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STEM CELLS: The Guardian of the Immune System- A Review Article

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Abstract

Stem cells serve as the foundational cells of all multicellular organisms having the potency to differentiate into wide range of adult cells. Stem cells are marked by their remarkable capacity for self-renewal and totipotency. While totipotency is predominantly exhibited by embryonic stem cells in their earliest stages, adult stem cells exhibit multipotency and adaptive plasticity, which harbors tremendous potential for harnessing as a wellspring of innovative therapeutic prospects in the future. Embryonic stem cells have the capacity to generate every specialized cell type in an organism (in other words, they are pluripotent). Adult stem cells, in contrast, have the capacity to give rise to the diverse cell types that specify a particular tissue. Multiple adult organs harbor stem cells that can give rise to mature tissue-specific cells. The Haematopoietic stem cells (HSCs) are considered the paradigmatic adult stem cell because it can differentiate into all the types of blood cells. Regenerative medicine is a multidisciplinary field concerned with the replacement, repair or restoration of injured tissues. This field emerged from the need for reconstruction in children and adults in whom tissue has been damaged by diseases, trauma and congenital anomalies. This promising area of science is also leading scientists to investigate the possibility of cell-based therapies to treat disease. Therapeutic benefits of bone marrow transplantation are well known but characterizing the potentialities of haematopoietic and mesenchymal cells is essential. Haematopoietic stem cells have been used for treating both haematopoietic and non-haematopoietic disorders. Ease of isolation, in vitro expansion, and hypoimmunogenecity have brought mesenchymal stem cells (MSCs) into limelight. Genetic regulation of adult stem cells in the form of Bmi-1, Notch, sonic hedgehog & wnt gene is also being worked upon and future can be regulation of stem cell differentiation in vitro, in vivo or both. It is the knowledge of regulators of stem cells which has opened the therapeutic usage of stem cells in the form of neuron regeneration, treatment of bone defect, drug testing, gene therapy and cell based therapy in the form of muscle damage, spinal cord injury, cancer therapy etc. In this study, we tried to provide the information about stem cells and their significant

Keywords: Stem cells, embryonic stem cells, adult stem cells, stem cells treatment, regenerative medicine, stem cell therapy**.**

Introduction

Stem cells have the remarkable potential to renew themselves. They can develop into many different cell types in the body during early life and growth. Researchers study many different types of stem cells. There are several main categories: the "pluripotent" stem cells (embryonic stem cells and induced pluripotent stem cells) and nonembryonic or somatic stem cells (commonly called "adult" stem cells). Pluripotent stem cells have the ability to differentiate into all of the cells of the adult body. Adult stem cells are found in a tissue or organ and can differentiate to yield the specialized cell types of that tissue or organ. Regenerative medicine is an emerging and rapidly evolving field of research and therapeutics to restore, maintain and improve body functions. Modern therapeutics is having a lot of hope from stem cell research in the field of organ transplantation and replacement of lost tissue. By virtue of self-renewal and potency, stem cells can form various types of tissue cells. The regulators of stem cell growth at genomic and proteomic level are identified and we might be able to control stem cell in vitro. In developed countries, stem cell transplant has become a therapeutic option but in developing countries, it is still under trial phase. There can be two sources of stem cells – Autologous and Allogenic. Autologous embryonic stem cells generated through therapeutic cloning and highly plastic adult stem cells from the umbilical cord blood or bone marrow are promising candidates. Allogenic stem cells can be derived from marrow, peripheral blood, cord blood, family donors or HLA typed or untyped unrelated donors.

Although the first attempts were made to fertilize mammalian eggs outside the body in 1878, research in human stem cell field grew out of findings by Canadian scientists Ernest A. McCulloch and James E. Till in the 1960s. The first use of bone marrow transplant in the present context to stem cell transplant (SCT) was done by Schretzenmyr in 1937 as these stem cells are known to be present in the bone marrow of adults. First animal made by in-vitro fertilization (IVF) in 1959 was also a step towards SCT. In late 1960s, teratocarcinomas were determined to originate from embryonic germ cells in mice and Embryonal Carcinoma (EC) cells were identified as a kind of stem cell. The first human egg was fertilized in vitro in 1968 and raised the possibility of exploitation of totipotency of stem cells. Cultured EC cells were explored as models of embryonic development in mice in 1970s. In 1981, it was proved that mouse Embryonic Stem (ES) cells are derived from the inner cell mass of blastocysts. Mouse ES cells were grown in vitro and ES cells injected into mice which formed teratomas. Between 1984-1988 pluripotent clonal cells called Embryonal Carcinoma (EC) cells were developed. When exposed to retinoic acid these cells differentiated into neuron-like cells and other cell types. A clonal line of human embryonal carcinoma cells was derived that yields tissues from all three primary germ layers in 1989.

They had limited replicative and differentiative capacity. In 1994, human blastocysts were generated and the inner cell mass was maintained in culture. Cells like ES cells formed in the center and retained stem cell like morphology. In 1995-96, non-human primate ES cells were maintained in vitro from the inner cell mass of monkeys. These cells were pluripotent and differentiated normally into all three primary germ layers. Embryonic Stem cells (ES) cells from the inner cell mass of normal human blastocysts were cultured and maintained normally for many passages in 1998. In 2000, scientists derived human ES cells from the inner cell mass of blastocysts. They proliferated in vitro for a long time and form all three germ layers and teratomas when injected into immune deficient mice. The onset of 21st century hampered the stem cell research due to changed US funding rules; however, the funding from The California Institute for Regenerative Medicine supported the research. Stem cell research became more promising as human ES cell lines were shared and new lines were derived, more research groups were focusing attention on the differentiation of cells in vitro.

STEM CELL- Definition

Stem cells are primal cells which are considered to be progenitor of more than 200 cell types present in adult body. All stem cells are unspecialized (undifferentiated) cells that are characteristically of the same family type (lineage). They retain the ability to divide throughout life and give rise to cells that can become highly specialized and take the place of cells that die or are lost. The rigorous definition

of a stem cell requires that it possesses two properties: self renewal and unlimited potency. Self renewal means the ability to go through numerous cycles of cell division while maintaining the undifferentiated state. Unlimited potency means the capacity to differentiate into any mature cell type. In a strict sense, this makes stem cells either totipotent or pleuripotent. Multipotent and unipotent are also described to define stem cell potency. These properties can be illustrated in vitro using methods such as clonogenic arrays where the progeny of cells is characterized. Two broad categories of stem cells exist: embryonic stem cells derived from blastocyst and adult stem cells which are found in adult tissue. In a developing embryo, stem cells are able to differentiate into all the specialized embryonic tissue. In adults, stem cells act as a repair system for the body replacing specialized damaged cells.

Potency specifies the differential potential of the stem cells. Totipotent stem cells are produced from the fusion of an egg and a sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent. These cells can differentiate into embryonic and extraembryonic cell types. Only the morula cells are totipotent able to become all tissues including a placenta. Pleuripotent stem cells are the descendents of totipotent cells and can differentiate into cells derived from 3 germ layers. Pleuripotent stem cells originate as inner cell mass within a blastocyst (Blastula). Blastocyst is a thin walled hollow sphere made up of an outer layer of cells, a fluid filled cavity and an inner cell mass containing pleuripotent stem cells. The blastocyst develops after cleavage and prior to implantation, in approximately 5 days. These stem cells become any type of tissue in the body excluding a placenta. Multipotent stem cells can produce only cells of a closely related family of cells e.g. hematopoetic stem cells differentiate into red blood cells, white blood cells, platelets etc. The process by which HSCs differentiate into mature blood cells is called hematopoiesis. Unipotent stem cells can produce only one cell type but have the property of self renewal which distinguishes them from nonstem cells.

Types of Stem Cell

There are two main types of stem cells, embryonic and non-embryonic. Embryonic stem cells (ESCs) are totipotent and, accordingly, they can differentiate into all three embryonic germ layers. On the other hand, non-embryonic stem cells (non-ESCs), also known as adult stem cells, are just multipotent; their potential to differentiate into different cell types seems to be more limited. Embryonic stem cells are derived from the inner cell mass of a blastocyst (a very early embryo) and the adult stem cells are derived from mature tissue. A large variety of cell types have been used for regenerative medicine, including adult cells, resident tissue specific stem cells, bone marrow stem cells, embryonic stem cells and the recent breakthrough discovery of induced pluripotent stem cells (iPS) from adult cells. Stem cells are broadly classified into two main categories: Embryonic stem cells (ESC) and Adult stem cells (ASC). Some important stem cells are as follows:

1. Human Embryonic Stem Cells

Embryonic stem cells (ESCs) are pluripotent cells which give rise to all somatic cell types in the embryo and ESCs are found in the inner cell mass of the human blastocyst, an early stage of the developing embryo lasting from the 4^{th} to 7^{th} day after fertilization. In normal embryonic development, they disappear after the 7^{th} day, and begin to form the three embryonic tissue layers. ESCs extracted from the inner cell mass during the blastocyst stage, however, can be cultured in the laboratory and under the right conditions will proliferate indefinitely. ESC can be a valuable tool for understanding the complex mechanisms involved in development of specialized cells and establishment of organ structures. Moreover, the indefinite self-renewal ability and plasticity of ESCs allows for *in vitro* generation of an unlimited number of distinct cell types, and has opened new avenues for regenerative medicine. To confirm that viable and stable ESCs lines are produced, the cells were continuously cultured for 4–5 months to demonstrate their ability to continuously proliferate, differentiate into cells from all three germ layers (endoderm, ectoderm, and mesoderm), and maintain a stable karyotype. Additionally, undifferentiated hESCs express a number of markers – including stage-specific antigens 3 and 4 (SSEA-3 and SSEA-4) and the transcription factors Oct4,

Sox2, and Nanog – that can be used to confirm the successful generation of a new hESC line and confirm the maintenance of a hESC state for existing lines.

2. Umbilical Cord Blood Stem Cells

The umbilical cord is the richest and purest source of stem cells. It contains two types of cells: haematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). Each type can transform into different cells and tissues, such as white and red blood cells, nerve and muscle tissue. In the late 1980s, umbilical cord blood was recognized as an important clinical source of HSCs. Blood from the placenta and umbilical cord is a rich source of hematopoietic stem cells, and these cells are typically discarded with the afterbirth. Cord blood stem cell technology has many advantages over embryonic and other adult stem cells for several reasons, including the following: (i) cord blood represents a potentially unlimited source of stem cells that can in theory be collected at every birth (ii) cord blood is relatively simple to process and store using tried and tested technology and, once frozen in liquid nitrogen, is biologically stable (iii) the collection of cord blood is a non-invasive procedure with no danger to either mother or baby. If cord blood is not collected, it is discarded as biological waste and (iv) cord blood carries low risk of infection.

3. Human Adult Stem Cells

Adult stem cells are undifferentiated cells that reside among differentiated cells in a tissue or organ. They have the ability to renew themselves and differentiate into specialized cell types.Adult stem cells are limited to differentiating into distinct cell types of their tissue of origin, and they are therefore multipotent or unipotent stem cells. The primary roles of adult stem cells are to maintain and repair the tissue in which they reside. Adult stem cells are rare and generally small in number, but they can be found in a number of various tissues of the adult organism; several examples of well-studied systems are presented below.

a. Hematopoietic stem cells: Hematopoietic stem cells (HSCs) reside in the bone marrow space, where they interact with complex and dynamic microenvironments. HSCs are multipotent precursors that have self-renewal capacity and the ability to regenerate all the different cell types that comprise the blood-forming system. The bone marrow is a primary lymphoid organ that supports self-renewal and differentiation of hematopoietic stem cells (HSCs) into mature blood cells. Although all bones contain marrow, the long bones (femur, humerus), hip bones (ileum), and sternum tend to be the most active sites of hematopoiesis. The bone marrow is not only responsible for the development and replenishment of blood cells, but it is also responsible for maintaining the pool of HSCs throughout the life of an adult vertebrate. The HSCs that is induced to differentiate loses its self-renewal capacity and makes one of two broad lineage commitment choices. It can become a common myeloid erythroid progenitor (CMP), which gives rise to all red blood cells (the erythroid lineage), granulocytes, monocytes, and macrophages (the myeloid lineage), or it can become a common lymphoid progenitor (CLP), which gives rise to B lymphocytes, T lymphocytes, and NK cells. Myeloid cells and NK cells are members of the innate immune system and are the first cells to respond to infection or other insults. Lymphocytes are members of the adaptive immune response and generate a refined antigen specific immune response that also gives rise to immune memory.

b. **Mesenchymal stem cells:** Mesenchymal stem cells (MSCs) are stromal cells that have the ability to self-renew and also exhibit multilineage differentiation. Due to their ability to differentiate into specialized cells developing from mesoderm, they were named as mesenchymal stem cells (MSCs). These are also known as multipotent cells, exist in adult tissues of different sources, ranging from murine to humans. MSCs can be isolated from a variety of tissues, such as umbilical cord, endometrial polyps, menses blood, bone marrow, adipose tissue, etc. This is because the ease of harvest and quantity obtained make these sources most practical for experimental and possible clinical applications.

c. Neural stem cells: Neural Stem Cells (NSCs) are the most primordial and uncommitted cells of the nervous system, and are believed to give rise to the vast array of more specialized cells of the CNS and peripheral nervous system. During development, the central nervous system (CNS) is generated from a small number of neural stem cells lining the neural tube. A great deal of experimental evidence has demonstrated that radial glia, the NSCs during mammalian CNS development, undergo both symmetric divisions to expand the NSC pool, and asymmetric divisions to give rise to intermediate progenitors (IPCs) and the differentiated cell types. The three major cell types in the CNS arise from NSCs in a temporally defined sequence, with neurons appearing first, followed by astrocytes, and then oligodendrocytes.

d. Pancreatic stem cells: Pancreatic progenitor cells are the multipotent stem cells originating from the developing fore-gut endoderm which have the ability to differentiate into the lineage specific progenitors responsible for the developing pancreas. They give rise to both the endocrine and exocrine cells. Exocrine cells constitute the acinar cells and the ductal cells. The endocrine cells constitute the beta cells which make insulin, alpha cells which secrete glucagon, delta cells which secrete somatostatin and the PP-cells which secrete pancreatic polypeptide. Pancreatic progenitor cells have been shown to arise from cells originating from the developing foregut during mammalian development.

e. Skin stem cells: Skin stem cells are multipotent adult stem cells present in the adult skin, which can self-renew and differentiate into different cell lineages of the skin. Skin stem cells are active during skin renewal, which occurs throughout life, and in skin repair after injury. The primary function of the skin is that of a physical barrier against the environment and diverse pathogens; therefore, its integrity is essential for survival. Skin regeneration depends on multiple stem cell compartments within the epidermis, which, despite their different transcriptional and proliferative capacity, as well as different anatomical location, fall under the general term of skin stem cells (SSCs).

Stem Cell Treatment for some important diseases

1. Stem cells therapy in neurological disorders: The mature central nervous system (CNS) has a limited capacity for self-repair; therefore many different cell-engineering strategies are used to regenerate damaged neurons. Stem cells will provide an inexhaustible source of neurons and glia for therapies aimed at cell replacement or neuroprotection in disorders affecting the brain and spinal cord. The most obvious and familiar application of stem cell research for nervous system disorders is through cell replacement therapy. The possibility of using stem cells as a source of neurons that can be implanted to replace cells and circuits lost in Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, or Alzheimer's disease is an exciting prospect.

a. Parkinson's disease (PD)- Parkinsons disease (PD) is a progressive neurodegenerative disorder initially described in 1817 by Dr. James Parkinson in "An Essay on the Shaking Palsy." PD is characterized clinically by the asymmetric and slowly progressive onset of parkinsonism benefiting from dopaminergic medication, and pathologically by the loss of dopaminergic cells and occurrence of Lewy bodies in the substantia nigra and specific brain stem areas. Typically, PD presents in the 60s with a slowly progressive bradykinesia (slowness) tremor at rest, and rigidity affecting one of the limbs, that benefits from dopaminergic medication, in the absence of atypical features (i.e., falls, dementia, or autonomic features early in the course of the disease).

Regarding human stem cell therapy, scientists are developing a number of strategies for producing dopamine neurons from human stem cells in the laboratory for transplantation into humans with Parkinson's disease. To overcome the shortcomings of fetal/embryonic tissues as sources for neural grafts and invasive surgical procedures, embryonic stem cells, neural stem cells derived from fetal or adult brain and other tissue stem cells derived either from bone marrow or umbilical cord blood have

been experimentally applied to generate dopaminergic neurons. Such cells will help to provide a clinically competent and effective therapeutic regime without the need for further interventions. Stem cells graft strategies are: *in vitro* pre-differentiation to dopaminergic neurons prior to transplantation; or *in vivo* differentiation of stem cells after implantation into the striatum or substantia nigra.

b. Alzheimer's disease (AD): Alzheimer's disease (AD) is an age-related neurodegenerative disease that is the most prevalent source of dementia in the elderly. Though primarily afflicting those aged 65 and over, AD also is increasingly being observed in younger people starting from around age 40. The pathological hallmarks of AD include extracellular deposit of Aβ amyloid plaques derived from *APP* (β-amyloid precursor protein) and intraneuronal neurofibrillary tangles (NFTs) from hyperphosphorylation of tau. Much of the efforts in AD research have been devoted to molecular pathways centered at Aβ or tau. The vast majority of novel treatment strategies are also targeting either Aβ or tau. To date, almost all advanced clinical trials on specific AD-related pathways have failed mostly due to a large number of neurons lost in the brain of patients with AD. Also, currently available drug candidates intervene too late. Stem cells have improved characteristics of self-renewal, proliferation, differentiation, and recombination with the advent of stem cell technology and the transformation of these cells into different types of central nervous system neurons and glial cells. Stem cell treatment has been successful in AD animal models. Recent preclinical studies on stem cell therapy for AD have proved to be promising. Cell replacement therapies, such as human embryonic stem cells or induced pluripotent stem cell–derived neural cells, have the potential to treat patients with AD, and human clinical trials are ongoing in this regard. However, many steps still need to be taken before stem cell therapy becomes a clinically feasible treatment for human AD and related diseases.

2. Stem cell therapy in cardiac repair: Cardiovascular disease is a major cause of morbidity and mortality throughout the world. Most cardiovascular diseases, such as ischemic heart disease and cardiomyopathy, are associated with loss of functional cardiomyocytes. Unfortunately, the heart has a limited regenerative capacity and is not able to replace these cardiomyocytes once lost. In recent years, stem cells have been put forward as a potential source for cardiac regeneration. Pre-clinical studies that use stem cell-derived cardiac cells show promising results.

Regenerative therapies are of major interest in cardiovascular medicine. Most cardiovascular diseases, including ischemic heart disease and cardiomyopathy, are associated with loss of functional cardiomyocytes and in other diseases, such as sick sinus syndrome, specific cardiac cell properties are missing. Unlike the Lernaean Hydra or the human liver, the heart does not have the ability to regenerate itself spontaneously once damaged. Cardiomyocytes are terminally differentiated and have a limited proliferative capacity. Lost cardiomyocytes are replaced by fibroblasts and connective tissue with the remaining cardiomyocytes becoming hypertrophic, which may eventually lead to heart failure. On the contrary, stem cells proliferate indefinitely and can be directed to differentiate into specialized cell types such as cardiomyocytes. The goal of stem cell-based regenerative medicine in cardiovascular disease, therefore, is to create healthy, functional cardiac cells that are able to integrate in the injured heart and restore its function. In the past decades, several stem cell types have been discovered. These stem cells can be subdivided based on their differentiation capacity. Pluripotent stem cells, such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), can differentiate into all three embryonic germ layers, whereas multipotent stem cells can differentiate into a number of closely related cell types of a single embryonic germ layer. Cardiomyocytes were derived from several stem cell sources. Other types of stem cells do not differentiate into cardiomyocytes themselves but support cardiac repair by different mechanisms.

3. **Regeneration of skeletal muscle cells:** Muscle injuries and trauma are common phenomena and may result in diminished muscle function and structural deformation. Although muscle tissue has a regenerative ability, it is limited and decreases with the age of the patient; once muscle loses its ability to regenerate, the defect fills up with scar and adipose tissue. Muscle dystrophies are severe diseases

and often lethal, as in the case of Duchenne muscular dystrophy (DMD). DMD is caused by the absence of a key protein, dystrophin, which causes chronic degeneration of the myofibers. Although extensive studies of this disease have been made, there is still no therapy that will prevent or halt the muscle deterioration. Muscle regeneration thus seems an attractive treatment. The capacity for this regenerative response is primarily due to a mononuclear cell population termed satellite cells.

Satellite cells, also known as myosatellite cells, muscle stem cells or MuSCs, are small multipotent cells with very little cytoplasm found in mature muscle. Satellite cells are precursors to skeletal muscle cells, able to give rise to satellite cells or differentiated skeletal muscle cells. They have the potential to provide additional myonuclei to their parent muscle fiber, or return to a quiescent state. More specifically, upon activation, satellite cells can re-enter the cell cycle to proliferate and differentiate into myoblasts. Myosatellite cells are located between the basement membrane and the sarcolemma of muscle fibers, and can lie in grooves either parallel or transversely to the longitudinal axis of the fibre. Their distribution across the fibre can vary significantly. Non-proliferative, quiescent myosatellite cells, which adjoin resting skeletal muscles, can be identified by their distinct location between sarcolemma and basal lamina, a high nuclear-to-cytoplasmic volume ratio, few organelles (e.g. ribosomes, endoplasmic reticulum, mitochondria, golgi complexes), small nuclear size, and a large quantity of nuclear heterochromatin relative to myonuclei. On the other hand, activated satellite cells have an increased number of caveolae, cytoplasmic organelles, and decreased levels of heterochromatin. Satellite cells are able to differentiate and fuse to augment existing muscle fibers and to form new fibers. These cells represent the oldest known adult stem cell niche, and are involved in the normal growth of muscle, as well as regeneration following injury or disease.

In undamaged muscle, the majority of satellite cells are quiescent; they neither differentiate nor undergo cell division. In response to mechanical strain, satellite cells become activated. Activated satellite cells initially proliferate as skeletal myoblasts before undergoing myogenic differentiation. Satellite cells express a number of distinctive genetic markers. Current thinking is that most satellite cells express PAX7 (Paired box protein Pax-7) and PAX3. Satellite cells in the head musculature have a unique developmental program and are Pax3-negative. Moreover, both quiescent and activated human satellite cells can be identified by the membrane-bound neural cell adhesion molecule (N-CAM/CD56/Leu-19), a cell-surface glycoprotein. Myocyte nuclear factor (MNF), and c-met proto-oncogene (receptor for hepatocyte growth factor (HGF)) are less commonly used markers. CD34 and Myf5 markers specifically define the majority of quiescent satellite cells. Activated satellite cells prove problematic to identify, especially as their markers change with the degree of activation; for example, greater activation results in the progressive loss of Pax7 expression as they enter the proliferative stage. However, Pax7 is expressed prominently after satellite cell differentiation. Greater activation also results in increased expression of myogenic basic helix-loop-helix transcription factors MyoD, myogenin, and MRF4 – all responsible for the induction of myocyte-specific genes. HGF testing is also used to identify active satellite cells. Activated satellite cells also begin expressing muscle-specific filament proteins such as desmin as they differentiate.

4. Stem cells in orthopedic Surgery: Mesenchymal stem cells have an ability to develop into any mesodermal tissue. Thus, they can be prompted to form precursor cells to develop into tissues including bone, cartilage, muscle, tendon, and ligament. Nonunion/Delayed union and bone defects following trauma, tumor or infection are challenging aspects of orthopaedic surgery that may require biologic augmentation for optimum healing. Tissue engineering, involving the use of stem cells with scaffolds such as hydroxyapatite (HA), demineralized bone matrix (DBM) and tri-calcium phosphate (TCP), have been studied and found to be useful for bridging bone defects. Due to absence of an extracellular matrix to grow on, MSCs alone have not proven to be beneficial for filling defects caused by simple/aneurysmal bone cysts. Healing rates, are however, enhanced when these are used in conjunction with scaffolds. Regenerative medicine with the use of stem cells is expected to

revolutionize patient treatment. Their utilization for bone tissue engineering with appropriate scaffolds provides us with exciting opportunities for research and development.

5. Stem cell in cancer therapies: Cancer is the most common cause of mortality and morbidity in U.K. Despite recent advances in the treatments of cancer, the clinical outcome is yet far away from expectation. Use of stem cells in immuno-modulation or reconstitution is one of the methods used for decades in cancer therapy. Stem cells have self-renewal capacity with highly replicative potential in multilineage differentiation capacity. Stem cell transplants are most often used to treat people with cancers that affect blood cells, such as leukemia, lymphoma, multiple myeloma, and myelodysplastic syndromes. They may also be used for neuroblastoma, Ewing sarcoma, brain tumors that have come back in children, germ cell tumors, and testicular cancer.

Stem cell transplantation may also constitute an option as adjuvant therapy for cancer, particularly in the patients receiving high doses of chemotherapeutic agents and/or radiation that, along with killing cancer cells cause the severe damage to normal tissues and/or destroy the hematopoietic cells. Thus, the stem cell transplants might replace the endogenous stem cells destroyed by high-dose cancer treatment, thereby producing healthy hematopoietic cell lineages and improving the immune system defense. For over 30 years, stem cells have been used in the replenishment of blood and immune systems damaged by the cancer cells or during treatment of cancer by chemotherapy or radiotherapy. Apart from their use in the immuno-reconstitution, the stem cells have been reported to contribute in the tissue regeneration and as delivery vehicles in the cancer treatments.

6. Diabetes Type I: In people who suffer from type I diabetes, the cells of the pancreas that normally produce insulin are destroyed by the patient's own immune system. New studies indicate that it may be possible to direct the differentiation of human embryonic stem cells in the cell culture to form insulin-producing cells that eventually could be used in transplantation therapy for diabetics.

7. Low blood supply: Now the method to produce large numbers of Red blood cells has been developed. In this method precursor Red blood cells, called hematopoietic stem cells are grown together with stromal cells, creating an environment that mimic the conditions of bone marrow, the natural site of red blood cell growth. Erythropoietin, a growth factor, is added coaxing the stem cells to complete terminal differentiation to red blood cells.

8. Treatment of baldness: Hair follicles also contain stem cells, and some researchers predict research on these follicle. Stem cell may lead to successes in treating baldness through "hair multi-placation" and known as "hair cloning" as early 2011. This treatment is expected to work through taking stem cells from existing follicles, multiplying them in cultures, and implanting the new follicle cells which have shrunk during the ageing process, which in turn respond to these signals by regenerating and once again making healthy air.

9. Teeth missing: The work on tooth generation has reached to a stage that it will be available to the general population in that decade. In theory, stem cells taken from the patient could be coaxed in the lab into turning into a tooth bud which, when implanted in the gums, will give rise to a new tooth, which would be expected to take two months to grow. It will fuse with jaw bones and release chemicals that encourage nerve and blood vessels to connect with it.

Genetic Regulations of Stem Cells

Each step a hematopoietic stem cell takes toward commitment to a particular cellular lineage is accompanied by genetic changes. Multiple genes that specify lineage commitment have been identified. Many of these are transcriptional regulators. For instance, the transcription factor *GATA-2* is required for the development of all hematopoietic lineages; in its absence animals die during embryogenesis. Another transcriptional regulator, *Bmi-1*, is required for the self-renewal capacity of

HSCs, and in its absence animals die within 2 months of birth because of the failure to repopulate their red and white blood cells. *Ikaros* and *Notch* are both families of transcriptional regulators that have more specific effects on hematopoiesis. Ikaros is required for lymphoid but not myeloid development; animals survive in its absence but cannot mount a full immune response.

Notch1, one of four Notch family members, regulates the choice between T and B lymphocyte lineages. More master regulators of lineage commitment during hematopoiesis continue to be identified. The rate of hematopoiesis, as well as the production and release of specific cell lineages, is also responsive to environmental changes experienced by an organism. For instance, infection can result in the release of cytokines that markedly enhance the development of myeloid cells, including neutrophils. Investigators have also recently shown that the release of mature cells from the bone marrow is responsive to circadian cycles and regulated by the sympathetic nervous system.

Conclusion

Stem cells pose a bright future for the therapeutic world by promising treatment options for the diseases which are considered as non-curable now a days. However, because of significant peri and post-transplant morbidity and mortality further research and trials are required to refine and optimize conditioning regimens and modalities of supportive care. Stem cell niches are discrete and dynamic functional domains that influence stem cell behavior to govern tissue homeostasis under diverse physiological (development and aging) and pathological (injury and disease) conditions. The niche must be flexible in order to coordinate stem cell behavior with homeostasis and repair; however, the plasticity of a niche may be co-opted in cancer and chronic disease.

Cell therapy and tissue engineering are part of the broader field of regenerative medicine, whose aim is the delivery of safe, effective and consistent therapies. The human body has an endogenous system of regeneration and repair through stem cells, where stem cells can be found almost in every type of tissue. This process is highly evolved through evolution, and so it is logical that restoration of function is best accomplished by these cells. Therefore, stem cells hold great promise for the future of translational medicine. Regenerative medicine is also a primer for pediatricians. By virtue of funding of stem cell research, we hope to see new horizon of therapeutics in the form of organ development and replacement of lost tissue such as hairs, tooth, retina and cochlear cells.

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