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STEM CELLS IN CURRENT TREATMENT-OVERVIEW

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ABSTRACT

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A Stem cells are biological cells found in all multicellular organisms, that can divide through mitosis and differentiate into diverse specialized cell types and can self renew to produce more stem cells. Umbilical cord blood is blood that remains in the placenta and in the attached umbilical cord after childbirth. Cord blood is collected because it contains stem cells which can be used to treat hematopoietic and genetic disorders. Stem cell treatments are a type of intervention strategy that introduces new cells into damaged tissue in order to treat disease or injury. The ability of stem cells to self-renew and give rise to subsequent generations with variable degrees of differentiation capacities, offers significant potential for generation of tissues that can potentially replace diseased and damaged areas in the body, with minimal risk of rejection and side effects. Physicians and researchers have begun to make progress evaluating the safety and efficacy of umbilical cord blood stem cells for certain therapeutic uses beyond blood cancers and genetic diseases of the blood, Type 1 diabetes mellitus, Parkinson's disease, Huntington's disease, Celiac Disease, cardiac failure, muscle damage and neurological disorders, and many others.

INTRODUCTION

Stem cells are biological cells found in all multicellular organisms, that can divide (through mitosis) and differentiate into diverse specialized cell types and can self-renew to produce more stem cells. In mammals, there are two broad types of stem cells: embryonic stem cells, which are isolated from the inner cell mass of blastocysts, and adult stem cells, which are found in various tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing adult tissues. In a developing embryo, stem cells can differentiate into all the specialized cells, but also maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues. Stem cells can now be artificially grown and transformed into specialized cell types with characteristics consistent with cells of various tissues such as muscles or nerves through cell culture. Highly plastic adult stem cells are routinely used in medical therapies. Stem cells can be taken from a variety of sources, including umbilical cord blood and bone marrow. Embryonic cell lines and autologous embryonic stem cells generated through therapeutic cloning have also been proposed as promising candidates for future therapies.^{1, 2, 3.} There are three sources of autologous adult stem cells: Bone marrow, which requires extraction by *harvesting*, that is, drilling into bone (typically the femur or iliac crest), Adipose tissue (lipid cells), which requires extraction by liposuction, and Blood, which requires extraction through pheresis, wherein blood is drawn from the donor, (similar to a blood donation) passed through a machine that extracts the stem cells and returns other portions of the blood to the donor.

POTENCY SPECIFIES THE DIFFERENTIATION POTENTIAL OF THE STEM CELL

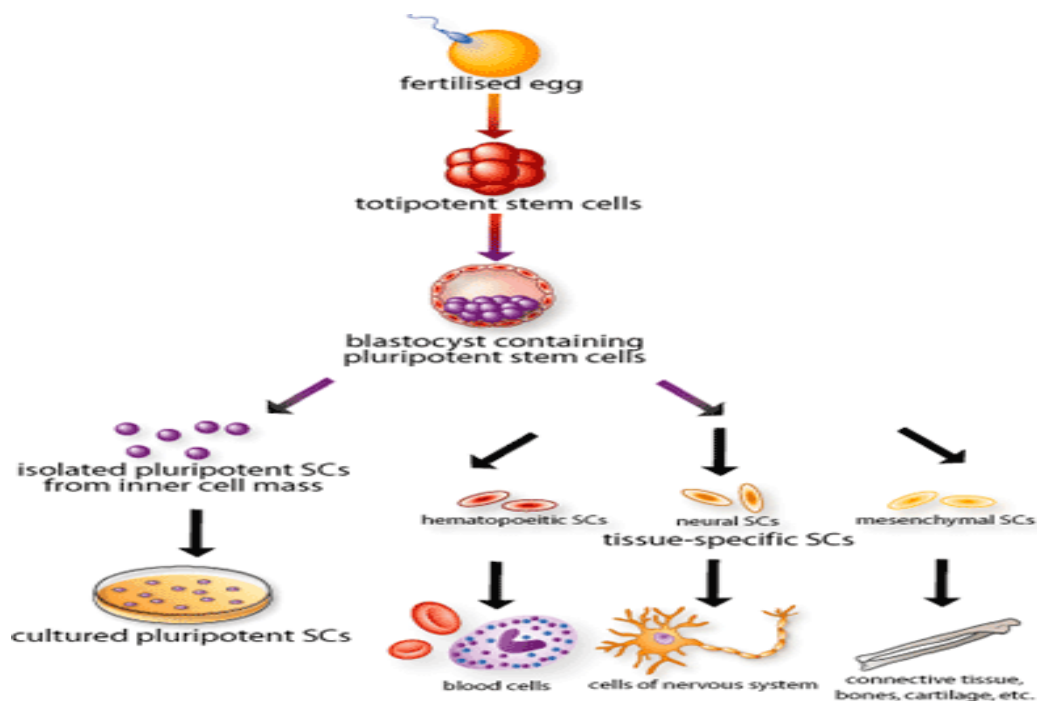
- Totipotent stem cells can differentiate into embryonic and extraembryonic cell types. Such cells can construct a complete, viable organism.⁴ These cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent.⁵
- Pluripotent stem cells are the descendants of totipotent cells and can differentiate into nearly all cells,⁴ i.e. cells derived from any of the three germ layers.⁶

- Multipotent stem cells can differentiate into a number of cells, but only those of a closely related family of cells.⁴
- Oligopotential stem cells can differentiate into only a few cells, such as lymphoid or myeloid stem cells.⁴
- Unipotent cells can produce only one cell type, their own,⁴ but have the property of self-renewal, which distinguishes them from non-stem cells (e.g., muscle stem cells).

TYPES OF STEM CELLS

Embryonic stem cells (ES cells)

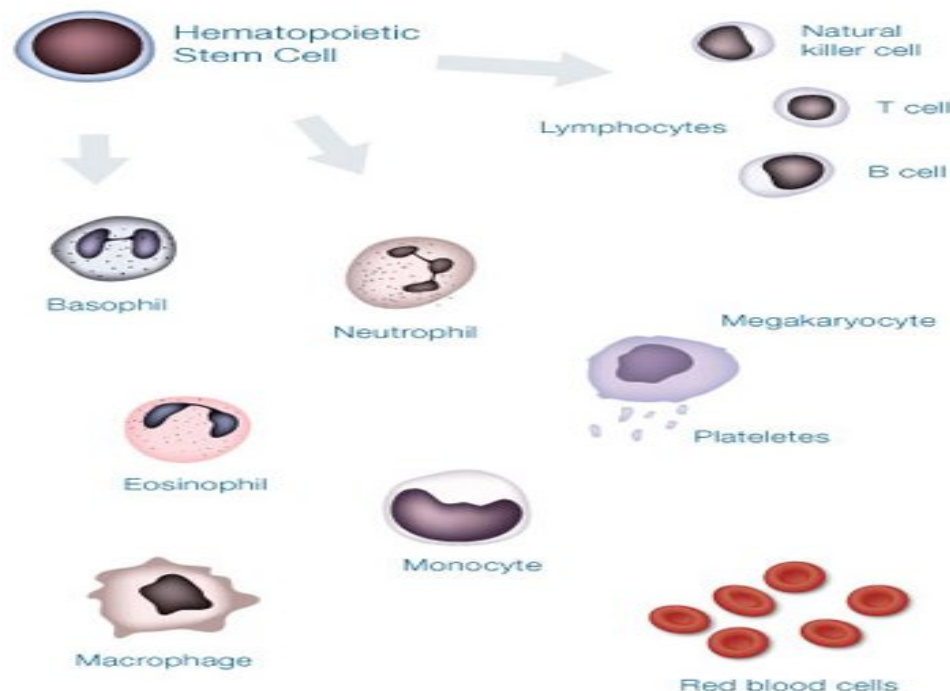
ES cells are pluripotent stem cells derived from the inner cell mass of the blastocyst, an early-stage embryo.^[1] Human embryos reach the blastocyst stage 4–5 days post fertilization, at which time they consist of 50–150 cells. Isolating the embryoblast or inner cell mass (ICM) results in destruction of the fertilized human embryo, which raises ethical issues. ES cells are pluripotent and give rise during development to all derivatives of the three primary germ layers: ectoderm, endoderm and mesoderm. In other words, they can develop into each of the more than 200 cell types of the adult body when given sufficient and necessary stimulation for a specific cell type. They do not contribute to the extra-embryonic membranes or the placenta.



Nearly all research to date has taken place using mouse embryonic stem cells (mES) or human embryonic stem cells (hES). Both have the essential stem cell characteristics, yet they require very different environments in order to maintain an undifferentiated state. Mouse ES cells are grown on a layer of gelatin and require the presence of Leukemia Inhibitory Factor (LIF). Human ES cells are grown on a feeder layer of mouse embryonic fibroblasts (MEFs) and require the presence of basic Fibroblast Growth Factor (bFGF or FGF-2). Without optimal culture conditions or genetic manipulation, embryonic stem cells will rapidly differentiate.

Hematopoietic Stem Cells (HSCs)

Hematopoietic stem cells (HSCs) are multipotent stem cells that give rise to all the blood cell types from the myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T-cells, B-cells, NK-cells). The definition of haematopoietic stem cells has undergone considerable revision in the last two decades. The hematopoietic tissue contains cells with long-term and short-term regeneration capacities and committed multipotent, oligopotent, and unipotent progenitors. HSCs constitute 1:10.000 of cells in myeloid tissue.



HSCs are found in the bone marrow of adults, which includes femurs, hip, ribs, sternum, and other bones. Cells can be obtained directly by removal from the hip using a needle and syringe, or from the blood following pre-treatment with cytokines, such as G-CSF (granulocyte colony-stimulating factors), that induce cells to be released from the bone marrow compartment. Other sources for clinical and scientific use include umbilical cord blood, peripheral blood a small number of stem and progenitor cells circulate in the bloodstream, in the past 10 years, researchers have found that they can coax the cells to migrate from marrow to blood in greater numbers by injecting the donor with a cytokine, such as granulocyte-colony stimulating factor (GCSF) and recent study shown that ex-vivo expansion of HSCs is possible in 3D bioreactor. Because HSCs are not generated in the adult but during the embryogenesis, many scientific groups are studying HSCs during the embryonic development. It is now well described in mammals that the first definitive HSCs are detected in the AGM (Aorta-gonad-mesonephros), and then massively expanded in the Fetal Liver prior to colonize before birth the bone marrow. Such fundamental research could help to understand the mechanisms that are responsible of HSCs generation and/or amplification, and to the discovery of new molecules that could eventually be used to maintain or expand HSCs *in vitro*.

Peripheral blood stem cells

While most blood stem cells reside in the bone marrow, a small number are present in the bloodstream. These peripheral blood stem cells, or PBSCs, can be used just like bone marrow stem cells to treat leukemia, other cancers and various blood disorders.

Since they can be obtained from drawn blood, PBSCs are easier to collect than bone marrow stem cells, which must be extracted from within bones. This makes PBSCs a less invasive treatment option than bone marrow stem cells. PBSCs are sparse in the blood stream, however, so collecting enough to perform a transplant can pose a challenge.

Umbilical Cord Blood Stem Cells

Newborn infants no longer need their umbilical cords, so they have traditionally been discarded as a by-product of the birth process. In recent years, however, the stem-cell are rich blood found in the umbilical cord has proven useful in treating the same types of health problems as those treated using bone marrow stem cells and PBSCs.

Umbilical cord blood stem cell transplants are less prone to rejection than either bone marrow or peripheral blood stem cells. This is probably because the cells have not yet developed the features that can be recognized and attacked by the recipient's immune system. Also, because umbilical cord blood lacks well-developed immune cells, there is less chance that the transplanted cells will attack the recipient's body, a problem called graft versus host disease.

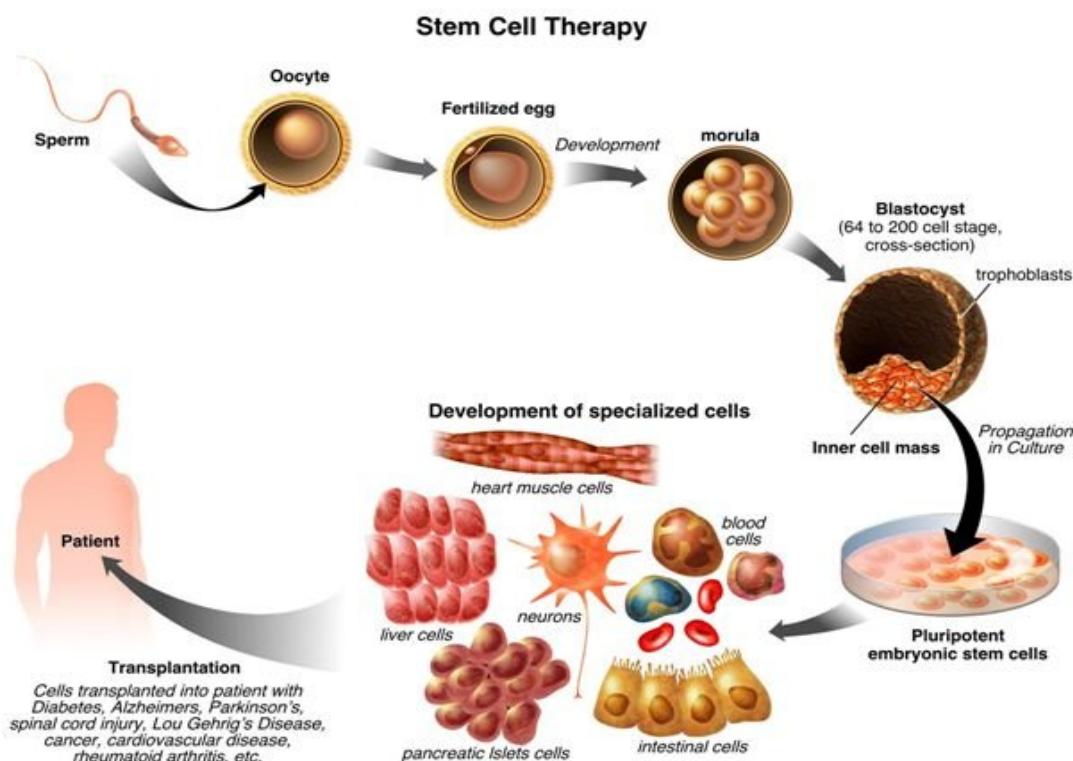
Both the versatility and availability of umbilical cord blood stem cells makes them a potent resource for transplant therapies.

Stem Cell Treatments

Several new studies have started to address this issue. This has been done either by genetically manipulating the cells, or more recently by deriving diseased cell lines identified by prenatal genetic diagnosis (PGD). This approach may very well prove invaluable at studying disorders such as Fragile-X syndrome, Cystic fibrosis, and other genetic maladies that have no reliable model system. Russian-American medical researcher who specialized in embryo and cellular genetics (genetic cytology), developed prenatal diagnosis testing methods to determine genetic and chromosomal disorders a month and a half earlier than standard amniocentesis. The techniques are now used by many pregnant women and prospective parents, especially those couples with a history of genetic abnormalities or where the woman is over the age of 35, when the risk of genetically-related disorders is higher. In addition, by allowing parents to select an embryo without genetic disorders, they have the potential of saving the lives of siblings that already had similar disorders and diseases using cells from the disease free offspring.⁷

As stem cells, HSC are defined by their ability to replenish all blood cell types (Multipotency) and their ability to self-renew. It is known that a small number of HSCs can expand to generate a very large number of daughter HSCs. This phenomenon is used in bone marrow transplantation, when a small number of HSCs reconstitute the hematopoietic system. This indicates that, subsequent to bone marrow transplantation, symmetrical cell divisions into two daughter HSCs must occur. Stem cell self-renewal is thought to occur in the stem cell niche in the bone marrow, and it is reasonable to assume

that key signals present in this niche will be important in self-renewal. There is much interest in the environmental and molecular requirements for HSC self-renewal, as understanding the ability of HSC to replenish themselves will eventually allow the generation of expanded populations of HSC *in vitro* that can be used therapeutically.



The cancer stem cells (CSCs) has several implications in terms of future cancer treatment and therapies. These include disease identification, selective drug targets, prevention of metastasis, and development of new intervention strategies. Normal somatic stem cells are naturally resistant to chemotherapeutic agents- they have various pumps (such as MDR) that pump out drugs, DNA repair proteins and they also have a slow rate of cell turnover (chemotherapeutic agents naturally target rapidly replicating cells). CSCs that have mutated from normal stem cells may also express proteins that would increase their resistance towards chemotherapeutic agents. These surviving CSCs then repopulate the tumor, causing relapse. By selectively targeting CSCs, it would be possible to treat patients with aggressive, non-resectable tumors, as well as preventing the tumor from metastasizing. The hypothesis suggests that upon CSC elimination, cancer would regress

due to differentiation and/or cell death. What fraction of tumour cells are CSCs and therefore need to be eliminated is not clear yet. A number of studies have investigated the possibility of identifying specific markers that may distinguish CSCs from the bulk of the tumor (as well as from normal stem cells).⁸ Proteomic and genomic signatures of tumors are also being investigated. In 2009, scientists identified one compound, Salinomycin, that selectively reduces the proportion of breast CSCs in mice by more than 100-fold relative to Paclitaxel, a commonly used chemotherapeutic agent.⁹

Diseases and conditions where stem cell treatment is promising or emerging.¹⁰ Bone marrow transplantation is, as of 2009, the only established use of stem cells. Medical researchers believe that stem cell therapy has the potential to dramatically change the treatment of human disease. A number of adult stem cell therapies already exist, particularly bone marrow transplants that are used to treat leukemia.¹¹ In the future, medical researchers anticipate being able to use technologies derived from stem cell research to treat a wider variety of diseases including cancer, Parkinson's disease, spinal cord injuries, Amyotrophic lateral sclerosis, multiple sclerosis, and muscle damage, amongst a number of other impairments and conditions.^{12,13} However, there still exists a great deal of social and scientific uncertainty surrounding stem cell research, which could possibly be overcome through public debate and future research, and further education of the public. One concern of treatment is the risk that transplanted stem cells could form tumors and become cancerous if cell division continues uncontrollably.¹⁴ Stem cells are widely studied, for their potential therapeutic use and for their inherent interest.¹⁵

Supporters of embryonic stem cell research argue that such research should be pursued because the resultant treatments could have significant medical potential. It has been proposed that surplus embryos created for in vitro fertilization could be donated with consent and used for the research. The recent development of induced pluripotent stem cells (iPS) cells has been called a bypass of the legal controversy. Laws limiting the destruction of human embryos have been credited for being the reason for development of iPS cells, but it is still not completely clear whether hiPS cells are equivalent to or human embryonic stem cells (hES). Recent work demonstrates hotspots of aberrant epigenomic reprogramming in hiPS cells.

CONCLUSION

Stem cell treatments are a type of intervention strategy that introduces new cells into damaged tissue in order to treat disease or injury. The ability of stem cells to self-renew and give rise to subsequent generations with variable degrees of differentiation capacities, offers significant potential for generation of tissues that can potentially replace diseased and damaged areas in the body, with minimal risk of rejection and side effects. Medical researchers believe that stem cell therapy has the potential to dramatically change the treatment of human disease. A number of adult stem cell therapies already exist, particularly bone marrow transplants that are used to treat leukemia. In the future, medical researchers anticipate being able to use technologies derived from stem cell research to treat a wider variety of diseases including cancer, Parkinson's disease, spinal cord injuries, Amyotrophic lateral sclerosis, multiple sclerosis, and muscle damage, amongst a number of other impairments and conditions.

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