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Editorial

Stem cells in modern medical therapy: An overview☆

1. Introduction

The stem cells are found in multicellular organisms which can develop into specialized cells. Research into stem cells grew out of findings by Ernest A. McCulloch and James E. Till at the University of Toronto in the 1960s.[1,2] The characteristic features of stem cells include:

- Unspecialised cells capable of renewing themselves.
- Are undifferentiated Master cells that do not yet have a specific function but can change to any other cell type.
- Can be induced to become tissue or organ specific cells.
- Have unique regenerative abilities and serve as Internal repair system.

2. Classification

The stem cells are commonly classified into two types: Embryonic stem cells and Somatic stem cells. According to their potency they are further classified into five subtypes viz;

(a) Totipotent -can form all adult cell types plus the specialized tissues to support development of the embryo (e.g., zygote, morula)[3] (b) Pluripotent -can form most or all cell types in the adult (e.g., embryoblast) (c) Multipotent-can form multiple types of cells and tissues (e.g., placenta, cord blood, mesenchymal cells), (d) oligopotent -form only few cell types (e.g., lymphoid or myeloid stem cells) and (e) Unipotent -form only one specialized cell type (e.g., muscle stem cells) (Fig. 1).

The Embryonic stem cells (ESC) are cells of the inner cell mass at blastocyst stage of embryo. They are capable of forming embryonic tissue or any cell type of the body. They can be taken out from embryoblast and cultured.

The Adult Stem Cells (ASC) are found in adult tissues viz: bone marrow, muscle, brain etc. They are less versatile and more difficult to identify, isolate and purify. The adult stem cell types and hierarchies are as follows (a) Hematopoietic stem cells (HSCs) (b) Mesenchymal stem cells (MSCs), (c) Gut stem cells (GSCs), (d) Neural stem cells (NSCs). The others are surfaces of eyes (limbal), Skin, Testicles.

3. Stem cell niche

The future of a stem cell: i.e., decision to self-renew or differentiate based on the individual components and combinations of the factors in the extracellular environment.

The term stem cell niche refers to a micro-environment where stem cells are found, which interacts with stem cells to regulate cell fate. The word 'niche' can be in reference to the *in vivo* or *in vitro* stem cell micro-environment. During embryonic development, various niche factors act on embryonic stem cells to alter gene expression, and induce their proliferation or differentiation for the development of the fetus. Within the human body, stem cell niche maintains adult stem cells in a quiescent state, but after tissue injury, the surrounding microenvironment actively signals to stem cells to either promote self renewal or differentiation to form new tissues.

The various niche mechanisms are (a) Direct contact between the stem and niche cells. (b) Soluble factors released by the niche that travel to the stem cells. (c) Intermediate cells that 'communicate' between the niche and the stem cells.

The stem cells self-renew and differentiate to: (a) Make all the different kinds of cells in the body during development of an embryo from a single fertilized egg. (b) Maintain a pool of stem cells to be used throughout life. (c) replace damaged cells of body to carry on working.

3.1. *Functions of stem cells in body*

Normally the functions of stem cells in the body are, to: (a) regularly divide to repair and replace worn out tissues (as the gut and bone marrow) OR (b) only divide under special conditions (the pancreas and the heart). The stem cells in brain, viz. neural stem cells divide and differentiate to become neurons and glial cells however there is reduction in cerebral neurons at the rate of 1% a year beginning at the age of 50 but if the brain is kept active with analytical skills the stem cells become specialized to function as neurons and delay the onset of degeneration and dementia. Further without neural stem cells in the hippocampus, it would not be able to learn or remember.

☆"In the beginning there is the stem cell; it is the origin of an organism's life. It is a single cell that can give rise to progeny that differentiate into any of the specialized cells of embryonic or adult tissues" – STEWART SELL.

3.2. *Stem cell therapy*

Somatic (adult) cells reprogrammed to enter an embryonic stem cell–like state called Induced pluripotent stem cells (iPSCs) viz; Mouse iPSCs in 2006 and Human iPSCs in 2007, thus there is no need of embryo.[4]

Currently however the Hematopoietic Stem Cell Transplantation is being started in number of medical centers in India and abroad.

Hematopoietic Stem Cell Transplantation (HSCT) is the transplantation of blood stem cells derived from the bone marrow (in this case known as bone marrow transplantation) or blood. The matching is performed on the basis of variability at three or more loci (HLA) gene, and a perfect match at these loci is preferred, even if there is a good match at these critical alleles, the recipient will require immunosuppressive medications to mitigate graft-versus-host disease. The different types of donors for HSCT are:

(a) Allogenic Transplant Donor
- Related-usually a closed HLA matched sibling.
- Syngenic- A monozygotic or 'identical' twin of the patient. Extremely rare since few patients have an identical twin, but they offer a source of perfectly HLA matched stem cells.
- Unrelated-donor who is not related and found to have very close degree of HLA matching.

The HLA Antigens are a set of proteins on the surface of the cells. These set of HLA proteins are inherited equally from parents. The chances of having a full match are 1 in 3, the higher the number of matching HLA antigens, the greater the chance that the patient's body will accept the donor stem cells.

The HLA Compatibility is done as under: (a) Compatible donor is found by doing additional HLA testing from blood of potential donors. (b) The HLA genes fall in two categories Type I and Type II. (c) Mismatches of the Type I genes (i.e. HLA-A HLA-B, or HLA-C) increase the risk of graft rejection. (d) Mismatch of an HLA Type II gene (i.e. HLA-DR, or HLA-DQB I) increases the risk of graft –versus host disease.

(b) Xenogenic – Stem Cells Transplant

In this stem cells from different species are transplanted. There are no major ethical concerns and large amount of tissue is available but lifelong immune-suppression and risk of rejection are the major drawbacks.

4. Applications of stem cells

(A) Cell replacement therapy: The cell replacement therapies could treat injuries and various genetic and degenerative conditions such as muscular dystrophy, retinal degeneration and Alzheimer's disease and blood disorders (hemophilia) by the way of (a) Repair of defective cell types. (b) Delivery of genetic therapy and (c) Delivery of chemotherapeutic agents.

The various other diseases treated by cell replacement therapy are

(a) Burns via transplanting stem cells derived from the skin of the patient's unburned area (viz: only epidermis)
(b) Leukemias, by transplanting HSCs.
(c) Diabetes mellitus, by transplanting beta cells from donor organs[5]

The other areas where stem cell replacement therapy can be used are Heart diseases, Rheumatoid arthritis, Parkinsons disease etc.

(B) Drug testing

The role of stem cells in drug testing is as under

(a) Stem cells could allow scientists to test new drugs using human cell lines which could speed up new drug development
(b) Only drugs that are safe and have beneficial effects in cell line testing would graduate to whole animal or human testing
(C) Cloning: It refers to the process of creating copies of DNA fragments, cells, or organisms. There are two very different types of cloning: (a) Reproductive cloning (fusing somatic cell with enucleated oocyte). It is used to make two identical individuals. Dolly, the sheep, the first cloned mammal (5th July 1996–14th Feb. 2003) was a female domestic sheep and the first mammal to be cloned by Ian Wilmnut. It is difficult to do and unethical and illegal on humans. (b) Molecular cloning (amplifying DNA fragments containing whole genes). It is done in biotechnology research labs to study what a gene does

5. Discussion

The use of stem cell in medical therapy has given a new hope to millions of people who are suffering from the so called incurable diseases such as Dementia, Alzheimer's disease, Thalassemia, leukemia, Cerebral Stroke, muscular Dystrophies, cardiomyopathies, chronic obstructive pulmonary disease (COPD),[6] interstitial lung disease etc. The discovery of stem cells has revolutionized the modern medical therapy and has given birth to a new branch of medicine termed *Regenerative Medicine*. The Cord Blood (CB) has clearly emerged as a relevant source of rare, but precious, primitive hematopoietic stem cells that allow for long & short term repopulation of the blood system to replace diseased & damaged cells. Earlier the CB was used mainly for routine laboratory tests & to assess the health characteristics of the infant beyond these tests, CB was essentially considered a waste product scheduled for discard. But with the discovery of stem cells the CB turned from 'garbage to gold'.

"If the potential of stem cells is realized, it would mean an end to the sufferings of millions of people"

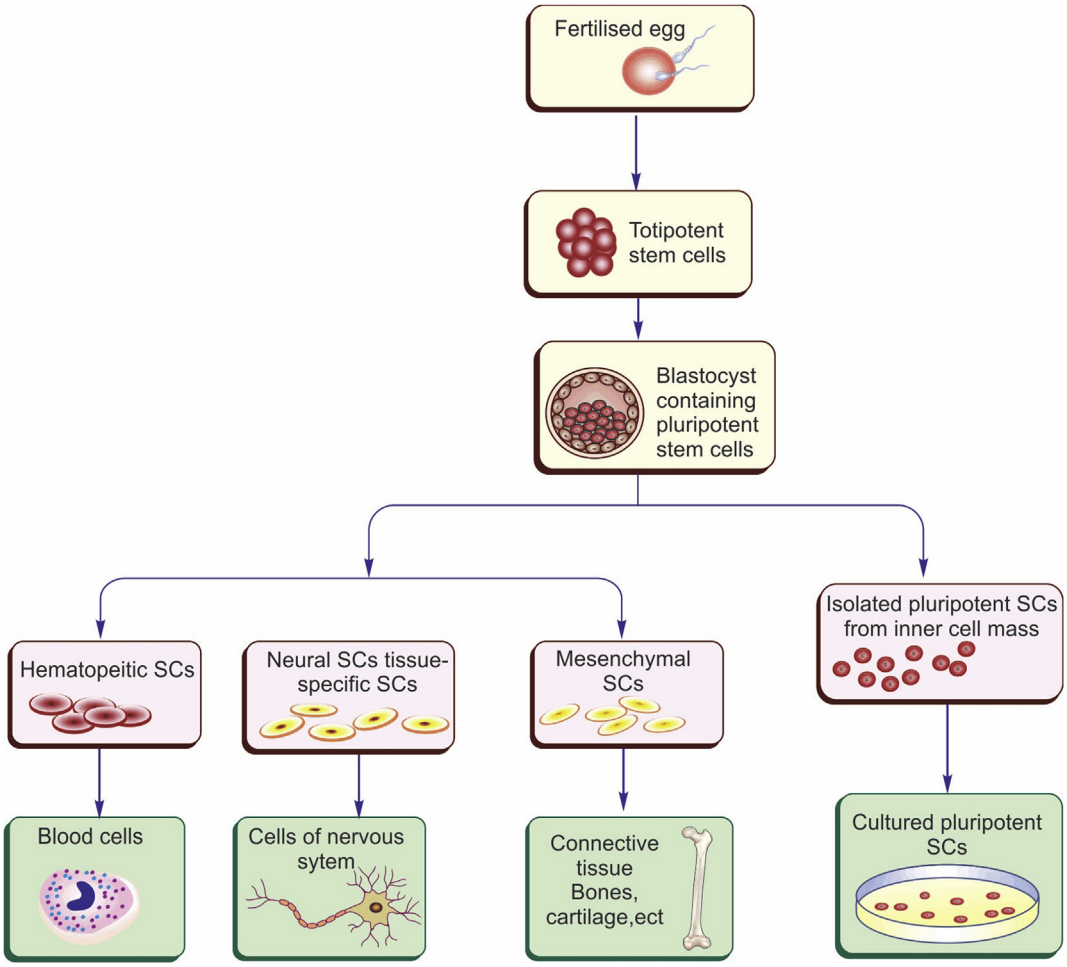

Fig. 1 – Stem cell types according to potency.

Therefore, I strongly feel that the need of the hour is, young researchers should take interest in this upcoming research area.

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