Stem Cell Therapy for End Stage Liver Disease

Essay

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Abstract

Stem cells are undifferentiated cells characterized by self renewal, multipotency, long term tissue repopulation after transplantation, serial transplant ability and when divide the daughter cell can either fully differentiated or remain stem cell. Haematopoietic stem cells can be differentiated into hepatocytes, cardiomyocytes, brain cells, hair follicles and sebaceous glands, epithelial and nonepithelital cell types in the kidney, islet cells in pancreas, type II pneumocytes in the lungs, mucous secreting cells in the stomach, goblet cells and enteroendocrine cells in the intestine. For treatment of genetic diseases, transplantation of genetically modified autologous marrow would avoid many of the risks of allogerric transplants. It is used in treatment of many diseases as cystic fibrosis, Duchenne muscular dystrophy, immunodeficiency diseases, some types of anemias like thalassemia and sickle cell anemia and wound healing, gasterointestinal diseases and autoimmune diseases. Hepatocyte transplantations have been performed for a variety of indications, including inborn errors of metabolism. Cells derived from other tissues, such as bone marrow, monocytes, endothelium, and pancreas, are also being explored as potential therapies for liver based metabolic disorders.

Stem cells are not only units of biological organization, responsible for the development and the regeneration of tissue and organ systems, but are also targets of carcinogenesis. Bone marrow stem cells can be used to accelerate liver regeneration before extended hepatectomy for hepatocellular carcinoma.

Key words: Stem cells, Haematopoietic stem cells, genetic diseases, Hepatocyte cell transplantation

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2-AAF	2-acetylamino-fluorene
ABMI	Autologous bone marrow cell infusion
AFP	Alpha fetoprotein
AGM	Aortogonadal mesonephros
αl-AT	αl-antitrypsin
AW	Adeno-associated viral vectors
BCLC	Barcelona clinic liver cancer
BFU-E	Burst forming unit-Erythroid
BM	Bone marrow
BMSCs	Bone marrow stem cells
BMT	Bone marrow transplantation
CAFC	Cobble stone area forming cells
CD	Cluster of differentiation
CDKs	Cyclin dependent kinases
CFC	Colony forming cells
CFC-Mix	Colony forming cells-mixed erythroid colonies
CFU-E	Colony forming unit- Erythroid
CFU-GM	Colony forming unit- Granulocyte, Macrophage
CFU-S	Colony forming unit-spleen
CK	Cytokeratin
CLD	Chronic liver diseases
CSPH	Clinically significant portal hypertension
CTP	Pugh modification of Child Turcotte classification
DMSO	Dimethyl sulfoxide
ECM	Extracellular matrix
ED	Embryonal day
ELTC	Extended long term culture
Eo-CFC	Eosinophil- Colony forming cells
EPC	Endothelial progenitor cell
Epo	Erythropoietin
ERK-1&2	Extracellular signal-regulated kinases 1 and 2
ES cells	Embryonic stem cells
FAH	Fumaryl acetoacetate hydrolase
FAK	Focal adhesion kinase
FGFs	Fibroblast growth factor-2
GM-CSF	Granulocyte, macrophage colony stimulating factor
GST	Glutathione-S-transferase

GVHD	Graft versus host disease
HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
HE	Hepatic encephalopathy
HGFs	Haematopoietic growth factors
HPC	Haematopoietic progenitor cells
HRS	Hepatorenal syndrome
HSCs	Haematopoietic stem cells
HVPG	Hepatic venous pressure gradient
IL	Interleukin
INR	International normalized ratio
IVF	In vitro fertilization
kDa	Kilo Dalton
UK	Leukemia inhibition factor
LPSCs	Liver progenitor/stem cells
LTC-IC	Long term culture initiating cells
MAPC	Multipotent adult progenitor cells
M-CSF	Macrophage colony stimulating factor
MDR-1	Multidrug resistance gene-1
Meg-CFC	Merakaryocyte- Colony forming cells
MELD	Model for end-stage liver disease
MGI-2A	Macrophage-granulocyte inducing factor 2A
MHC	Major histocompatability complex
MIP-1β	Macrophage inhibitory protein-1β
MIP-lα	Macrophage inhibitory protein- l α
MNCs	Mononuclear cells
M2-PK	Pyruvate kinase
MSCs	Mesenchymal stem cells
NAFLD	Non alcoholic fatty liver disease
NOD/SCID	Non-obese diabetic severely immunodeficient mice

NTCB	2-nitro 4-trifluoro-methylbenzyol-l, 3 cyclohexanedion
OLT	Orthotopic liver transplantation
PB	Peripheral blood
PBPCs	Peripheral blood progenitor cells
PBSCs	Peripheral blood stem cells
PDGF	Platelet derived growth factor
PDGFR	Platelet derived growth factor receptor
PECAM	platelet endothelial cell adhesion molecule
PF-4	platelet factor 4
PHx	partial hepatectomy
PKC	protein kinase C
PMN	polymorphonuclear leucocytes
PPG	portal pressure gradient
Pyk-2	proline-rich tyrosine kinase 2
RTK	Receptor tyrosine kinase
SBP	Spontaneous bacterial peritonitis
SCF	Stem cell factor
SCNT	Somatic cell nuclear transfer
SDF-1	Stromal derived growth factor
SRC	SCID repopulating cells
TRF	Telomere restriction fragment
TSSC	Tissue-specific stem cells
UCB	Umbilical cord blood
VCAM-1	Vascular endothelial cell adhesion molecule
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VLA	Very late antigen

Introduction

End stage liver disease is the final stage of acute or chronic liver damage and is irreversibly associated with liver failure. End stage liver disease can develop rapidly, over days or weeks (acute and sub-acute liver failure, respectively), or gradually, over months or years (chronic liver failure) (***Heidelbaugh 2006).***

In Egypt the high incidence of HCV infection the legacy left from the mass use of tartar emetic to eradicate schistosomiasis, as in other high prevalence areas will take years to reduce. Steatohepatitis due to non-alcoholic fatty liver disease is developing into a new and major health problem as a result of rising levels of obesity in populations worldwide. Hepatic steatosis also has an adverse influence on the progression of other liver diseases including chronic HCV infection and alcoholic liver disease. In many countries, considerable public concern is on the rise due to increased levels of alcohol consumption adversely affecting younger and affluent age groups. With the rising prevalence of cirrhosis, primary hepatocellular carcinoma (HCC) is increasing in frequency as is that of primary intrahepatic cholangiocarcinoma. ***(Williams 2006.)***

Currently, liver transplantation is the most effective therapy for patients with end stage liver disease (***Francoz et al., 2007)***. However, its potential benefits are hampered by many drawbacks, such as the relative shortage of donors, operative risk, post-transplant rejection, recidivism of the pre-existing liver disease, and high costs.

In an Egyptian experience for living related liver transplantation recipient and graft survivals were 86.6% at the end of the follow-up which was comparable to literature reports for deceased donor liver transplantation. Clinical HCV recurrence was observed in 10/38 patients (26.3%). Four patients developed mild fibrosis with a mean fibrosis score of 0.6 and mean grade of histological activity index of 7.1. None of the recipients developed allograft cirrhosis during the mean follow-up period of 16 +/- 8.18 months (range, 4-35 months). Estimated and actual graft volumes were negatively correlated with the incidence and early clinical HCV recurrence. None of the other risk factors were significantly correlated with clinical HCV recurence: gender, donor and recipient ages, pretransplantation Child-Pugh or model for end-stage liver disease (MELD) scores, pre- and postoperative viremia, immunosuppressive drugs, pulse steroid therapy, and preoperative anti-HBc status. Which made them conclude that postoperative patient and graft survival rates for HCV (genotype 4)-related cirrhosis were more or less comparable to DDLT reported in the literature. Clinical HCV recurrence after LDLT in our study was low. Small graft volume was a significant risk factor for HCV recurrence. A longer follow-up and a larger number of patients are required to clarify these issues (***Yosry et al., 2008.)***

In this scenario, stem cell therapy sounds particularly attractive for its potential to support tissue regeneration requiring minimally invasive procedures with few complications. This field of research, which represents the ground from which the new discipline of “regenerative medicine” has germinated, has rapidly developed in recent years, arising great interest among scientists and physicians, and frequently appearing in newspapers headlines touting miracle cures, but arising ethical crises as well (***Mimeault et al., 2007***.)

Preliminary experience with clinical hepatocyte transplantation during the past decade has provided proof of concept that cell therapy can be effective for the treatment of some liver diseases. Recent progress in cell biology resulting in the isolation and characterization of bone marrow stem cells and progenitor cells further increases the expectation for a new approach to the treatment of genetic and chronic liver disease **(*Sakaida et al., 2005*.)**

There are at least two types of stem cells in the human bone marrow; mesenchymal stem cells, and hematopoietic stem cells (HSCs). HSCs are $CD34^+$ and $CD133^+$ and they can give rise to all lineages of blood cell differentiation. Recently, intracoronary infusion of bone marrow stem cells was reported to be safe and effective in patients with acute myocardial infarction **(*Schachinger et al., 2006)***

Furthermore, *in vivo* trans-differentiation of human HSCs to functional hepatocytes has been demonstrated **(*Almeida-Porada et al., 2004)***. Also, it has been shown that infusion of bone marrow stem cells to animal models of liver cirrhosis can lead to regression of liver fibrosis ***(Sakaida 2004)*** . Recently, ***(am Esc et al., 2005)***reported that portal administration of autologous $CD133^+$ HSCs accelerated liver regeneration. We hypothesized that infusion of HSCs may help to reverse liver failure in patients with decompensated cirrhosis.

The most debated issue pertains to the use of human ESCs, as it implies, with current technologies, the destruction of human embryos. Opponents of ESC research argue that ESC research represents a slippery slope to reproductive cloning, and can fundamentally devalue human life. Contrarily, supporters argue that such research should be pursued because the resultant treatments could have significant medical potential. It is also noted that excess embryos created for *in vitro* fertilization could be donated with consent and used for the research(***Furcht 2008)***.

The ensuing debate has prompted authorities around the world to seek regulatory frameworks and highlighted the fact that stem cell research represents a social and ethical challenge. Thus, current legislation on ESC use widely varies, with some countries being more permissive (such as UK, Netherlands, Spain and France) than others (such as North America and most of the North European countries) (***Furcht .,2008.)***

In Japan (***Terai et al 2006)*** reported his result done on nine liver cirrhosis patients that underwent autologous bone marrow cell infusion (ABMI) from the peripheral vein. Subjects were patients with LC with total bilirubin of less than 3.0 mg/dl, platelet count of more than 50 % and no viable hepatocellular carcinoma on diagnostic imaging. Autologous bone marrow (BM; 400 ml) was isolated from the ilium under general anesthesia. Mononuclear cells (MNCs) were separated by cell washing and were infused via the peripheral vein. MNC characteristics were confirmed by fluorescence-activated cell sorting analysis (CD34, CD45, and c-kit). After ABMI therapy, liver function was monitored by blood examination for 24