Stem Cells and Its Therapeutic Uses in Liver Diseases

Essay
Submitted for partial Fulfillment of Master Degree in Anatomy and Embryology

By

Mohammed Fathi Mohammed Mohammed ElRefai
M.B, B.Ch (Anatomy&Embryology)
Under Supervision of

Prof.Dr.Kariman Mohammed Abdel Fatah ElGohari
Professor of Anatomy and Embryology
Head of Anatomy and Embryology Department
Faculty of Medicine-Ain Shams University

Prof.Dr. Ibtisam Ahmed Bahei Eldin
Professor of Anatomy and Embryology
Faculty of Medicine-Ain Shams University

Ass. Prof. Dr. Faten Mohammed Abdel Wahed ElKholy
Assistant Professor of Anatomy and Embryology
Faculty of Medicine-Ain Shams University

Anatomy and Embryology Department
Faculty of Medicine
Ain Shams University
2009

Acknowledgement

Thanks to **Allah** *the greatest of all for helping me to complete this work.*

I would like to express my sincere and deep gratitude to ***Prof.Dr.kariman Mohammed Abdel Fatah ElGohary*** *Professor of Anatomy and Embryology, Head of Anatomy and Embryology department, Faculty of Medicine, Ain Shams University, for giving me the privilege of supervising this essay and her constructive encouragement, illuminating guidance as well as her support throughout this work.*

I am really very grateful and deeply indebted to ***Prof. Dr. Ibtisam Ahmed Bahi-Eldin*** *Professor of Anatomy and Embryology, Faculty of medicine, Ain shams university, for her unfailing help, valuable suggestions and good support which helped me to put this work in its best form. It was a great honor and a chance of a lifetime to work with her.*

I really wish to express my deep gratitude to ***Ass. Prof.Dr.Faten Mohammed Abdel Wahed ElKholy****, Assistant Professor of Anatomy and Embryology, Faculty of medicine, Ain Shams University, for her kind assistance, precious and effective effort.*

Abbreviations

AAF : Acetyl amino fluorine

AAT : Alannine amino transaminase.

ABCB4 : Adenosine tri posphatase binding cassette B4.

AFP : Alpha fetoprotein.

ALB : Albumin.

BMPs : Bone morphogenetic proteins.

BMSCs : Bone marrow stem cells.

BECs : Biliary epithelial cells.

CK8 : Cytokeratin 8.

Ck18 : Cytokeratin 18.

DMEM : Dulboecco's modified Eagle's medium.

DNA : Dioxy ribo nucleic acid.

DPPIV : Dipeptidyl peptidase IV.

ESCs : Embryonic stem cells.

EBs : Embryoid bodies.

ECM : Extra cellular matrix.

FBS : Fetal bovine serum.

FGF : Fibroblast growth factor.

FACS : Fluorescence activated cell sorting.

G6P : Glucose 6 phosphatase.

GEP : Green fluorescent protein.

HAAT : Human alpha anti trypsin.

HSCS : Hematopoietic stem cells.

HGF : Human growth factor.

hEscs : Human embryonic stem cells

hMSCs : Human mesenchymal stem cells.

IVF : In vitro fertilization.

ICG : Indocyanine Green.

ISH : In situ hybridization.

IGF1 : Insulin growth factor one.

LPCS : Liver progenitor cells.

LIF : Leukemia inhibitory factor.

MAPCS : Multi potential adult progenitor cells.

MSCs : Mesenchymal stem cells.

MHC : Major histocompitability complex.

mESCs : Mouse embryonic stem cells.

NL : Normal liver.

NIH : National institute of health.

OSM : Oncostatin M.

OLT : Orthotopic liver transplantation.

PBC : Primary biliary cirrhosis.

PBS : Purified based saline.

PCR : Polymerase chain reaction.

Rag : Recombination activating genes.

RT-PCR : Reversed transcriptase Polymerase chain reaction.

SCF : Stem cell factor.

SCID : Severe Combined immuno deficiency disease.

TAT : Tyrosine amino transferase.

TGF : Transform growth factor.

List of Figures

List of tables

Introduction

The liver performs a wide range of metabolic activities required for homeostasis, nutrition and immune defense. It is the major site for detoxification and excretion of drugs, hemoglobin metabolites and ammonium **(Standring, 2008).**

Liver diseases have expanded dramatically in the past decade. The current epidemic of hepatitis C infected millions and approximately 20% of these patients develop cirrhosis or hepatocellular carcinoma **(Gupta et al, 2000).**

Preliminary experience with clinical hepatocyte transplantation during the past decade has provided proof of the concept that cell therapy can be effective for treatment of some liver diseases. Recent progress in cell biology, resulting in isolation and characterization of hepatic stem cells and progenitor cells further increased expectation for a new approach to the treatment of genetic and chronic liver diseases by hepatocyte transplantation **(Muraca et al, 2006).**

Stem cells are unspecialized cells, which has the ability of self renewal. There are two main categories of stem cells embryonic stem cells which are derived from blastocysts and adult stem cells which are found in adult tissues. In a

developing embryo, stem cell can differentiate into all of the specialized embryonic tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the tissues, replenishing specialized cells. As stem cells can be grown and transformed into specialized cells with characteristics consistent with cells of various tissues through cell culture, their use in medical therapies has been proposed **(Strain et al, 2002).**

Oval cells are considered to be progenitor cells of both hepatocytes and cholangiocytes and other hepatic cells **(Paku et al, 2001).** Fetal hepatoblasts represent a potentially highly valuable source of human liver stem cells **(Rogler, 1997)**.

Hepatocyte cell lines are grown in tissue cultures and provide the advantage of uniformity, sterility and freedom of pathogens. The natural plasticity of stem cells means that they could generate hepatocytes in vivo. Hematopoietic stem cells, pancreatic stem cells, and umbilical blood stem cells generate functional hepatocytes in vivo after cell transplantation. Cell fusion could be the reason why stem cells with different origins can transdifferentiate into other cell types, and cell fusion is sufficient for treating some gene disorders. Therefore, mostly stem cells in any organ could be feasible cell source candidates for cell

transplantation to manage liver disease in the clinical setting. However, an efficient method for the trans differentiation of stem cells with other origins to hepatocytes should be developed before such cells can be used clinically. Another potential cell source could be embryonic stem cells. However, the efficacy and safety of this approach should be carefully determined before clinical use can begin **(Gupta et al, 2000).**

Identification of stem cells, their culture directing their differentiation into hepatocytes, and transplantation methods will have a great impact on treating liver diseases **(Gupta et al, 2000).**

Aim of work

The aim of this work is to review basics of stem cells which include their types, differentiation, general uses and their potential therapeutic value in case of liver disease.

The utilization of stem cells in case of liver diseases will be discussed.

History of stem cells

Stem cell research began in the mid 1800s with the discovery that some cells could generate other cells. In the early 1900s physicians administered bone marrow by mouth to patients with anemia and leukemia. Although such therapy was unsuccessful, laboratory experiments eventually demonstrated that mice with defective marrow could be restored to health with infusion into the blood stream of marrow taken from other mice. This caused physicians to speculate whether it was feasible to transplant bone marrow from one human to another allogeneic transplant **(Eiseman, 2000).**

James (1998) isolated cells from the inner cell mass of early embryos and developed the first embryonic stem cell lines. The blastocysts used for human stem cell research typically came from ***in vitro*** fertilization (IVF) procedures. Human embryonic stem cell lines were shared and new lines were derived. Many researchers focused on making human tissues for transplantation **(Woo-Suk, 2005).**

Haris (2005) described cord blood embryonic like stem cells. It was suggested that these stem cells had the ability to differentiate into more cell types than adult stem cells

and opened up greater possibilities for cell based therapies. **Atta et al (2007)** claimed that a new type of stem cell had been isolated from amniotic fluid, which could be a viable alternative to the controversial use of embryonic stem cells.

Over the last few years, national policies and debate among the public as well as religious groups, government officials and scientists had led to various laws and procedures of stem cell development and treatment for research or disease purposes. The goals of such policies were to safeguard the public from unethical stem cell research and use while still supporting new advancements in the field **(Dorff, 2006).**

Types of stem cells

Stem cells have two important properties that distinguish them from other types of cells. First, they are unspecialized cells that renew themselves for long periods through cell division. The second is that under certain physiologic or experimental conditions, they can be induced to become cells with special functions such as the beating cells of the heart muscle or the insulin producing cells of the pancreas. Scientists primarily work with two kinds of stem cells from animals and humans: adult stem cells and embryonic stem cells, which have different functions and characteristics **(Kondo and Raff, 2000, and Fletcher, 2000).**

Adult stem cells:

Types:

1-Hematopoietic stem cells (HSCs):

The hope that many diseases could some day be treated with stem cell therapy was inspired by the historical success of bone marrow transplants in increasing the survival of patients with leukemia and other cancers, inherited blood disorders and diseases of the immune system **(Thomas and Blume, 1999).**