Role of Stem Cell Therapy in Management of Hepatic Pathology

Essay
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

3D	3 dimensional
ASCs	Adult stem cells
AT-MSC	Adipose tissue derived mesenchymal stem cells
BM	Bone marrow
BMSCs	Bone marrow stem cells
CCL4	Carbon tetrachloride
CK	Cytokeratin
CTP	Child Turcotte Pugh
EB	Embryoid bodies
ECs	Embryonic cells
EMT	Epithelial mesenchymal transformation
EpCAM	Epithelial cell adhesion molecule
ESCs	Embryonic stem cells
ESLV	End stage liver disease
FSCs	Fetal stem cells
FVII	Factor 8
G-CSF	Granulocyte colony stimulating factor
GFP	Green fluorescence protein
GVHD	Graft vs. host disease
hBTSCs	Human billiary tree stem cells
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HGF	Hepatocyte growth factor
hHBs	Human hepatoblasts
hHpSCs	Human hepatocyte stem cells
HLA	Human leucocyte antigen
HSCs	Hematopoietic stem cells
HSCT	Human stem cell therapy
ICM	Inner cell mass
IL 6	Interleukin 6
INR	International normalized ratio

LIST OF ABBREVIATIONS. CON

IP	Induced pluripotency
iPSCs	Induced pluripotent stem cells
MELD	Model for end stage liver disease
MHC	Major histocompatibility complex
mRNA	Messenger ribonucleic acid
MSCs	Mesenchymal stem cells
OB	Obliterative bronchiolitis
OLT	Orthotopic liver transplantation
PCR	Polymerase chain reaction
PDSCs	Placenta derived stem cells
Ptc	Patched receptor
PVE	Portal vein embolisation
SCNT	Somatic cell nuclear transfer
SCs	Stem cells
STAT	Signal transducer and activators of transcription
TGF-β	Transforming growth factor beta
TNF	Tumor necrosis factor
UCB	Umbilical cord blood
UCE	Umbilical cord epithelium
UC-HS	Umbilical cord hematopoietic cells
UC-MS	Umbilical cord mesenchymal cells

List of Figures

INTRODUCTION

The liver has a remarkable regenerative capacity in response to acute injury. Mature hepatocytes can reenter the cell cycle and undergo several cell divisions to restore the hepatic mass. However, following chronic liver damage, the regenerative ability of hepatocytes is lost. In such conditions, the liver is unable to maintain its functional mass; this is clinically mirrored by the so-called "liver failure." Currently, orthotopic liver transplantation (OLT) represents the most suitable therapeutic option for patients with advanced liver diseases and hepatic failure. Liver transplantation, however, has the disadvantage of requiring lifelong immunosuppression and follow-up, with 10–15% of patients dying whilst on the waiting list due to the shortage of donated organs. In 2005, only one-third of patients waiting for a liver transplant were transplanted *(UNOS; 2006).* Hence, alternative strategies for the treatment of decompensated liver diseases are needed to be developed ***(Forbes; 2008)***.

Cell-based therapy has been proposed as a potential alternative to OLT. Cell therapy can be defined as the use of living cells to restore, maintain, or enhance the function of tissues and organs. Cell therapies in hepatology have numerous promising potential advantages when compared to OLT, since transplantable cells can be (1) in vitro expanded and

cryopreserved, abolishing the limit of organ shortage; (2) genetically manipulated, to correct inborn errors of metabolism; (3) cryopreserved for future use; (4) infused without major surgery; (5) obtained from the same patient, avoiding risk of rejection and need for lifelong immunosuppression ***(Piscalgia et al; 2008)***.

The use of isolated viable cells has emerged as an experimental therapeutic tool in the past years due to progress in cell biology and particularly in techniques for the isolation and culture of cells derived from several organs and tissues ***(Jean;2002).***

It has been known for more than 30 years that hepatocytes isolated from a donor liver and infused intraportally in animal models of liver damage can be engrafted into the recipient hepatic parenchyma and express metabolic activity. These results have encouraged clinical trials using hepatocytes transplantation to treat a variety of liver diseases *(Muraca; 2011).* Since the first successful hepatocyte transplantation in a rodent model of Crigler-Najjar syndrome, many preclinical studies and clinical applications of this technique have been made to cure metabolic liver disorders and end-stage liver diseases *(Kung et Forbes; 2009).* In most instances, hepatocyte transplantation has been able to grant a clinical improvement for up to 12 months *(Sancho-Bru*

et al; 2009). Despite some encouraging results, the interpretation of these studies is hampered by the limited number and heterogeneity of patients, the lack of controls, the variety in terms of experimental design, outcome parameters, and follow-up duration. The evaluation of the efficacy of hepatocyte transplantation and bioartificial liver support systems is further complicated by the shortage of human hepatocytes. Moreover, primary cultured hepatocytes are hard to expand in vitro and cryopreserved cells are easily damaged during the freezing-thawing procedure.

As a consequence, alternative solutions are being examined in the hepatic cell therapy field. Among these, of particular interest is the so-called "regenerative medicine", based on the therapeutic potential of stem cells (SCs**) *(Piscalgia et al; 2002)***.

A growing enthusiasm has greeted the development of stem-cell-based therapies for liver diseases. SCs are undifferentiated cells, able to give rise to diverse mature progenies and to self-renew, through the alternation of symmetrical and asymmetrical divisions. SCs exist in all multicellular organisms and play a central role in tissue genesis, regeneration, and homeostasis, by providing new elements to increase tissue mass during pre- and postnatal growth, and by replacing cell loss due to senescence or damage ***(Piscalgia et al; 2011)***.

Different types of SCs with hepatic differentiation potential are theoretically eligible for liver cell replacement. These include Embryonic SCs, induced pluripotent SCs, fetal hepatoblasts, annex SCs, and adult SCs, such Hepatic Progenitor Cells, Hematopoietic SCs, and Mesenchymal SCs. Despite encouraging results in vitro, the use of hepatocyte like cells derived from these stem/progenitor cell populations is still confined to preclinical studies, given the scarce tissue-specific functionality and, up to now, the lack of evidence of strong liver repopulation levels in animal models. Nowadays, the most promising source for SC-based therapies is represented by the intraportal or intrahepatic infusion of freshly isolated or in vitro expanded HSCs **(Mallet et Gilgenkrantz; 2005)**.

The major role for stem cell therapy at the time being is as a bridge to transplantation or as a way of maintaining those patients who are not eligible for OLT. Nonetheless, critical aspects need to be further addressed, including the long-term safety, tolerability, and efficacy of these SC-based treatments, as well as their carcinogenic potential.

AIM OF THE WORK

This essay aims to review the literature about the concept of stem cell based therapy and its possible application in experimental animal and clinical studies in hepatic pathology.

LIVER CIRRHOSIS AND LIVER REGENERATION

1.1 LIVER CIRRHOSIS

Cirrhosis is the final stage attained by various chronic liver diseases after years or decades of slow progression. There are, however, ways to prevent cirrhosis, because the diseases that most commonly lead to it progress slowly, and measures are available to prevent and treat them. Moreover, most cases of hepato- cellular carcinoma (HCC) arise in a cirrhotic liver, so cirrhosis prevention is, in fact, also HCC prevention. The risk of developing HCC depends on the underlying disease: It is low, for example, when the underlying disease is autoimmune hepatitis (2.9% in 10 years), and high when the underlying disease is chronic hepatitis B with a viral burden greater than 10^7 copies/mL (19.8% in 13 years). Aside from chronic viral hepatitis, fatty liver disease due to any of the very common underlying disorders (obesity, diabetes, alcohol abuse) commonly progresses to cirrhosis and thus merits both specialized medical treatment and close follow-up by the primary-care physician. ***(Chen et al., 2011).***

1.1.1 The etiology of cirrhosis

Cirrhosis can arise in consequence of an exogenous/ toxic, infectious, toxic/allergic, immune-pathological/ autoimmune, or vascular process or an inborn error of metabolism. The commonest causes of cirrhosis are alcoholic and non-alcoholic fatty liver disease and viral hepatitis (B or C). Among these causes, the most common of all in Egypt is viral hepatitis. As for the pediatric age group, the following figure summarizes the most common causes according to European Liver Transplant Registry (1968-2010).

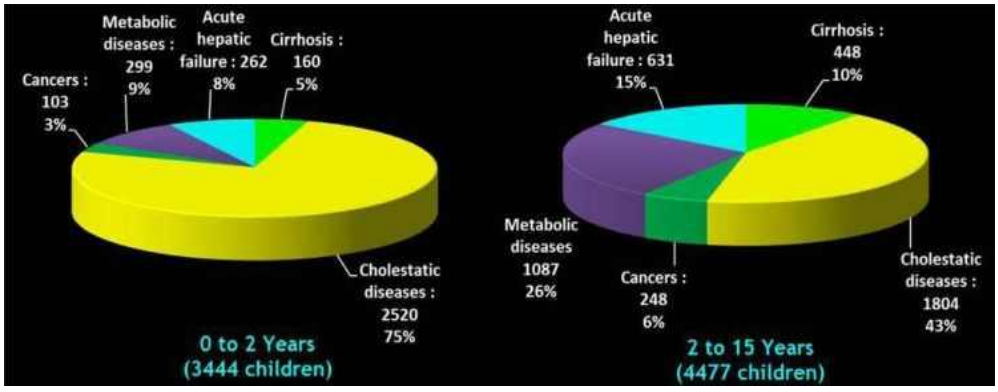

Figure 1: Primary indication for liver transplantation in pediatric age group according TR ***(Noush D et al ., 2013)***

1.1.2 The diagnosis of liver cirrhosis

Cirrhosis is histologically characterized by fibrous septa between the portal fields; it comes in micro- and macro-nodular forms. The condition is diagnosed by its characteristic

findings on clinical examination, laboratory tests, and ancillary studies.

The typical findings in cirrhosis include ● cutaneous signs of liver disease, ● a firm liver on palpation, and ● certain risk constellations such as:

1. metabolic syndrome
2. Heavy alcohol consumption – exposure to hepatotoxic substances – use of hepatotoxic medications. ***(Schuppan and Afdhal, 2008)***

The early signs of cirrhosis in B-ultrasonography include inhomogeneity of the hepatic tissue, irregularity of the hepatic surface, or enlargement of the caudate lobe. Portal hypertension leads to splenomegaly.

In advanced liver disease approaching the stage of cirrhosis, thrombocytopenia is seen, along with impaired hepatic biosynthesis (as shown by, e.g., low concentration of albumin and cholinesterase and an elevation of the international normalized ratio [INR]) and impairment of the detoxifying function of the liver (as shown by, e.g., elevated bilirubin concentration). The transaminase concentrations are generally in the normal range or only mildly elevated. There is no well-defined threshold value of any laboratory test that can be used to determine when screening for cirrhosis should be performed.