Basics of Stem Cell Therapy and Its Application in Pediatric Surgery Field

An Essay

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By:

Mohamed Ali Mahmoud
Faculty of Medicine - Ain Shams University
(M. B., B.Ch)

Supervised by

Prof. Dr. Tarek Ahmed Hassan
Professor of Pediatric Surgery
Faculty of Medicine, Ain Shams University

Dr.Amr Abdel-Hamed Zaki
Lecturer of Pediatric Surgery
Faculty of Medicine, Ain Shams University

Dr. Khaled Mohamed El-Asmar
Lecturer of Pediatric Surgery
Faculty of Medicine, Ain shams University

Faculty of Medicine
Ain Shams University
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Mohamed Ali Mahmoud

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List of Abbreviations

ACLF	:	Acute and chronic liver faliure
AD MSCs	:	Adipose derived Mesenchymal stem cells
ADSCs	:	Adipose derived stem cells
AFMS	:	Amniotic fluid mesenchymal cells
AFS	:	Amniotic fluid stem cells
ASCs	:	Adult Stem cells
BMSCs	:	Bone marrow mesenchymal stem cells
BOO	:	Bladder outlet obstruction
CSCs	:	Cardiac stem cells
DM	:	Diabetes Mellitus
EGFP	:	Enhanced green fluorescent protein
EHBA	:	Extra hepatic biliary atresia
ENSCs	:	Enteric nervous stem cells
ENSPC	:	Enteric nervous system progenirator cells
EPCs	:	Endothelial progenirator cells
ESCs	:	Embryonic Stem cells
G-CSF	:	Granulocyte colony stimulating factor
GSCs	:	Germ line stem cells
GVHD	:	Graft versus host disease
HDAC	:	Histone Deacetylase
HGF	:	Hepatocyte Growth Factor
HLA	:	Human leukocyte Antigen
HSCs	:	Hematopoietic stem cells
HSCT	:	Hematopoietic stem cell transfer
HSD	:	Hirschsprung's disease
IPSCs	:	Induced pluripotent stem cells
IVF	:	In vitro fertilization
LSCs	:	Limbal stem cells
MDCs	:	Muscle derived cells
MSCs	:	Mesenchymal stem cells
NLBs	:	Neurosphere like bodies

List of Abbreviations (Cont.)

NSCs	:	Neural Stem cells
OBs	:	Organoid bodies
PSCs	:	Pancreatic stem cells
PUUUO	:	Partial unilateral upper ureteric obstruction
SCI	:	Spinal cord injury
SCNT	:	Somatic cell nuclesr transfer
SDF1	:	Stomal cell derived factor 1
SIS	:	Small intestinal submucosa
SMCs	:	Smooth muscle cells
UCBSCs	:	Umblical cord blood stem cells
VEGF	:	Vascular endothelial growth factor
VPA	:	Valproic acid

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Introduction

A stem cell is an undifferentiated cell in the body with undetermined function capable of forming various tissues under definite signals received from the body. Also it can proliferate in-vitro while maintaining the potential to differentiate into derivatives of all three embryonic germ layers ***(Gupta and Sharma,2005)(Thomson et al.,2005).***

Stem cell offers tremendous potential not only for research but also for clinical applications as an unlimited source of cells for transplantation and tissue regeneration ***(Li et al., 2010)***.

Stem cell clinical application started in 1968, where the first bone marrow transplant was performed. And since then researcher tried to make a much progress in that field. In 1998, Thompson, from the University of Wisconsin, isolated stem cells from the inner cell mass of early embryos and developed the first embryonic stem cell lines. Then, in 1999 and 2000, scientists discovered that manipulating adult mouse tissues could produce different cell types. This meant that cells from bone marrow could produce nerve or liver cells and cells in the brain could also yield other cell types. These discoveries were exciting for the field of stem cell research, with the promise of greater scientific control over stem cell differentiation and proliferation***(Murnaghan, 2013).***

Stem cell research in animals using embryonal stem cells has been an ongoing program with fruitful results. However, only limited information is available with the use of stem cells in human beings. Of the various sources of stem cells, umbilical cord blood stem cell have already been effectively used in treatment of sickle cell anemia ,Non-Hodgkin's lymphoma and some other cancers, life threatening anemia and autoimmune diseases ***(Gupta and Sharma,2005).***

Stem cells have many applications in pediatric surgery with promising results. Esophageal tissue engineering could represent a valid alternative in esophageal replacement, thanks to biomaterial science and cellular biology. Enteric nervous stem cells derived from human gut mucosa represent a practical advance in treatment of enteric nervous system disorders such as Hirschsprung's disease. Also, tissue engineering can be used in treatment of neurogenic bladder, Short bowel syndrome and hepatobiliary diseases as biliary atresia ***(Metzger et al., 2009); (Markel et al., 2008); (Aejaz et al., 2006); (Zaniet al., 2009); (Lewis and Cheng, 2007).***

Current challenges with the use of stem cells in clinical practice include the provisions to direct the differentiation of embryonic stem cells into specialized cell populations, and also devise ways to guard their development or proliferation once placed in vivo. Only further research and its clinical application may solve the many unanswered queries ***(Gupta and Sharma, 2005).***

Aim of the work

This assay is aiming to review the literature about stem cell therapy, and its recent applications in pediatric surgery field.

Chapter 1
Basics of Stem Cells

The stem cell is the origin of life. As stated first by the great pathologist Rudolph Virchow "All cells come from cells".The ultimate stem cell, the fertilized ovum, is formed from fusion of the haploid progeny of germinal stem cells ***(Sell, 2004).***

In most cases our bodies use tissue stem cells to replace damaged or worn cells. This repair mechanism is so efficient that, even though it occurs on a daily basis, we hardly notice it. However, where the damage is extensive, this repair mechanism can fail. Also, not all of the tissues in our body, for example brain tissue, can repair themselves efficiently, and many degenerative diseases are not yet treatable by modern medicine ***(Rubin,2008).***

Transplantation of organs such as the liver and heart can be an option, but it relies on a plentiful source of transplant organs, and many are in short supply. Over the past decades, stem cell research has gained a lot of attention because it has the potential to fill this gap in human medical therapies. It is hoped that stem cell research may lead to new therapies for disorders like diabetes, motor neuron disease, cancer and liver and heart disease ***(Rubin,2008).***

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. All stem cells regardless of their source, have general properties: they are capable of, dividing and renewing themselves for long periods, are unspecialized and give rise to specialized cell types such as those of the brain, heart, kidney and muscle, the process is called differentiation ***(NIH, 2009)***.

In a broad sense, stem cells are a population of cells capable of indefinite self-renewal that give rise to "daughter" cells committed to specific differentiation lineages through asymmetrical cell division. Their ability to control proliferation, differentiation, and apoptosis distinguishes them from neoplastic cells ***(Yu and Silva, 2008).***

To ensure self-renewal, stem cells undergo two types of cell division. Symmetric division gives rise to two identical daughter cells both endowed with stem cell properties. Asymmetric division produces only one stem cell and a progenitor cell with limited self-renewal potential. Progenitors can go through several rounds of cell division before terminally differentiating into a mature cell. ***(Beckmann et al., 2007).***

The normal function of stem cells includes maintenance of homeostasis mediated by providing trophic support ,as well as serving as a reservoir for replacing dysfunctional & aging cells throughout lifetime of the organism ***(Yu and Silva,2008).***

History of stem cell research :

The history of stem cell research began in the mid 1800's with the discovery that some cells could generate other cells. In the early 1900's the first real stem cells were discovered when it was found that some cells generate blood cells. A prominent application of stem cell research has been bone marrow transplants using adult stem cells ***(Eiseman,2000).***

In the early 1900's 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 infusions 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).***

A bone marrow transplant between identical twins guarantees complete HLA compatibility between donor and recipient. These were the first kinds of transplants in humans. It was not until the 1960's that physicians knew enough about HLA compatibility to perform transplants between siblings who were not identical twins. In 1973 a team of physicians performed the first unrelated bone marrow transplant. The 1990's saw rapid expansion and success of the bone marrow program with more than 16,000 transplants to date for the treatment of immunodeficiencies and leukemia. Adult stem cells also have shown great promise in other areas. These cells have shown the potential to form many different kinds of cell types and tissues, including functional hepatocyte-like (liver) cells. Such cells might be useful in repairing organs ravaged by diseases ***(Eiseman,2000).***

In 1998, James Thompson (University of Wisconsin - Madison) isolated cells from the inner cell mass of early embryos, and developed the first embryonic stem cell lines. In the same year, John Gearhart (Johns Hopkins University) derived germ cells from cells in fetal gonadal tissue (primordial germ cells). Pluripotent stem cell "lines" were developed from both sources. The blastocysts used for human stem cell research typically come from in vitro fertilization (IVF) procedures ***(Woo-Suk,2005).***

The ethical concerns over this type of embryonic stem cell research has been expressed in the following regulations:

In 2000, President Bill Clinton allowed funding of research on cells derived from aborted human fetuses, but not from embryonic cells. On August 9, 2001, President George W. Bush announced his decision to allow Federal funding of

research only on existing human embryonic stem cell lines created prior to his announcement. His concern was to not foster the continued destruction of living human embryos. In 2004, both houses of Congress have asked President George W. Bush to review his policy on embryonic stem cell research. President George W. Bush released a statement reiterating his moral qualms about creating human embryos to destroy them, and refused to reverse the federal policy banning government funding of ESC research (other than for ESC lines established before the funding ban) ***(Woo-Suk,2005)***.

Haris described cord blood embryonic like stem cells in 2005. 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 ***(Haris,2005).***

Atta and his collegues in 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 ***(Atta et al.,2007).***

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).***

Properties of Stem Cells:

There are five minimal functional states of stem cells **'SMART'** (**S**elf-renewal, **M**aturation, **A**poptosis, **R**esting mode and **T**rafficking) that constitute an interesting model for maintaining stem cell homeostasis *in vivo.* The lack of any of these '**SMART**' features would make stem cells much less

physiological and particularly useless in therapeutics ***(Cheng, 2008) (Fig. 1).***

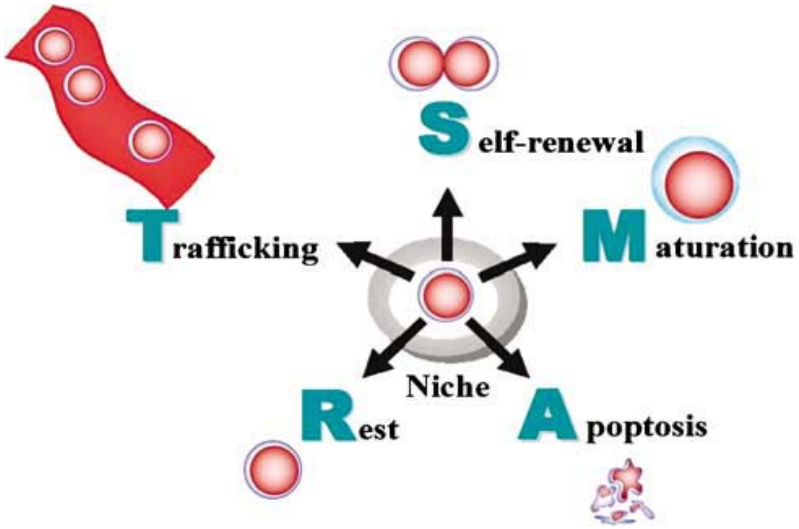

Fig. (1): A diagram illustrating the **'SMART'** physiological features of stem cells *in vivo* ***(Cheng, 2008).***

1-Self-Renewal:

It is a common misconception that all stem cell self-renewal occurs in the same way that general cells proliferate. In fact, stem cells show two different methods of self-renewing: one is symmetrical (stochastic differentiation) which divides into two daughter stem cells, and the other is asymmetrical (obligatory asymmetric replication) that gives one daughter stem cell and one differentiated cell. Embryonic stem cells (ESCs) can only undergo symmetrical self-renewing division, whereas adult stem cells (ASCs) [for example, hematopoietic stem cells (HSCs) and neural stem cells (NSCs)] are thought to undergo asymmetrical self-renewing division under homeostatic conditions ***(Morrison and Kimble, 2006).***