematopoietic stem cells) from male donors, some females were found to carry liver cells derived from transplanted bone marrow cells of their male donors [7]. Approximately 0.01% of the total cells in the bone marrow are hematopoietic stem cells. These stem cells are known for their plasticity, which is the capacity to differentiate into non-hematopoietic lineages such as hepatic oval cells, hepatocytes, and cholangiocytes. Hematopoietic stem cells were observed in peripheral circulation after liver injury and they also found to participate in liver repair. Several growth factors including HGF, stromal cell-derived factor-1 and MMP9 system were found to influence migration of hematopoietic cells into the liver after stress and injury [4].

The patient's own bone marrow stem cells were used as a source for new hepatocytes to treat different liver diseases in several clinical trials, with chances of rejection found to be very low in these experiments. Recently scientists observed that G-CSF can stimulate bone marrow stem cells to move to the circulation and after that these cells can be easily collected from the circulation and then processed for transplantation into a recipient. This method was proved safe with long lasting (12 months) effects when it was used to treat patients with alcohol and hepatitis B-related end stage liver diseases [7,8].

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are considered as 'multipotent' stem cells because of their ability to differentiate into a variety of different cell types in the body. MSCs are found in bone, muscle, cartilage and fat in adult tissues as well as in the bone marrow, cord blood, placenta, liver tissue and teeth among different fetal tissues. These stem cells have immunomodulatory properties. They can differentiate and replace damaged hepatocytes, promote regeneration from residual hepatocytes, and can inhibit hepatic stellate cell activation or induce their apoptosis [8,9]. According to Shiota and Itaba, transplantation of MSCs gave good results in different liver diseases in experimental models. In experiments, adipose tissue, amniotic fluid and bone marrow-derived MSCs were also found to be effective in reducing acute liver injury as well as having anti-inflammatory effects on non-alcoholic steatohepatitis models. Experiments also revealed that liver

fibrosis, acute liver failure, and fatty liver disease can be treated in the lab using these stem cells. More research is needed in this field to find out how to produce liver cells from mesenchymal stem cells in large numbers and whether this will prove to be a safe procedure in the long run [4].

Embryonic Stem Cells

Dr. James Thomson's work led to derivation of human Embryonic Stem cells in 1998. It was presumed that human embryonic stems cells would help to overcome the shortage of transplantable tissues and it would help to cure many untreatable diseases. Human embryonic stem cell research started raising concerns on ethical issues of embryo disruption and immune incompatibility with the donor. To solve these issues scientists developed induced pluripotent stem cells, which are adult cells that have been genetically reprogrammed to an embryonic stem cell–like state by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells [5].

Induced Pluripotent Stem Cells

Development of the induced pluripotent stem cell (iPSC) technology brought together the pluripotency and self-renewable potential of embryonic stem cells. Furthermore, this technology was also able to overcome the ethical concerns of embryo destruction because iPSCs were produced from somatic cells *in vitro* without using embryonic tissues or oocytes. Development of patient specific iPSCs for replacement therapy was also able to remove the risks of immune-incompatibility [9,10]. The iPSCs were initially produced in the lab using retroviral vector. However, use of efficient reprogramming methods resulted in production of human iPSCs with almost no risk of tumor formation in the recipient. Cells obtained from iPSCs are termed hepatocyte-like cells and these cell are characterized by their low levels of albumin production, cytochrome p450 activity, and urea cycle activity as well as their expression of high levels of α-fetoprotein [4].

Human Induced Pluripotent Stem Cells and Hepatocyte Like Cells

Hepatocyte Like Cells (HLCs) are differentiated from human induced pluripotent stem cells. Transplantation of HLCs derived from hiPSCs could represent an alternative to liver transplantation for the treatment of acute liver failure (ALF), liver cirrhosis, viral hepatitis, and the correction of inherited metabolic liver disorders resulting from genetically deficient states. Moreover, HLCs derived from human iPSCs (hiPSCs) of patients with the inherited metabolic conditions may be used to model inherited liver diseases. However, long-term safety, tolerability, and efficacy of the iPSC-based treatments, as well as their carcinogenic potential need to be rigorously assessed before these cells can be used for treatment in human liver diseases [9,10].

Direct Reprogramming of Hepatic Myofibroblasts into Hepatocytes

In a recent study [10] using transcription factor induction and genetic fate tracing scientists developed induced hepatocytes (iHeps) from fibroblasts in mouse models of chronic liver disease. They were successful in converting pro-fibrogenic myofibroblasts in the mice liver into hepatocyte-like cells capable of performing functions of hepatocytes. Moreover, the experiment also showed decreased fibrosis in the damaged liver where these iHeps were generated. Further research in this field is needed to find the effect of this direct reprogramming method inside human body and its use in the treatment of different chronic liver diseases.

Overcoming barriers

Initially there were concerns regarding need for immunosuppression after stem cell therapy. As iPSC-Hep and iHep cells are both human leukocyte matched and patient customized immunosuppression, if at all required, should be very minimum. Another worry is about development of tumours after cell therapy. Pluripotent cells have inherent property to develop Teratomas. However, iHep cells are produced by direct re-programming of fibroblasts bypassing the pluripotent stem cell stage. Furthermore, rigorous cell purification was also able to reduce contamination with undifferentiated pluripotent stem cells. In addition, pluripotent stem cells have the intrinsic ability to self-renew and are capable of producing vast quantities of Hep cells needed for clinical use [4].

Finding a suitable route for delivering these stem cells was an issue. In end stage liver disease, damaged hepatic architecture results in deterioration in liver function and transplantation of liver cells into the portal vein of a cirrhotic liver can give rise to severe portal hypertension [11,12]. Current technologies including use of "liver bud", "perfusion decellularization and recellularization systems", and "hepatic cell sheets" was able to solve many of these issues [4]. Organ de-cellularization is a new technology in which cells from a donor organ are removed leaving the extra cellular matrix intact and thereby producing a biologic, architecturally normal scaffold for transplanted cells. An auxiliary liver graft can be produced by adding donor hepatocytes and non-parenchymal cells into this scaffold. However, it is feared that although hepatocyte transplantation may result in improved liver function and may also help in reducing fibrosis, the management of coexisting portal hypertension and the risk of developing hepatocellular carcinoma in the native liver may continue to exist [11,12].

Ethical Issues

Stem cell transplantation and some of the stem cell therapies were proven effective in human subjects and newer therapies are ready for clinical trials. Like any other new modalities of treatment, before going from bench to bedside, stem cell therapy will need to ensure that there should be very minimum "risks of harm" to the patient. There should be proper selection and recruitment of patient-subjects and the decision making should be informed and facilitated by clinicians following proper protocol and consenting process. Furthermore, the clinician in charge of the patient must be careful about avoiding any 'therapeutic misconception' which may give rise to undue high expectation in the patient or subject. Furthermore, every clinical study should be carefully designed, thoroughly justified, and appropriately conducted in order to protect the rights, interests, and welfare of the subjects included in the study. In addition, there should also be efforts to keep regenerative medicine and stem cell therapy affordable and accessible to patients who need them [13].

Conclusion

Regenerative medicine is expected to play an important role in recovering liver function in patients with liver failure and end stage liver disease in future. Several adult stem cells and induced pluripotent stem cells showed good results when transplanted in experimental animals. Stem cells engineered from patients' own tissue proved to be safe, as well as non-immunogenic in clinical trials. Successful transplantation will need mass production of stem cells. Furthermore, stem cell based therapies will need to go through rigorous scrutiny and repeated clinical trials before those can be applied in human beings. It is expected that scientists will be able to overcome all these barriers and make stem cell transplantation a successful treatment for not only liver failures and end stage liver diseases but also cirrhosis, non-alcoholic steatohepatitis and many metabolic and genetic liver diseases.

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