STEM CELL THERAPY IN LIVER DISEASES

(Essay)

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CLINICAL & CHEMICAL PATHOLOGY

By

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LIST OF ABBREVIATIONS

ABMI - Autologous bone marrow infusion
ADA - Adenosine deaminase
AFP - Alpha feto protein
ALC - Alcoholic liver cirrhosis
ALT - alanine transaminase
ASC - Adult stem cells
AST - aspartate transaminase
BMCs - Bone marrow cells
BMSCs - Bone marrow Stem cells
BMP - Bone morphogenetic proteins
CCl_4 - Carbon tetrachloride
CNS - Central nervous system
DE - Definitive endoderm
DIC – Disseminated intravascular coagulopathy
EBs - Embryoid Bodies
ERT – Enzyme replacement therapy
ESC - Embryonic stem cells
ESLD - End stage liver disease
FGF - Fibroblast growth factor
G-CSF - Granulocyte colony-stimulating factor
GFP - Green Fluorescence Protein
GSCs - Germ stem cells
hESC - human Embryonic Stem cells
HGF - Hepatocyte growth factor
HLAs - Human leukocyte antigens
HLC - Hepatocyte-like cell
HLSC – Human liver Stem cells
HNF4 - Hepatocyte nuclear factor 4
HSC - Haemopoeitic Stem Cells
ICG - Indocyanine green
ICM - Inner cell mass
IMD - Inherited metabolic disorders
KFT - Kidney function tests
LC - Liver cirrhosis
LFT - Liver function tests
LIF - Leukemia inhibitory factor
LPC - Liver progenitor cell

MEF - mouse embryonic fibroblast
MEF CM - mouse embryonic fibroblast conditioned medium
MELD Score – Model for End Stage Liver Disease Score
MIT - mechanical isolation technique
MNCs - Mononuclear cells
MSC - Mesenchymal stem cells
NSCs - Neural stem cells
OSM – Oncostatin M
PIIIP - Pro-collagen-III peptide
PMT - Porous Membrane Technique
PS - Primitive streak
PSIS – Posterior superior iliac spine
PT - Prothrombin time
QOL score - Quality of life score
RT-PCR - Reverse transcriptase Polymerase chain reaction
SCF – Stem Cell Factor
SCH - Small Cell Hepatocytes
SCI - Spinal cord injury
SCID-X1 - severe combined immunodeficiency-X1
SCH - Small cell hepatocytes
SCNT - Single cell nuclear transfer
SCT – Stem cell therapy
TGF - Transforming Growth Factor
TNCC - total nucleated cell count
UCB - Umbilical Cord Blood
VEGF - vascular endothelial growth factor

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ABSTRACT

A stem cell is a cell capable of dividing, leading thereby to the production of a copy of itself as well as a differentiated cell progeny, that's characterized by having different, more restricted properties. Stem cells have been recognized as a potential tool for the development of innovative therapeutic strategies. Regenerative medicine is a new branch in medicine involving a multidisciplinary effort to replace or repair diseased tissue. Stem cell therapy is playing a crucial part in this new field.

The liver is a remarkable organ in both form and function. The liver is responsible for a number of biochemical functions, essential for man's survival. Hence, the need for effective modes of therapy is crucial. Liver-directed cell therapy is of much interest for several reasons. Firstly, most genetic diseases are amenable to cell therapy. Secondly, a large numbers of people carry the burden of acquired liver disease, such as, chronic viral hepatitis, if some how it is concomitant with an effective mode of disease eradication, it will be a breakthrough. Thirdly, all terminal liver disease patients will benefit by improving their quality of life. Finally, there are many sources of liver stem cells that can be researched and used.

Stem cell therapy in liver diseases is starting now to show great results in human trials; however it's still too early to standardize the approach and further studies especially well designed randomized controlled studies are still needed to prove the effectiveness of stem cell administration on the clinical course of these patients.

Keywords: Stem cell therapy**,** Regenerative medicine, Liver-directed cell therapy, liver stem cells.

INTRODUCTION AND AIM OF WORK

The stem cell is the origin of life. As stated first by the great pathologist Rudolph Virchow, “All cells come from cells”. Stem cells are a unique cell population capable of self-renewal and differentiation into different cell lines. Stem cells have been recognized as a potential tool for the development of innovative therapeutic strategies. Stem cell therapy is a new approach in medicine and is part of a new medical branch called “Regenerative Medicine” ***(Sell, 2004).***

There are two important types of stem cells; they are the ASC and the ESC. ASC have already proven its great value, and are used in a number of fields with extreme success indeed, adult stem cells have long been used in the treatment of hematological malignancies. On the other hand, many scientists believe that ESC might be a future solution to most of man’s diseases; however it’s under researched because of the ethical barriers related to its usage ***(Gardner, 2006).***

Of all the new biological technologies, none have been more controversial than stem cell therapies. Creation of human embryos for the sole purpose of providing stem cells has been extremely condemned and banned in most countries. The goal of the intense research on stem cells is for human application. Recently, knowledge of stem cells has progressed rapidly and experimental therapies are already in clinical trials. However, for more far reaching application and successful therapy much more remains to be learned about stem cells ***(Khurdayan, 2007).***

Applications of stem cells include many fields of medicine such as: cardiology, neurology, hematology, hepatology, immunological diseases, diabetes mellitus, and as cell Models for Drug trials ***(Kirschstein et al., 2001)***.

In the field of Hepatology, liver transplantation is the only available therapy for end stage liver diseases and there is an ever increasing shortage of donor livers ***(Lysy et al., 2008).*** Stem cells turning into hepatocytes by transdifferentiation introduce new functioning liver cells into a diseased organ, which can support intrinsic liver regeneration or bridge the time gap until a definitive treatment is available. Transplantation of hepatocytes or hepatocyte-like cells of extrahepatic origin is a promising strategy for treatment of acute and chronic liver failure. Hepatocyte-like cells induced from bone marrow cells are under animal and human trials ***(Gupta et al., 2004).***

Many research groups have focused their efforts on cirrhosis, in particular. Chronic liver disease is one of the most common diseases all over the world. In Egypt, because of the high prevalence rates of hepatitis C, this condition has turned to be a major health problem. This fact directed the focus of a number of groups towards this serious problem especially towards cell base therapies owing to the facts that organ transplantation has its difficulties ***(Al-Garem et al., 2008).***

Aim of work:

The work aims to focus on the different types of stem cells and their advantages, biological features as well as the ethical dilemma associated with this research and therapy mode. We will discuss the general strategy of stem cell therapy in liver disease, shedding light on stem cells therapy as an evolutionary break through treatment option in general and in liver diseases specifically which is showing promising results in early human trials and many centers. We hope it will add to better understanding of the breaking discoveries regarding the mechanism and treatment in such cases, especially in our country where there is a high prevalence of chronic liver disease.

I. STEM CELLS

INTRODUCTION AND DEFINITIONS

The stem cell is the origin of life. As stated first by the great pathologist Rudolph Virchow, "All cells come from cells." It is the origin of an organism's life. Stem cells with less than totipotentiality are called "progenitor cells". Except for germinal cells, which retain totipotency, most stem cells in adult tissues have reduced potential to produce cells of different types (i.e. are determined). Extensive research in most adult stem cells have shown restricted potential in proliferation, subsequent expansion of the stem cells in culture is still not routine ***(Gardner, 2006).*** However, there is increasing evidence for the retention of some toti/multi-potent cells in the tissues of adults, especially in the bone marrow **(*Sell, 2004*).**

Stem cells have recently generated more public and professional interest than almost any other topic in biology. Stem cells are defined functionally as cells that have the capacity to self-renew as well as the ability to generate differentiated cells ***(Weissman et al., 2001)***, this simply means that a stem cell is a cell capable of dividing, leading thereby to the production of a copy of itself as well as a differentiated cell progeny, that's characterized by having a different, more restricted properties ***(Smith, 2006).*** Some researchers define it even more clearly as a cell that divides to generate one daughter cell that is a stem cell and another daughter cell that produces differentiated descendants ***(Gardner, 2006).*** The first ability is called self-renewal and the second differentiation ***(Guillot et al., 2007)***. Experimental work and research have proven without doubt that the concept of “stem cell” is indissolubly linked with growth via the multiplication rather than the enlargement of cells ***(Marshak et al., 2002).***

The research in the field of stem cells aroused from the pioneering studies of Till and McCullogh on the hematopoietic stem cell and those of Leblond on spermatogenesis and the intestinal crypt ***(Gardner, 2006)*.** Stem cell research is in many ways no different than many other areas of modern biology; it is advancing because new tools and new knowledge are providing the opportunities for new insights. Like all fields of scientific inquiry, research on stem cells raises as many questions as it answers ***(Kirschstein and Skirboll, 2001).***

Scientists used to regard tissues as belonging to one of the following basic types: renewing, expanding, and static. Obvious examples of the first are intestinal epithelium and skin, and of the second, liver. The third category was held to include the central nervous system ***(Marshak et al., 2002)***, recent stem cell studies have shown that neurogenesis does continue in adulthood, for example, with regard to production of neurons that migrate to the olfactory bulbs ***(Gage, 2000)***. Another break through was knowing that a single epiblast being a source of pluripotent cells(Later called embryonic stem (ES) cells) has the ability to form an entire adult vertebrate, usually being composed of more than 200 different types of cells. At least in the mouse, these cells retain the capacity to contribute both to all somatic lineages and to the germ line after an indefinite period of proliferation in vitro**.** Theses examples clearly show us how stem cell research is changing and introducing new concepts in the field of molecular biology ***(Marshak et al., 2002)*.**