STEM CELL TRANSPLANTATION

Essay

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د ر ا سة
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List of abbreviations

ALF	Acute liver failure
ALL	Acute lymphoblastic leukemia
AML	Acute myelogenous leukemia
ANT	Altered nuclear transfer
BM	Bone marrow
BMDW	Bone Marrow Donors Worldwide
BMT	Bone marrow transplantation
BSA	Body surface area
CNS	Central nervous system
DM	Diabetes mellitus
ESC	Embryonic stem cell
G-CSF	Granulocyte colony stimulating factor
GVHD	Graft versus host disease
GVL	Graft versus leukemia
hESC	Human embryonic stem cell
HLA	Human leukocyte antigen
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplantation
IVF	In vitro fertilization

LIF	Leukemia inhibitory factor
MAPC	Multipotent adult progenitor cell
MP	Methylprednisolone
MPB	Mobilized peripheral blood
MSC	Mesenchymal stem cell
NCI	National cancer institute
NSC	Neural stem cell
PBSCT	Peripheral blood stem cell transplantation
PUVA	Psoralen + ultraviolet A
S.C.	Subcutaneous
SCNT	Somatic cell nuclear transfer
SCT	Stem cell transplantation
TNF	Tumor necrosis factor
UCB	Umbilical cord blood

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Introduction

Stem cells are unspecialized cells that can self renew indefinitely, and can also differentiate into more mature cells with specialized functions. Depending on the origin, stem cells are classified as embryonic stem cells that are found in blastocysts, and adult stem cells that are found in adult tissues ***(Vats et al., 2005)***.

Stem cells possess two properties: Self-renewal which is the ability to go through numerous cycles of cell division while maintaining the undifferentiated state and Potency which is the capacity to differentiate into specialized cell types ***(Tuch, 2006)***.

Potency specifies the differentiation potential (the potential to differentiate into different cell types) of the stem cell into **Totipotent** stem cells that can differentiate into embryonic and extra-embryonic cell types, **Pluripotent** stem cells that can differentiate into cells derived from any of the three germ layers, **Multipotent** stem cells that can produce only cells of a closely related family of cells and **Unipotent** cells that can produce only one cell type ***(Ratajczak et al., 2007)***.

Hematopoietic stem cells are the progenitors for the lympho – hematopoietic system with long life span and high proliferation potential. They are derived from three sources: The bone marrow, the mobilized peripheral blood stem cells and the umbilical cord blood ***(Bron et al., 2002)***.

In recent years, umbilical cord blood which is extremely enriched in hematopoietic stem cells that migrate from the liver to bone marrow stroma has emerged as an alternative source of hematopoietic stem cells for allogenic

stem cell transplantation mainly in patients who lack a HLA matched marrow donor ***(Cohen and Nagler, 2004)***.

Many medical researchers believe that stem cell treatments have the potential to change the face of human disease and alleviate suffering. A number of stem cell treatments exist, although most are still experimental and/or costy, with the notable exception of bone marrow transplantation as in brain damage, cancer, spinal cord injury, heart damage, Parkinson's disease, blindness and metabolic diseases. Medical researchers anticipate one day being able to use stem cell derived technologies to treat Type 1 diabetes mellitus and muscle damage, as well as a number of other diseases and impairments ***(Kassem, 2004)***.

Human stem cell research is an example of bioethical value conflict. On the one hand, the prospect of new therapies, even in the far future, is attractive in offering an alternative to organ and tissue donation. On the other hand, when this research involves the use of human embryos, it raises the question of its ethical acceptability and of the limits and conditions for such research ***(Skottman and Hovatta, 2006)***.

Aim of the work

The aim of this work is to highlight the stem cells and its definition, classification, different types, sources, uses in different diseases and ethical issues.

Historical review:

In the *19th century*, bone marrow (BM) was first in some way considered to be responsible for blood formation and might have healing properties and could be useful in the treatment of anemia. It was at this time, for example, that the health tonic derived from BM fats *"Virol"* became popular (Figure 1). The earliest attempts at using BM therapeutically were made in *1891* by **Brown-Sequard** and **D'Arsenoval** and reported by **Quine** in *1896*. BM was administrated orally to treat defects in blood formation ***(Quine, 1896).***

Fig. (1): *(Virol) Bone marrow has nutritive properties* ***(Quine, 1896).***

Further attempts using a glycerol extract of animal BM administrated orally to treat pernicious anemia were made. The rationale of treatment with BM was to provide missing nutrient ***(Fraser, 1894)***.

However, **Billings** in *1894* and **Hamilton** in *1895* attributed any positive effects of treatment to the mineral content of the elixir ***(Billings, 1894 and Hamilton, 1895)***. The first use

of BM administrated by a technique likely to result in the transfer of living cells was by **Schretzenmayr** in *1937*. Patients suffering from parasitic infection were treated with intramuscular injections of freshly aspirated autologous marrow with some benefits ***(Schretzenmayr, 1937)***. Subsequently in *1944*, **Bernard** injected allogeneic BM into the medullary cavity in patients with BM deficiency but without success ***(Bernard, 1944)***.

The first clinical application of BM followed rapidly on the heels of experimental work. The first attempts to intensify antitumor treatment by myeloablative therapy and autologous marrow transplant rescue were carried out in *1956* by **Ferribee** in the United States and others in Europe ***(Kurnick et al., 1958)***. Treatment success was limited by lack of knowledge of how to administer high-dose therapy and inability to provide adequate supportive care for marrow failure. Early clinical marrow transplant attempts are well reviewed by **Pegg**. In retrospect, it appears that there may have been at least 6 patients with aplastic anemia rescued from marrow failure by marrow donation from their identical twin ***(Pegg, 1966)***.

In *1980s*, the indication for bone marrow transplantation (BMT) expanded to include a wide variety of malignant and non-malignant disorders and donors other than human leukocyte antigen (HLA)-identical siblings, including matched but unrelated donors, have been increasingly used ***(Lehn, 1990).***

The progress in BMT was faced by the biological problems of graft versus host disease (GVHD) and BM graft rejection on one hand and the relapse of leukemia on the other hand. The introduction of cyclosporine A for GVHD prophylaxis in *1980* made BMT safer and less toxic ***(Apperley et al., 1988).***

In *1990s*, a period of increasing uses of cytokines and growth factors supported the hematological and metabolic recovery ***(Barret, 1992).***

In *2000* and beyond, it has become increasingly necessary to use the term "hematopoietic stem cell transplantation (HSCT)" rather than "bone marrow transplantation" ***(Radeva et al., 2005).***

Definition of stem cells

Stem cells are unspecialized cells that can self-renew indefinitely, and can also differentiate into more mature cells with specialized functions. Depending on the origin, stem cells are classified as embryonic, fetal and adult stem cell ***(Vats et al., 2005).***

Embryonic stem cells (ESCs)

Human embryonic stem cells (hESCs) are Pluripotent cells which are isolated from the inner cell mass of human embryos. They have the potential to differentiate into all the tissues of the human body ***(Odorico et al., 2004).***

When a sperm fertilizes an egg it becomes what is known as zygote, many scientists view zygote as the ultimate stem cell because it can develop into any cell not only of embryo but also of surrounding tissues, such as placenta. Because the zygote has the highest degree of transdifferentiation, it is referred to as a *totipotent* stem cell. So totipotent cells are the first stage stem cells that can be found in zygote and develop into both embryonic and extra-embryonic tissues. Thirty hours after fertilization, the zygote begins to divide, and by fifth or sixth day the cells form a *blastocyst*. These cells are somewhat less potential for differentiation and more specialized than totipotent zygote stem cell; those on the outer surface of the blastocyst develop into placenta and other tissues that surround the fetus, while those inside, referred to as ESCs become the cells of the fetal organs and tissues. Such stem cells that can become any of the more than 200 types of cells in the body are called *pluripotent* stem cell as shown in *figure (2)* ***(Tzukerman et al., 2003).***