Stem Cell Transplantation in Liver Diseases

Essay

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El-Sheshtawy Sayed Ahmed

List of Contents

List of Abbreviations

2-AAF	:	2-acetylaminofluorene
AA	:	Allylalcohol
AAT	:	Alpha 1- antitrypsin deficiency
ABMI	:	Autologous bone marrow cell infusion
AECs	:	Amniotic epithelial cells
AFP	:	´Alpha-fetoprotien
AGPR	:	Asialoglycoprotein receptor
ALD	:	Alcoholic liver disease
ALL	:	Acute lymphoblastic leukemia
allo-HCT	:	Allogeneic hematopoietic cell transplantation
ALS	:	Amyotrophic lateral sclerosis
ALT	:	Alanine aminotranferease
AML	:	Acute myeloid leukemia
APC	:	Activated protein C
APS	:	Anti phospholipid syndrome
ASCs	:	Adult Stem Cells
AST	:	Aspartate aminotransferase
ATG	:	Anti-thymocyte globulin
AVN	:	Avascular necrosis of bone
BAL	:	Bio-artificial liver
BAL	:	Bronchoalveolar lavage
Bcl-2	:	Prototype for a family of mammalian genes and the proteins they produce multidrug resistant gene MDRI
BMC	:	Bone marrow-derived cells
BMCs	:	Bone marrow cells
BMD	:	Bone mineral density
BMMSCs	:	Bone marrow mesenchymal stem cells
CB	:	Cord blood
CCl4	:	Carbon tetrachloride
CD	:	Crohn's disease
CIMF	:	Chronic idiopathic myelofibrosis
CLL	:	Chronic lymphocytic leukemia
CML	:	Chronic myeloid leukemia
CR1	:	First clinical remission
CR2	:	Second clinical remission
CSA	:	Cyclosporine
DAH	:	Diffuse alveolar haemorrhage
DDPIV+	:	Dipeptidyl peptidase IV-positive
DFS	:	Disease free survival

DMARDs	:	Disease-modifying antirheumatic drugs
EBMT	:	European Group for Blood and Marrow Transplantation
ECM	:	Extracellular matrix
ESCs	:	Embryonic stem cells
EULAR	:	European League against Rheumatism
F344	:	Nagase analbuminemic rat
FAH	:	Fumarylacetoacetate hydrolase
FBS	:	Fetal bovine serum
FISH	:	Fluorescence in situ hybridization
FL	:	Follicular lymphoma
FLRV	:	Future liver remnant volume
FSCs	:	Fetal stem cells
GFP	:	Green fluorescence protein
GFR	:	Glomerular filtration rate
GGT	:	Gamma-glutamile transpeptidase
GVHD	:	Graft-versus-host disease
HD	:	Hodgkin's disease
HGF	:	Hepatocyte growth factor
HHV-6	:	Human herpes virus-6
HLA	:	Human leukocyte antigen
HSCs	:	Hematopietic stem cells
HSCT	:	Hematopietic stem cell transplantation
ICMs	:	Inner cell masses
IHBC	:	Intermediate hepatobiliary cells
IL-11	:	Interleukin-11
ISEMFs	:	Intestinal subepithelial myofibroblasts
LCT	:	Liver cell transplantation
LVEF	:	Left ventricular ejection fraction
MACS	:	Magnetic cell sorting
MDS	:	Myelodysplastic syndromes
MELD	:	Model of End-Stage Liver Disease
MHC	:	Major histocompatibility complex
MIBE	:	Measles inclusion body encephalitis
MMP-9	:	Matrix metalloproteinase 9
MNCs	:	Mononuclear cells
MOH	:	Ministry of Health
MPB	:	Mobilized peripheral blood
MRI	:	Magnetic resonance imaging
MS	:	Multiple sclerosis
MSCs	:	Mesenchymal stem cells
MUD	:	Matched unrelated donors
NARs	:	Nagase analbuminemic rats
NASH	:	Non-alcoholic steatohepatitis
NHL	:	Non-Hodgkin lymphoma

OLT	:	Orthotopic liver transplantation
P450	:	Phenobarbital-inducible cytochrome-P450
PCNA	:	Proliferating cell nuclear antigen
PDSCs	:	Placenta-derived stem cells
PVE	:	Portal vein embolization
RA	:	Rheumatoidarthritis
REPAIR-AMI	:	Reinfusion of Enriched progenitor cells and Infarct Remodeling in A cute Myocardial Infarction
RSV	:	Respiratory syncytial virus
RT- PCR	:	Reverse Transcription-Polymerase Chain Reaction
Sca-1	:	Stem cell antigen-1
SCF	:	Stem cell factor
SCs	:	Stem cells
SCT	:	Stem cell transplantation
SDF-1	:	Stromal cell-derived factor-1
SDF-1 alpha	:	Stromal cell-derived factor-1 alpha
SEC	:	Sinusoidal endothelial cells
SS	:	Systemic sclerosis
STZ	:	Streptozotocin
TBI	:	Total body irradiation
TPO	:	Thrombopoietin
TRM	:	Transplant-related mortality
UC	:	Ulcerative colitis
UCB	:	Umbilical cord blood
VOD	:	Veno-occlusive disease
α-MEM	:	α minimal essential medium

List of Tables

List of Figures

Introduction

Transplantation is an accepted treatment today for many people suffering from organ failure. More and more patients are referred for transplant surgery, and the waiting lists are growing longer because not enough organs and tissues are donated for transplantation. This has led to several potentially viable alternatives being considered, including bio-artificial support devices, the transplantation of mature cells or stem/progenitor cells and the potential transplantation of xenogenic organs and cells ***(Burra et al., 2004)***.

Orthotopic liver transplantation (OLT) is the gold standard treatment for end-stage liver failure and for numerous liver based inborn errors of metabolism. However, organ shortage remains a major limiting factor and alternative solutions are being examined in the liver therapy field. Liver cell transplantation (LCT) is emerging with heartening success, but is still limited by cell viability, modest engraftment and limited tissue availability ***(Stephenne et al., 2006)***. Increasing interest is carried to stem cells regarding the recent demonstration of their plasticity ***(Verfaillie et al., 2002).***

A stem cell is an undifferentiated cell capable of renewing itself throughout its life and of generating one or more types of differentiated cells. While embryonic stem cells (ESCs) are the only ones to be totipotential, adult tissues with high cellular turnover (e.g. skin, gut mucosa and bone marrow) retain a population of stem cells with restricted differentiation potential that constantly supply the tissue with new cells ***(Heidelbaugh and Bruderly, 2006).***

The two broad types of mammalian stem cells are: embryonic stem cells that are found in blastocysts, and adult stem cells that are found in adult tissues. In a developing embryo, stem cells can differentiate into all of the specialized embryonic tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing specialized cells, but also maintain the normal turnover of regenerative organs, such as blood, skin or intestinal tissues. As stem cells can be grown and transformed into specialized cells with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture, their use in medical therapies has been proposed. In particular, embryonic cell lines, autologous embryonic stem cells generated through therapeutic cloning, and highly plastic adult stem cells from the umbilical cord blood or bone marrow are touted as promising candidates ***(Tuch, 2006).***

The discovery of the pluripotent stem cells made the prospect of cell therapy and tissue regeneration a clinical reality that hold a great promise to repair, restore, replace affected organs ***(Levicar et al., 2007).***

Bone marrow derived stem cells represents a candidates for liver directed gene therapy and tool for the regenerative medicine ***(Idilman et al., 2007).***

Aim of the Essay

The aim of the essay is to review the subject of stem cell transplantation and to highlight its role in management of various liver diseases.

Stem Cell

Stem cell definition:

Stem cells are unspecialized cells that have two defining properties: the ability to differentiate into other cells and the ability to self regenerate ***(Piscalgia et al., 2008).***

Properties of stem cells

The classical definition of a stem cell requires that it possess two properties:

- Self-renewal - the ability to go through numerous cycles of cell division while maintaining the undifferentiated state.
- Potency - the capacity to differentiate into specialized cell types. In the strictest sense, this requires stem cells to be either totipotent or pluripotent - to be able to give rise to any mature cell type, although multipotent or unipotent progenitor cells are sometimes referred to as stem cells ***(Takahashi and Yamanaka, 2006)***.

Potency specifies the differentiation potential (the potential to differentiate into different cell types) of the stem cell.

Totipotent stem cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent. These cells can differentiate into embryonic and extraembryonic cell types.

Pluripotent stem cells are the descendants of totipotent cells and can differentiate into cells derived from any of the three germ layers.

Multipotent stem cells can produce only cells of a closely related family of cells (e.g. hematopoietic stem cells differentiate into red blood cells, white blood cells, platelets, etc.).

Unipotent cells can produce only one cell type, but have the property of self-renewal which distinguishes them from non-stem cells (e.g. muscle stem cells) ***(Yu et al., 2007)***.

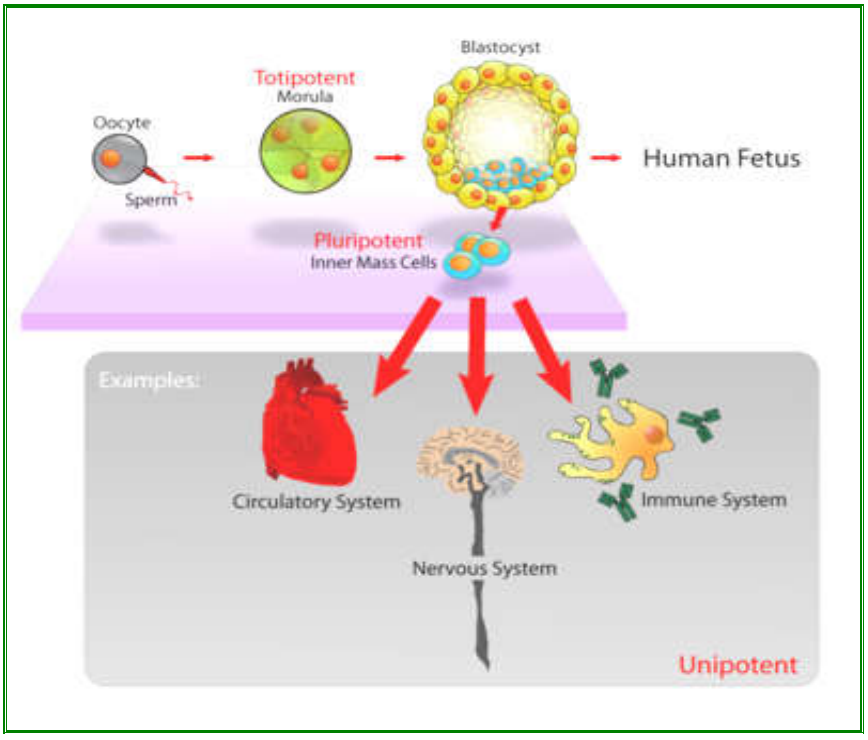

Fig. (1): Pluripotent, embryonic stem cells originate as inner mass cells within a blastocyst. The stem cells can become any tissue in the body, excluding a placenta. Only the morula's cells are totipotent, able to become all tissues and a placenta ***(Jaenisch, 2004)***.

History of stem cell

Hematopoietic stem-cell transplantation was originally conceived more than 50 years ago as a treatment for injury from irradiation and, later, for cancer, associated problems needed to be solved before the procedure could be used clinically. Bone marrow, the source of hematopoietic stem cells, is not a solid organ but is rather diffuse and not directly accessible.

Studies from the mid-20th century demonstrated that massive total-body irradiation causes fatal damage to the gastrointestinal and central nervous systems. Lower doses lead to delayed death from hemorrhage and infection. In animal models, the transplantation of genetically identical (syngeneic) marrow or the animal's own (autologous) stored marrow averted death. Grafts from histocompatible littermates also permitted survival. The transplantation of marrow that was not genetically identical (allogeneic) to that of the recipient resulted in an immunologic reaction by the donor lymphocytes against the recipient, causing inflammation of the target tissues, termed graft-versus-host disease (GVHD). Treatment with methotrexate suppressed GVHD. As an alternative to total-body irradiation, cyclophosphamide as a preparative regimen also permitted the engraftment of allogeneic marrow.

Thomas was a pioneer in applying the results from early studies in animals to the treatment of leukemia in people. In 1959, he and his colleagues reported that a patient with end-stage leukemia who was treated with total-body irradiation, followed by infusion of her identical twin's marrow, had a three-month remission ***(Thomas et al., 1959).***