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Mini Review

Experimental and Clinical Application of Hepatocyte Transplantation

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Abstract

Bio-artificial liver support system can be created by the ability of maintaining a long term stable culture of primary hepatocytes, for the investigation of liver pathophysiology and physiology, certain platforms are required for the screening of drug toxicity. Liver plays the vital role in detoxification and drug metabolism, it is the principal target organ of drug toxicity study, therefore, hepatocytes are widely used for numerous clinical and research applications but their short life span and limited capacity of replication limits the usefulness of the culture of primary hepatocytes. Hepatocytes can be isolated from whole liver, wedge fragments of liver unsuitable for liver transplantation and mostly from the primary and secondary tumor or some other diseased part. Hepatocytes isolated in this way exhibits the identical functions and structures with their *in-vivo* counterparts. For long survival, a substratum is needed for attachment. When the hepatocytes obtained by this way plated in a culture condition, they reconstitute bile canaliculus like structure by re-aggregating and exhibit early phenotypic alteration by showing the short life span of few days.

Keywords: Transplantation; Toxicity; Hepatocytes; Orthotopic Liver; Cryo-preservation.

Introduction

The liver is the largest internal organ of the body which plays a vital role in detoxification of exogenous and endogenous substrate during metabolism [1]. Liver disease has been emerging as a major problem of the global health burden. According to DALYs (Disability Adjusted Life Year) study in 2010, it has been reported that 31 million people i.e. 1.2% of global DALYs have been affected by liver cirrhosis alone, out of them 1 million death (2% of all death) were registered in that year liver [2]. This evidence shows that liver disease is the leading cause of morbidity and mortality worldwide. Though Orthotopic Liver Transplantation (OLT) can significantly improve the prognosis in patient with fulminant hepatic failure, metabolic liver disease and end-stage liver disease, the process is invasive heaving complex surgical procedure with very expensive treatment and scarcity of healthy liver donor limits OLT, therefore, it is rational to develop the technique of isolation of human hepatocytes for the transplantation into recipient liver [3]. In the experimental animal's hepatocytes, transplantation has been investigated for a long time, the route of hepatocyte transplantation is either intra-spleen or intra-hepatic. It has been reported that the donor hepatocyte expresses differentiated functions in nearly identical manner as their natural condition and are found to maintain for a lifetime of the recipient [4]. For two types of situations hepatocyte transplantation has been purposed, one for gene therapy (used for the treatment of verity of inherited dysfunctions in the liver) and another is the treatment for liver failure due to acute and chronic liver injury [5]. It has also been reported that hepatocyte transplantation is used to provide hepatic uridine diphophoglucuronate (UDP) glucuronosyltransferase (the protein that is defective in Crigler-Najjar syndrome type I) [6]. For the treatment of liver disease and disorder, it has been widely believed that the optimal site for hepatocyte transplantation is liver, therefore majority of clinical trial that has been conducted to transplant hepatocyte by administration into the liver through splenic or portal circulation.

However, it has also been reported that transplantation of hepatocyte has been performed to another organ of the body (i.e. kidney capsule, subcutaneous space, peritoneal cavity, etc.) can also have therapeutic efficacy [7,8]. Hepatocyte transplantation has many advantages over OLT, it has much less morbidity, and several patients could receive cells from a single donor which alleviate the scarcity of organ. Although the cost of the immune-suppressive drug remains the same as OLT the initial expenses of hepatocyte transplantation remains very low in comparison to OLT. The liver used for the isolation of hepatocyte is the organ that would be otherwise discarded. For gene therapy, the hepatocytes can be genetically modified *in-vitro* to prevent immune rejection. In some cases, the hepatocyte transplantation could have several advantages over current gene therapy, in case of the appropriate shreds of evidence obtained from the experimental animal model; the method can be used for cell transplantation for the human. The hepatocytes obtained from host liver should have normal liver functions and potential of lifelong survival in a recipient which avoid immunological complications associated with the use of gene transfer vehicles and recombinant viruses [3]. From the various studies it has been reported in experimental animals undergone hepatocyte transplantation into liver, spleen and other ectopic sites, the transplanted hepatocytes displayed normal architecture while observed under electron and light microscope [9,10]. Furthermore, the survived and the integrated hepatocytes at the transplantation site displays the functions of differentiated hepatocytes including albumin secretion [9,11,12]. Glycolysis and glycogen storage [9,10]. Ammonia metabolism [9,13]. Cytochrome P450 expression [14] and bilirubin conjugation [11,15]. The subject of this review is the clinical and experimental progress in the field of hepatocyte transplantation including isolation of hepatocyte, *in-vitro* manipulation of hepatocytes with lentiviral and retroviral vectors and development of the animal model for hepatocyte transplantation.

OLT and the need for alternative therapy

Since the first human liver transplantation in 1963, Orthotopic Liver transplantation (OLT) has come a long way with improvement in immunosuppressive regimes, better selection of the recipient, preservation of donor organs and advancement in operating techniques. Because of the formidable and costly operating procedure with significant mortality OLT still, have problems. After OLT the lifelong use of immunosuppressive drugs create the risks of infections and malignancy. Furthermore, the success of surgical techniques and increased number of liver disease which requires OLT, the demands of liver transplantation is growing day by day but despite the promotion of organ donation there has been the shortage of compatible organ creating the way to formulate the alternatives of OLT in the patient with acute and chronic liver failure. From the alternative way of treatment of liver failure, it is possible to treat the children heaving metabolic disorders [16]. Several alternative therapies have been reported for the treatment of liver failure. They can be broadly divided into three categories, hepatocyte transplantation, extracorporeal artificial liver device and bioartificial liver device using hepatocytes [17]. The objective of alternative therapy is being to act as a bridge until the donor organ becomes available for transplantation or this therapy can also be utilized to support the regeneration of patient own liver [18].

In recent year, cell-based therapy has been the area of interest. Especially hepatocyte transplantation has been emerging as a promising alternative to OLT for a verity of diseases such as acute and chronic liver failure and metabolic liver disease. In comparison to OLT hepatocyte transplantation have the number of potential advantages because it has less risk of mortality and morbidity, considerably less invasive and the procedure can be performed repeatedly. Furthermore, it has been demonstrated that hepatocyte transplantation is a safe therapeutic option for improving the clinical outcomes for the children heaving inborn metabolic disorders. The clinical effectiveness hepatocyte transplantation relies on the functional performance of transplanted hepatocytes and their capacity to survive in the host liver.

For the transplantation, hepatocytes can be obtained from discarded organ but it has been experienced that the discarded organ is not suitable enough to isolate hepatocytes for transplantation. Therefore, the new source is required to isolate the suitable hepatocytes. The suitable source for obtaining the hepatocyte could be the donor with cardiac death and patient undergoing OLT. Moreover, for the treatment of metabolic liver disease stem cell therapy or differentiated progenitor cell therapy could represent the future of cell transplantation [19].

Nowadays, the hepatocyte transplantation becomes the subject of interest giving much emphasis on research with pre-clinical studies and animal modeling. These researches have demonstrated the ability of hepatocyte transplantation supporting the functions of the liver and corrected the abnormalities in the biochemical phenomenon in animal models. The liver is the optimum site for hepatocyte transplantation because of the existence of specialized

extracellular matrix and supply of portal blood to engraft and survival of hepatocytes. Therefore liver is considered as the most desirable site for hepatocyte transplantation [20]. Which can be done by the infusion of hepatocytes either into the portal vein or via spleen by injecting into the splenic pulp [21]. Intraportal infusion of hepatocyte is relatively a simple technique of transplantation. Therefore the majority of animal experiments and procedures performed in humans have used this technique. There are many other ectopic sites (peritoneal cavity, lung, spleen, kidney, pancreas, etc.) for transplantation of hepatocytes have been investigated [22].

Various techniques of hepatocyte transplantation described here showed the promise for improving engraftment efficiency. Pre-clinical studies in a rat in a dose-dependent manner have shown that irradiation of recipient's liver before hepatocyte transplantation may increase the engraftment and survival of transplanted hepatocytes. The effect of transplantation may further be enhanced when combined simultaneously with the techniques of partial hepatectomy or portal vein embolization for providing the hepatotrophic stimulations [23-25].

Clinical applications of hepatocytes

In 1965, Berry and Friend purposed the two-step collagenase perfusion method for the isolation of hepatocytes in rodent liver [26]. There are many reports that modified the process of isolation of hepatocytes in terms of rate of perfusion and concentration of collagenase [27,28] and applied to the clinical applications for the isolation of human hepatocytes [3,4,29]. For the allogeneic transplantation the availability of freshly isolated hepatocytes is one of the major limitations. It is difficult to find the donor liver at the necessary infusion time for the patient. Moreover, the possibility of getting quality liver that can be applicable anatomically for the transplantation of hepatocytes is also limited [30]. Almost all non-transplanted livers are of diseased states. In most of the clinical applications, isolation of hepatocytes is needed for acute situations. Hence it is necessary to determine the factors that would enable the primary hepatocyte culture, culture of hepatic progenitor cells and cryopreservation of hepatocytes to maintain the functional integrity.

Conclusion

The laboratory studies clearly indicate that hepatocyte transplantation could be alternative to whole organ transplantation for the treatment of a number of liver disease and disorders and there is evidence of significant progress, but, until an adequate supply of donor hepatocytes is identified it would be difficult to prove the efficacy of hepatocyte transplantation in the patients.

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