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International Journal of Clinical Biochemistry and Research

Journal homepage: https://www.ijcbr.in/

Review Article

Cognizance of stem cells: A gist

Debalina Sen[1], Venkata Bharat Kumar Pinnelli[2], Wilma Delphine Silvia C R[1,*], Priyanka A[1]

[1]*Dept. of Biochemistry, Sri Atal Bihari Vajpayee Medical College and Research Institute, Bangalore, Karnataka, India*
[2]*Dept. of Biochemistry, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka, India*

ARTICLE INFO

Article history:
Received 15-02-2021
Accepted 24-03-2021
Available online 30-04-2021

Keywords:
Stem cells
Differentiation
Adult stem cells
Embryonic stem cells
Induced pluripotent stem cells

ABSTRACT

Stem cells are undifferentiated cells which usually arises from one cell (clonal) and has the characteristic of self renewal i.e ability to proliferate and differentiate into various styles of cells (potent). Depending upon the potencies there are different sources of stem cells. Pluripotent cells have the flexibility to differentiate into tissues from the three germ layers. There are various sources of stem cells with varying potencies. Pluripotent cells have the ability to differentiate into tissue from all 3 germ layers (endoderm, mesoderm, and ectoderm). Multipotent stem cells may differentiate into tissue derived from a single germ layer like mesenchymal stem cells which form adipose tissue, bone, and cartilage thanks to the limited generation of most somatic cells, stem cells' capacity to replenish damaged somatic cells and maintain a self-renewing reservoir of progenitors is crucial for homeostasis in many tissues of the many organisms. Thus, there is an immense interest in understanding the mechanisms for self-renewal and differentiation in stem cells, given their potential applications in regenerative medicine and studies of human development or aging. This review article emphasizes on stem cells and its various types.

1. Introduction

Stem cells are undifferentiated cells that are present within the embryonic, fetal, and adult stages of life and gives rise to differentiated cells that are building blocks of tissue and organs.[1] The key characteristics feature of stem cells are: (a) self-renewal or the ability to extensively proliferate, (b) clonality which means that it usually arising from one cell, and (c) potency that is the ability to differentiate into different cell types. These properties may differ between various stem cells. For instance, embryonic stem cells (ESCs) derived from the blastocyst have a greater ability for self-renewal and potency while stem cells derived from the adult tissue have limited self-renewal capacity since they might not proliferate extensively and may only differentiate into tissue specific cells. The term stem cells was proposed by Valentine Hacker in 1968. There was a huge contribution by two Russian scientists - Alexander Maximov who proposed the existence of stem cells in the blood and Alexander Friedenstein who isolated the cells from the bone marrow and proposed that these cells can undergo differentiation into bone, cartilage and adipose tissue.[2] These cells were later called as mesenchymal stem cells (MSCs). There are two types of stem cells in the bone marrow: hematopoietic stem cells which has the ability to differentiate into various blood cells and mesenchymal stem cells (MSCs). Under no conditions these MSCs differentiate into blood cells despite the fact that MSCs belongs to the hematopoietic stroma. All stem cells incorporates a set of micro environmental factors referred to as "niche" that provides each the resting state of a stem cells and its mobilisation state needed for differentiation or division. Naturally, the cells that has the capability to differentiate into all sorts of adult tissues has a very short lifetime which is throughout the embryogenesis till the gastrula

* *Corresponding author.*
E-mail address: bowringbiochem@gmail.com (W. D. Silvia C R).

https://doi.org/10.18231/j.ijcbr.2021.001

stage. They can be cultivated in vitro (embryonic stem cells) or obtained from differentiated cells by introducing four reprogramming transcription factors – Oct3/4, Sox2, Klf4, and cMyc (induced pluripotent stem cells). Cells derived from the inner cell mass of blastocyst is cultured in vitro and are termed as embryonic stem cells (ESCs). Differentiated derivatives of ESCs have lot of therapeutic applications such as insulin producing cells, retinal pigment epithelium, neurons etc. Japanese scientists Takahashi and Yamanaka have used a technology, so that somatic cells are genetically reprogrammed into pluripotent state. This technology was developed in 2006 by which induced pluripotent stem cells (iPSCs) is obtained from the somatic cells of adults under laboratory conditions.[3] For instance, neural cells is created from iPSCs (Figure 5). Induced pluripotent stem cells (iPSCs) is cultured and can be grown unlimited, they additionally undergoes differentiation into each cell kind. iPSCs have already become a vital tool for modeling and learning human diseases, likewise as for drug screening. Cells differentiated from iPSCs potentially is used for replacement therapy in the treatment of diabetes, retinal degeneration, neurodegenerative pathologies, etc.

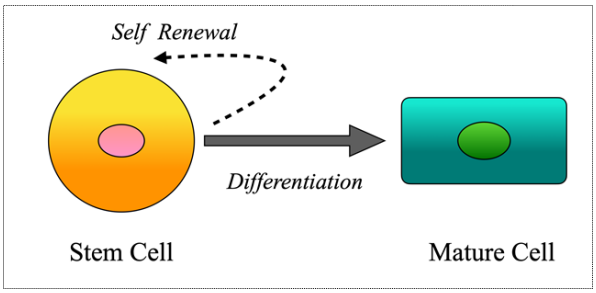

Fig. 1: Stem cells have the ability to **(a)** Self renew i.e it can create more stem cells indefinitely and **(b)** Differentiate into (become) specialized, mature cell types

2. Stem Cell Niche

In-vivo stem cell phenotype is mostly maintained because of its surrounding microenvironment or niche. This microenvironment is composed of cytokines, proteins, extracellular matrix, basement membrane. All these factors regulates the balance between differentiation and self-renewal of a stem cell. Hackney elucidated the genetic factors that maintains the balance between self-renewal and differentiation.[4] The stem cell niche provides an environment that maintains cells in an undifferentiated stem cell state. When there is a local injury in the surrounding tissue morphogenic signals are released which invokes differentiation and proliferation events within the stem cell niche. With the help of stem cell's intrinsic mechanisms a switch occurs from self-renewal (symmetric division) event to differentiation event (asymmetric division) ; thus mature stem cells are produced. Stem cell differentiation produces a mature cell also called progenitor cell and an addition stem cell. These progenitor cells further undergoes cell division to form fully differentiated cell with specific characteristics and function. Asymmetrical cell divisions maintains the stem cell pool by contributing mature differentiated cells for tissue growth, turnover, or repair. Symmetrical cell divisions maintains the increase or decrease in the stem cell pool by producing either two identical stem cells or two progenitor stem cells. Stem cells such as germ cells, HSC, cancer stem cells maintains their stem cell pool by utilising high telomerase activity without reaching replicative senescence.[5] Telomeres are the terminal ends of the eukaryotic chromosomes. It's primary role is to protect the chromosome from degradation; absence of telomerase activity results in shortening of chromosome until a threshold senescence limit is reached. Cells will be subjected to age dependent mortality, their replicative potential will be reduced and the cells cannot divide. On the other hand, theoretically it has been said that embryonic stem cells produces enough telomerase that their telomeres never get shorten. They are immortal.[6]

3. Embryonic State

3.1. Embryonic stem cells

Embryonic stem cells were first derived from mouse in 1981.[7] But a new era of stem cell biology began with the discovery of human embryonic stem cells in 1988. Zygote is formed after the fertilisation of sperm and ovum. Soon it develops into 8 cell stage known as the blastocyst. Blastocysts are composed of outer trophectoderm (TE) and the inner cell mass (ICM). TE forms the extra embryonic structure to support the developing embryo such as placenta whereas, ICM develops into epiblast and induces the development of a foetus. The cells from ICM is highly proliferative, pluripotent and remains undifferentiated. Human embryonic stem cells (hESCs) are isolated from the inner cell mass. During embryogenesis the cells divide into three germ layers: endoderm, mesoderm and ectoderm. Once they differentiate into one of the germ layers their potency becomes limited to the cells of the germ layers, in short they becomes multipotent stem cells.

3.2. Umbilical cord blood stem cells

After birth the umbilical cord and Placenta are generally discarded. The blood from the placenta and umbilical cord are rich in hematopoietic stem cells and it was recognised in 1980.[8] Advantages of cord blood stem cells includes (a) it has unlimited source of stem cells that can be collected after every birth (b) its collection does not have any risk to mother or child since it is a non invasive procedure (c) the risk of infection is very low[9] (d) when stored in liquid nitrogen it is biologically stable therefore cord blood is relatively simple to store and process.

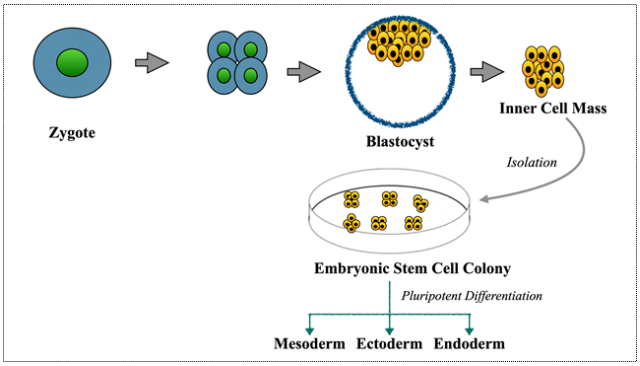

Fig. 2: Embryonic stem cells are isolated from cells in a blastocyst, a very early stage embryo. Once isolated from the blastocyst, these cells form colonies in culture (closely packed groups of cells). These cells are pluripotent, meaning they can differentiate into cells from all three germ layers (Mesoderm, Ectoderm and Endoderm) which later make up the adult body

3.3. Amniotic fluid-derived stem cells

These are multipotent, undifferentiated cells isolated from the amniotic fluid during the development of the embryo and expresses quite a range of embryonic stem cell markers. In vivo these cells were found to form teratomas and has the ability to form osteogenic, myogenic, adipogenic, neuronal, endothelial and hepatic cells. These cells shows characteristics of both embryonic and non - embryonic stem cells. Amniotic epithelial cells (AECs) are isolated from the amniotic membrane and expresses markers such as Nano, Oct-4 and alkaline phosphatase.[10] In addition, these cells has the ability to differentiate into Embryonic stem cells and Embryonic germ cells. When the cells are transplanted into immunodeficient mouse they can proliferate rapidly without loss of its pluripotent potential. Amniotic fluid stem cells is regarded to be the safest alternative to human embryonic stem cells.[11]

4. Non-embryonic State

Adult stem cells (ASC) or somatic stem cells are undifferentiated cells found among the differentiated cells in the human body after development. They play an important role in growth, repair and replacement of cells that are lost everyday.[12] Adult stem cells comprises of (a) Mesenchymal stem cells (MSC) - These cells are present in various tissues including bone marrow.[13] The cells from the bone marrow mainly differentiate into fat cells, bone and cartilage. (b) Neural stem cells (NCS) - gives rise to nerve cells and other cell types such as astrocytes and oligodendrocytes (c) Skin stem cells - gives rise to keratinocytes which acts as a protective layer of skin (d) Haematopoietic stem cells – give rise to all kinds of blood cells such as Red blood cell, White blood cells and platelets. They have a restricted differentiation option and a longer proliferation

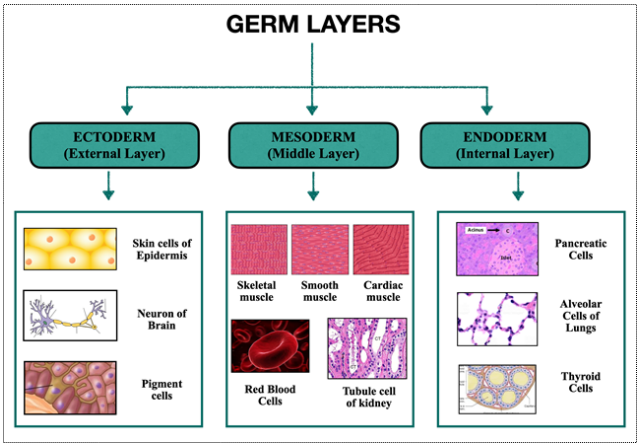

Fig. 3: Ectoderm: this is the outer layer of cells in the embryo and it will develop into skin, the nervous system, sensory organs, tooth enamel, eye lens, and other structures. Mesoderm: this is the middle layer of cells in the embryo and it will develop intomuscle, bone, blood, kidneys, connective tissue, and related structures. Endoderm: this is the inner layer of cells in the embryo and it will develop into lungs, digestive organs, the liver, the pancreas, and other organs

time than embryonic stem cells (ESCs). Adult stem cells can be reprogrammed back to their pluripotent state and this can be done by transferring adult nucleus into the cytoplasm of a oocyte or by fusing with a pluripotent cell. This technique was performed while cloning the famous sheep Dolly.[14]

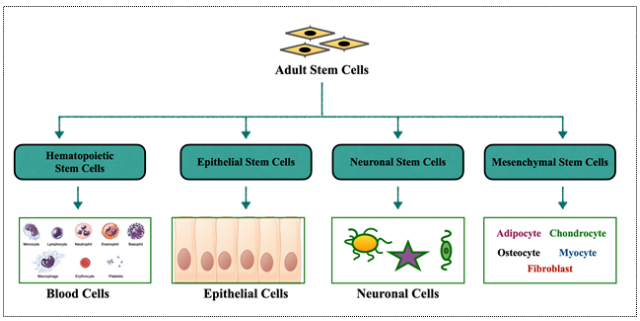

Fig. 4: Adult stem cells or Somatic Stem Cell are the cells that are harvested from tissues in an adult body. These cells are usually multipotent, that means they can differentiate into cells from some, but not all, of the three germ layers. They are thought to act to repair and regenerate the tissue in which they are found in, but usually they can differentiate into cells of completely different tissue types

4.1. Bone marrow stem cells

Bone marrow stem cells (BMCs) are of two types (a) Bone Marrow Hematopoietic Stem Cells, which constitutes only 0.05% of whole bone marrow, has the ability to form all blood lineages including erythrocytes, leukocytes,

and platelets. Since they have a unique morphology, with the help of labeled cell surface markers they can be easily tracked in the blood.[15] (b) Bone Marrow Stromal Stem Cells (BMSCs). The storma of the bone marrow is a heterogeneous population of connective tissue, which constitutes the niche of haematopoietic stem cells and supports bone marrow hematopoiesis. BMSCs can be isolated and cultured from the bone marrow after density gradient centrifugation. The mono nuclear cells isolated can be cultured in DMEM or alpha MEM media supplied with 10-15% fetal calf serum. BMSCs has the ability to get attached to the plastic dish used in cell and tissue culture laboratory, leaving behind adherent fibroblast-like cells. These cells has the capability to proliferate rapidly. Haematopoietic stem cells has been studied experimentally for 50 years and its the best characterized stem cell niche.[11] One of the most popular stem cell therapy is haematopoietic stem cell transplantation with a significantly high success rate and they have a great potential in regenerative medicine. Multipotent HSCs can be isolated from peripheral blood, umbilical cord blood and bone marrow, using autologous, allogenic or syngeneic procedure all the functional haematopoietic lineages in blood can be generated. Thus, leukaemia and anaemia which are due to poor haematopoietic system functioning can be treated with Haematopoietic stem cell transplantation.

4.2. *Mesenchymal stem cells*

Multipotent Mesenchymal stem cells (MSCs) are derived from various tissues such as skin, fat and bone marrow. It is reported that bone marrow and gingival tissue are the primary source of Mesenchymal stem cells.[16] Human adult MSCs are isolated from non hematopoietic tissues, for example, trabecular bone,[17] dental pulp,[18] synovium,[19] adipose tissue,[20] dermis,[21] lung.[22] The cells appears fibroblastic, have the ability to differentiate into multiple cell lineages and the cells can undergo many passages. Since the MSCs population is strongly adherent, they can be easily cultured on a appropriate substrate and wash other cells off. Dennis and Caplan, 2004 reported that Mesenchymal stem cells are essential to maintain the microenvironment which is required to support the hematopoietic stem cells in the bone marrow.[23] In vitro, MSC culture expresses certain surface markers, some of the positive markers include b-1-integrin, CD29, CD44, CD90, CD105, CD73 and shows negative expression of hematopoietic markers i.e, CD34, CD14, and CD45. Mesenchymal stem cells when cultured in vitro differentiate primarily into mesenchyme lineage - adipose tissue, bone and cartilage.[16,24]

4.3. *Pancreatic stem cells*

The adult pancreas has three types of tissue - the exocrine acini which secretes digestive enzymes, the ductal tree and the endocrine islets of Langerhans. There are five types of cells in the islets of Langerhans which includes alpha cell producing glucagon, beta cell producing insulin, delta cells secretes somatostatin, PP cells produces pancreatic polypeptide and epsilon cells secretes ghrelin. The ducts and the islets of the adult human pancreases contains multipotent cell progenitors.[25,26] The multipotent Pancreatic stem cells has been reported to be isolated from human fetal pancreas which expresses certain stem cell markers. When these cells are cultured ex vivo islet like cell clusters (ICCs) are formed which in turn can give rise to various pancreatic cell lineages such as insulin secreting alpha cells.[27] Type 1 diabetes which is due to autoimmune destruction of cells in the islets of pancreas can be reversed by islet cell transplantation.

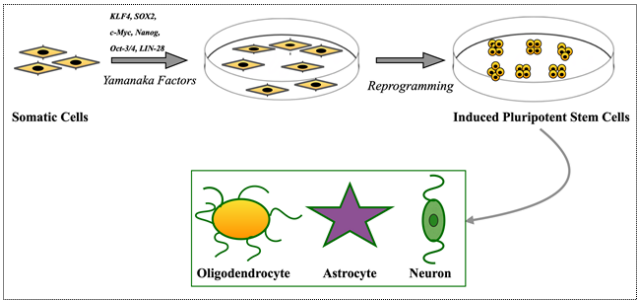

Fig. 5: The use of pluripotent stem cells for engineering neural tissue

4.4. *Skin stem cells*

The largest organ in the human body i.e the skin is derived from ectoderm germ layer during the process of embryogenesis. Multipotent stem cells were isolated from the dermis as reported in 2001, these cells can be cultured and it undergoes differentiation and proliferation to form mesodermal cells as well as neural cells. Previous studies have proved that the upper region of hair follicles and the bulge area is the niche for multipotent stem cells. They play an important role in epidermal regeneration after tissue injury and also responsible for long term hair follicle growth. To be more specific, multipotent epithelial stem cells (bESCs) which are present within the bulge area, expresses certain markers such as CD34, K5, 6 integrin which can proliferate to form follicular epithelium. The bulge area of the hair follicle also contains pluripotent epidermal neural crest stem cell (eNCSC) which has the property similar to embryonic neural crest stem cells, they undergoes self renewal and produces multiple cells such as neurons, Schwann cells, chondrocytes, melanocytes and smooth muscle cells.[28]

4.5. Neural stem cells

Neural stem cells (NSC) are multipotent cells which has continuous self-renewal capacity, can be isolated from the brain of embryos and adult and has the ability to generate cells of both neural and glial lineage.[29,30] When NSCs are cultured in vitro they cluster to form neurospheres and undergoes differentiation to form neuroectodermal lineages.[31] It was reported that when these neural stem cells injected into blastocysts of a mice they give rise to multiple types of tissues.[32] Adult neural stem cells differentiate to form multiple type of cells including neurones, astrocytes, oligodendrocytes thus providing a therapeutic advantage for Parkinson's disease as these cells can be used as transplants.

5. Application of Stem Cells in Major Diseases

5.1. Neurological disorders

Central nervous system (CNS) when matured, its self repair capacity decreases thus scientist are finding out new cell-engineering techniques to regenerate neurons which are damaged. Parkinson's and Alzheimer's are the most common neurodegenerative disorders with the advancement of age. In neurodegenerative disorders physiologically active neurons are lost over a period of time leading to morbidity and mortality.[33] Cell replacement therapy is one of the most common application of stem cells in Central nervous system disorders. With the help of this therapy there will be inexhaustible source of neurons which can be implanted to replace the damaged cells in Alzheimer's, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis.[29,34,35] In Alzheimer's disease, cognitive ability is hampered due to the damage of cholinergic neurons present in the basal forebrain. To prevent this, scientist have generated cholinergic neurons in vitro from neural stem cells and transplanted these neurons successfully. Lee and his group has converted mouse Embryonic stem cells to dopamine like characteristics cells,[36] similarly Kawasaki and his group have produced dopamine neurons without the formation of embroid body.[37] However transplantation of dopaminergic neurons shows long lasting improvement in few patients only.[38] The biggest limitation is the generation of functional dopamine neurons and the functions of other cell types for instance the glial cells. It is also important to integrate these cells successfully into the brain parenchyma as these cells are extremely site specific. The transplanted cells should have the capability to interlink with the host cells and establish the damaged neural circuit without immune rejection.

5.2. Skeletal muscle cells

Although skeletal muscle tissue has the ability to regenerate but it decreases as the age of the patient increases. When the muscle loses its regenerative ability, adipose tissue fills up the defect. Duchenne muscular dystrophy (DMD) is one of the serious diseases due to lack of dystrophin protein resulting in degeneration of the myofibers. Several studies have been carried out, however no therapy is available to prevent muscle deterioration; thus muscle regeneration seems to be an attractive treatment.[35,39] The regenerative capacity of the muscles is due to the presence of satellite cells. These are mononuclear cells which fuse together to form multinucleated myotubes. It is observed that transplanting one myofiber containing as less as seven satellite cells has the ability to give rise to more than hundred new myofibers.[40] DMD can affect various muscles in a multifocal manner therefore treating such damaged muscles using local implantation method becomes extremely challenging.[41] With the improvement of intra arterial and systemic cell delivery techniques this challenge can be addressed.

5.3. Bone disorders

Several molecular mechanisms has been established from stem cells for bone repair. One such advancement in replacing musculoskeletal tissues is manufacturing of scaffolds.[35] Several studies have shown that cells of ligament and tendon has multilineage differentiation potential. Lee and his group has observed that cells from synovial fluid has the capability to differentiate into chondrocytes, osteoblasts and adipocytes.[36] Cells from tendon also has the potential of multilineage differentiation. Stem cells have been extensively studied in meniscal healing by injecting synovium derived stem cells labelled with fluorescent protein in the knees of wild type rats which has defect in the meniscus.[42] Regeneration of bone is a complex process, there should be a well coordination between systemic and local soluble factors, endothelial progenitors, Bone marrow mesenchymal stem cells and extracellular matrix. Several studies demonstrated that bone marrow mesenchymal stem cells has the ability to expand ex vivo and can repair critical bone defects.

5.4. Cardiac disease

It has been estimated that approximately 16.7 million people die due to cardiovascular disease (WHO, 2006). The ultimate goal of stem cell therapy is to replace the damaged cardiovascular function. Various cell types required for properly functioning heart include Cardiomyocytes, vascular endothelial cell and smooth muscle cell. Recent studies have shown that embryonic and adult stem cells has the potential capability to develop into these cell types, establish new blood vessel and restore the damaged cardiac muscle. With such strategy patients with congestive heart failure and heart attacks can be treated. cardiomyocytes have been derived from human embryonic stem cells when engrafted in several rodent models; improvement in

cardiac function was noticed.[43] Studies have demonstrated that adult bone marrow stem cells have the capacity to give rise to endothelial cells, smooth muscle cells and myocytes in ischemic myocardium. Cardiac stem cells are undifferentiated cells recognised in many laboratories. Cardiac progenitor cells when cultured in vitro are multipotent while in vivo they give rise to cardiomyocytes and coronary vessels.[44] Messina identified clusters of self-adherent cells knows as cardiospheres that grew from adult cardiac tissue culture derived from murine and human hearts.[45] These cells have the properties of inducing myocardial and vascular regeneration after Myocardial Infarction. Smith and his group have demonstrated that these cardiospheres can be grown from human endomyocardial biopsy specimens.[46] Another population of stem cells known as unrestricted somatic stem cells derived from human umbilical cord blood stem cells when injected directly at thoracotomy immunosuppressed pigs after MI has minimised infarct scar size, enhanced perfusion, wall motion and cardiac function.[47] However, there are no clinical trials of human cardiac stem cells till date.

5.5. Cancer

To arrest the growth of cancer cell various studies have been carried out with several cancer cell line in vivo and in vitro. Cancer cells cause damage to hematopoietic cells and other normal tissues.[48,49] Patients receiving high doses of chemotherapeutic agents causes severe damage to the blood forming cells. The Hematopoietic stem cells from the bone marrow can be mobilised into the peripheral blood using AMD3100, G-CSF etc. These are the mobilizing agents which leads to the expansion of stem cells and their progenitors in bloodstream therefore the recovery time can be reduced after High-Dose Chemotherapy. Leukaemia stem cells also has the self renewal capacity and has specific phenotype such as CD123+ CD90-, CD117- thus maintaining the leukemic blasts.[50] Umbilical cord blood has CD16-/CD56+ natural killer cells. It shows high proliferation rate and cytotoxic effects against some cancers. These cells can be expanded in the presence of IL-12 or IL-15.[51] Dendritic cells derived from the Hematopoietic stem cells can be used as alternative treatment in cancer immunotherapy in order to replace the neoplastic cells. Stem cell transplants can be the promising therapy where the endogenous stem cells can be replaced with the new cells thus producing healthy hematopoietic cell lineages and immune defense system can be repaired.

5.6. Diabetes

With the technological advancements scientists have made considerable effort to restore the function of b cells or to generate surrogate b cells from various types of stem cells such as Adult stem cells, Embryonic stem cells for the treatment of Diabetes. Treatment using ESCs has not been approved yet therefore Adult stem cell is fairly used in research and medical practice.[52,53] Human pancreatic islets contains potential pancreatic stem cells; minute amount of pancreatic tissue has the ability to restore the maximum pancreatic b-cell mass. This might be due to the differentiation of b-cells and de differentiated b-cells produces pluripotent cells which in turn results in the production of more b-cells.[54,55] Studies have shown that in vitro adult pancreatic precursor cells can produce insulin and C-peptide.[56] It has been clearly established that insulin producing cells can be produced from stem cells however there are certain disadvantages such as teratoma formation, autoimmune response, transplantation issues which needs to be further explored. Various factors and pathways regulates the development of b cells, studies must be conducted to understand these pathways in order to find cure towards diabetes.[57] More research strategies are needed to activate pancreatic stem cells in the patients with diabetes to induce b-cell formation. Further research need to be conducted to isolate and expand these stem cells ex vivo for transplantation.

6. Conclusion

The stem cell concept developed in nineteenth century by some researchers who were working on the embryonic development. They proposed that these cells act as a starting point for the biological processes. During second world war the knowledge of stem cells advanced with the identification of a recovery factory in bone marrow which could regenerate the blood system. It was during this time stem cells were first used for bone marrow transplants for the treating cancer and other blood disorders. At present, there is a increasingly use of stem cells and every year 60,000 bone marrow operations are being conducted worldwide. Stem cells can not only be used in bone marrow transplants; the physicians are able to regenerate damaged tissue and develop new therapies in the field of regenerative medicine. Mechanism of cell signalling and cell differentiation can be understood with stem cells thus the underlying cause of the disease can be studied. Since stem cells can differentiate into large number of specialised cells it is used to test the safety of new medicines and therefore animal testing can be avoided. Today, many clinical studies have been conducted for the treatment of heart disease, retinal diseases, diabetes and neurological conditions. Use of stem cells have already being approved in south Korea and Canada for the treatment of osteoarthritis and myocardial infarction. Since 2008, eight successful patients have received trachea transplants. The tracheas were artificially created in the laboratory by growing the patients stem cells on a scaffold. Such approach can be used in future for creating other organs such as lungs, kidney,

heart valve etc. In 1981, scientists first isolated embryonic stem cells from mice blastocysts. Embryonic stem cells are extensively used to treat models of diabetes, parkinson's disease, myocardial infarction, spinal injury, and a severe genetic immune disorder. Embryonic stem (ES) cells are pluripotent and can differentiate into all three embryonic germ layers; because of this characteristics they are greatly used in transplantation therapies.

7. Source of Funding

None.

8. Conflict of Interest

The authors declare that there is no conflict of interest.

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Author biography

Debalina Sen, Tutor

Venkata Bharat Kumar Pinnelli, Professor

Wilma Delphine Silvia C R, Professor and HOD

Priyanka A, Tutor

Cite this article: Sen D, Pinnelli VBK, Silvia C R WD, Priyanka A. Cognizance of stem cells: A gist. *Int J Clin Biochem Res* 2021;8(1):1-8.