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A REVIEW: STEM CELLS AND CLASSIFICATION OF STEM CELLS BASED ON THEIR ORIGIN

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ABSTRACT

To personalize the treatment with stem cells, which is based on individual's symptoms and genetic condition, looks more promising, accurate and possible with the present available technology and to prove that prevention is better than cure, using stem cells therapy in treatment of many progressive diseases can help in preventing the severity of the condition. Stem cells have received considerable amount of attention since their discovery. Stem cell therapy has been studied and applied in real life situations, and it can be said that stem cells can be a promising tool to treat medical conditions and improve therapies based on individual's condition and interest. Stem cells are the future of personalized medicine and posses many applications in real life treatment. Stem cells are classified based on their origin and their properties. They posses multiple differential properties based on their origin and time of collection and kind of preservation.

KEYWORDS: Stem cells, personalized medicine, types of stem cells, different routes of administration, nanotech in stem cell, the future.

INTRODUCTION

Stem cells have received considerable amount of attention since their discovery. This discovery was a great breakthrough in medicine and exposed a new door for a whole new era

of technology and development. In newer ideas to treat the patient's illness with a safety deposit of cells from their own body.[1] Personalized medicine is the most promising avenue for treating degenerative diseases and injuries that could occur throughout lifetime. Stem cell therapy has been studied and applied in real life situations, and it can be said that stem cells can be a promising tool to treat medical conditions and improve self acceptance therapies on basis of patient's interests.[2] Stem cells are one of their kind, these are cells having the unique nature to give raise to specialized tissues; in addition they have capacity to self-renewal which is an extraordinary property they posses. Advancements in technology helped in identifying potency and efficacy of stem cells which is still an ongoing process till date, research is still going on to know the full potency and therapeutic effects stem cells can posses.[3] These cells are defined as clonogenic cells as they possess a unique capability of both self-renewal and multilineage differentiation.[1] Stem cells are undifferentiated cells capable of differentiation into multiple functional cell types. These cells are widely used in injury, repair and tissue regeneration. Adult stem cells have been isolated from a variety of tissues.[4] Several studies have been and are being carried out to verify if stem cells could become a source of stable differentiate cells capable of inducing tissue formation. Among which, mineralization of hard tissues is of great importance in normal growth and development. These cells make it a possible, fascinating source of stable differentiated cells.[5] As the technology is improving day by day, scientist's are further investigating the characteristics which are so specific making them ultimately special. The mechanisms by which they differentiate and repair must be understood, and reliability on stem cells is to be improved in future.[6]

Further knowledge on techniques for isolation, nature, and differentiation capability discussed below will have a strong supportive impact on our understanding and improvement of regenerative techniques in human beings. As we all know our body has a remarkable capability for regeneration. Different tissue cells such as blood and epithelia divide rapidly and are regenerated on timely basis throughout our body, however some cells in most of the tissues do not regenerate on timely basis but respond only to biological signals.[7] Human tissues are extremely different in term of regenerative properties; the connective tissues, like bone or cartilage can regenerate only small defects and in particular conditions, where as neural tissues or myocardium, does not show this property.[8]

Stem cells which are obtained from the fetus are said to have differentiating and self renewal capacity. These stem cells are found in fetal tissues and organs and have similar characteristics to in adult tissues, although they show a greater capacity to expand and multiply. They act as natural reservoirs for replacement cells and can be used for replacement when needed.[6] Stem cells are usually seen in high numbers before birth, and reduce considerably after birth and as reduce even further as age prolongs.[8]

The main properties that characterize stem cells are, the property to regenerate and multiply with differentiation going on simultaneously, as they divide symmetrically or asymmetrically.[6] Asymmetric mitosis is the process by which two intrinsically different daughter cells are obtained. The cells polarize themselves, so that cell fate deciding molecules are specifically are on one side, and later, the mitotic spindle aligns itself perpendicularly to the axis polarity. At the end of the process two different cells are obtained.[3] Several "loci" or "niches" with in our body are having pools of stem cells which can be used for regeneration later when needed. Although these pools exist accessing them is quite difficult with present day's technology. The interaction with biomaterials is a further point which needs to be considered for the therapeutic use of stem cells.[5]

CHARECTERISTICS

Stem cells are a promising tool for tissue regeneration, because of their particular characteristics.[5] Stem cells have differentiating capacity, with this property stem cells adapt and differentiate them self's by cross linkage method. Stem cells posses' simpler morphological structure compared to that of other cells in human body. It has often got a circular shape depending on its tissue lineage and a low ratio cytoplasm/nucleus dimension.[3]

TYPES

According to the ability and potency to differentiate into different cellular types, they are classified in to three types: **a) totipotent stem cells** - each cell has the capability of developing into an entire organism, **b) pluripotent stem cells** - cells which are grown under specific lab conditions and can be differentiated to multiple types of cells, **c) mlultipotent stem cells** – adult stem cells which are capability of multilineage differentiation.[1] Stem cell therapy has a promising future for tissue regenerative medicine. However, because SC technology is still in early stage of research, encouragement and support is needed to achieve successful clinical applications.[4]

Stem cells do have multiple applications in tissue engineering, regenerative medicine, cell therapy, and gene therapy as they have high differentiating capacity. There are various methods to treat a patient using stem cells out of which one method is directly injecting the cells in to the human body. Regenerative medicine is still in the verge of improvement, with process of restoration of cells, tissue which can be used for regenerative or personalized medicine.[6]

ORIGIN AND TYPES OF STEM CELLS

There are different sites in our body where stem cells can be found. Stem cells obtained from these locations are further classified on the basis of their anatomical origin and on function the cell with holds. As mentioned earlier the stem cells are primarily classified as (a) totipotent stem cells each cell has the capability of developing into an entire organism, (b) pluripotent stem cells embryonic stem cells that were grown in vivo under induced conditions and are capable of differentiating into all types of tissue, and (c) multipotent stem cells adult stem cells which are capable of differentiating in to many types of cells in wide diversity.[1]

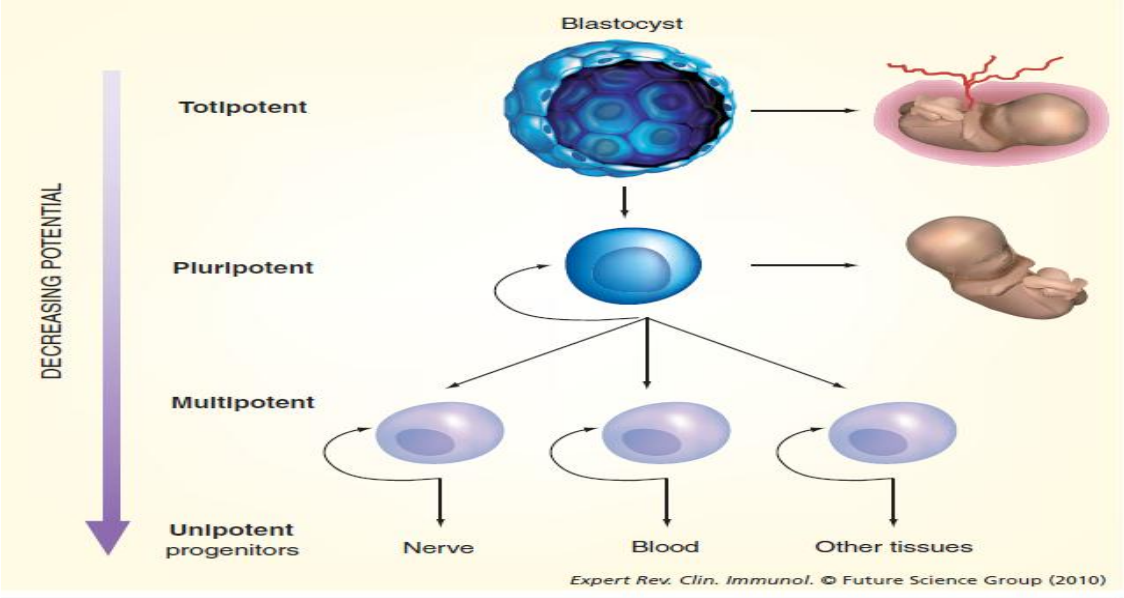

Fig 1: Potency of stem cells.

This schematic depicts the decreasing potential of stem cells as they undergo differentiation. The fertilized egg or blastocyst has the greatest potential of all and is said to be totipotent as it can give rise to not only all the cells and tissues comprising an embryo but also to extra-embryonic and placental tissue too. If the inner cell mass of the blastocyst (blue cluster of cells) is removed, the ability to generate placental tissue is lost, but these cells can still

generate the myriad of cell types within an embryo and, as such, are termed pluripotent cells. As pluripotent cells divide, they can form differentiated daughter cells, which can make cells of more than one cellular lineage (i.e., they are multipotent) while also maintaining the ability to self-renew (denoted by the curved arrow) which ensures maintenance of the stem-cell pool. Finally, unipotent cells can give rise to cells of only one particular lineage, such as nerve cells or hematopoietic cells, and cannot generate multiple lineages like pluripotent stem cells can.[24]

Further they are classified as below.

Table 1: Classification of stem cells.

Sl. No	Types	Classification	Sub-type
1.	Embryonic SC		
2.	Cord blood SC		
3.	Fetal SC		
4.	Adult	4.1:Mesenchymal SC.	
		4.2:Humal skeletal muscle derived SC.	
		4.3:Neural SC.	
		4.4:Neural crest SC.	
		4.5:Human epidermal neural crest Sc.	
		4.6:Neural preginator SC.	
		4.7:Hemopoitic SC.	
		4.8: Bone marrow stomal cells.	
		4.9:Olfactory enheathing SC.	
		4.10:Dental SC.	4.10.1: SHED.
			4.10.2: SC from apical papilla.
			4.10.3: Peridontal ligament SC..
			4.10.4: Denmtal follicle progenitor cells.
			4.10.5: Dental mesenchymal SC.
			4.10.6: Dental epithelial SC.
5.	Human induced pluripotent stem cells		

1. EMBRYONIC STEM CELLS

A zygote is the initial cell. Zygotes are produced by a fertilization process of two haploid cells, an ovum from a female, a sperm cell from a male, which combine to form one single cell. The blastocyst is the primary and initial stage called preimplantation stage where an embryo is aged approximately one week. Trophectoderm, is an outer shell like structure of cells filling cavity fluid and an inner cell mass (ICM). Embryonic cells (epiblast) are

contained in the ICM and generate the organism, whereas the surrounding trophoblast cells contribute to the placental chorion. Traditionally, embryonic cells are capable of a self-renewal and differentiation into cells of all tissue lineages, but not into embryonic annexes as such zygote. Embryonic cells can be cultured and maintained for a long time(1-2) yrs without alteration in the properties. Embryonic cells can be isolated by physical micro dissection or by complement-mediated immune dissection. Embryonic cells are preserved through fast freeze or vitrification techniques to avoid an early natural differentiation. Culturing embryonic stem cells requires a special care, in fact, under stem cells; a feeder layer of primary murine fibroblast is seeded in a permanent replication block that sustains continuously undifferentiated embryonic stem cells. They are maintained for a long time in culture to obtain a large pool of undifferentiated SCs for therapeutic and research applications.[1] Based on the proven evidence that the regeneration of conducive cell adhesion molecule, L1, enhances recovery in different types of mammalian nervous system lesions. In the context of regeneration after an injury, over expression of L1 may induce, for instance, erroneous growth/ sprouting axons, such as those of sensory nerve fibers causing allodynia and hyperalgesia. For therapeutic prospects, L1 expression levels should therefore be controllable in vivo. Furthermore a novel non viral doxycycline (DOX)-inducible human L1 expression system that comprises a single regulatable plasmid with a transrepressor along with a more efficient promoter, such as the CAG (chimeric cytomegalovirus and chicken b-actin) promoter, and that is efficiently regulatable in glioblastoma and neuroblastoma cells as well as predifferentiated H9-ESC-derived neural stem cells (H9NSCs) by DOX in vitro was developed.[9]

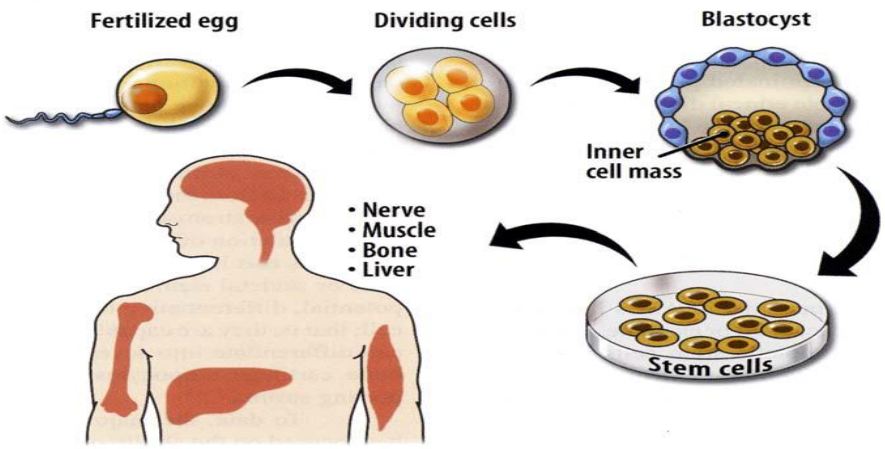

Fig. 2: Stem cells derived from the inner cell mass of blastocyst stage human embryos have been shown to differentiate into several different cell types and have the potential to one day replace or regenerate tissues.[7]

2. CORD BLOOD STEM CELLS

Stem cells present in and end of the cord tissues of the umbilical cord are called as cord blood stem cells. Controversies on embryonic cells still do exist as it does involve procedures needing insertion during the time of collection. Cord tissues are regarded as biological waste and are discarded after the child's birth; instead they can be used for collection and used along with mesenchymal stem cells for beneficial effects in neurological disorders like alzeihmers.[10] In UCB we can find two different types of stem cells, i.e. hematopoietic (UC-HS) and mesenchymal (UC-MS). It has been pointed out that UCB cells are characterized by a higher immunological tolerance than their adult counterpart. Umbilical cord mesenchymal stem cells can produce cytokines which provide grafting in the person donating the cells, in vitro SC survival and it is more efficient than bone marrow mesenchymal stem cells graft.[3]

3. FETAL STEM CELLS

Fetal stem cells are multipotent cells with the same functional properties of adult stem cells, but they are located in the fetal tissue and embryonic annexes. Further investigation is required to differentiate fetal stem cells from adult stem cells. Fetal stem cells are subdivided as (a)haemopoietic cells are located in blood, bone marrow etc., (b)mesenchymal ones located in blood, liver, BM, lung, kidney and pancreas, (c)endothelial ones found in BM and placenta, (d)epithelial cells are located in liver and pancreas whereas neural cells are located in spinal cord and brain.

The only source of fetal stem cells is fetal blood which is relatively safe for the fetus too. There is a routine procedure used now a days for diffuse technique for harvesting is ultrasound guided accession to fetal circulation.[3]

4. ADULT STEM CELLS

Since several decades research on regenerative potential of adult stem cells has been recognized. Recent studies have changed the older perception that adult stem cells are restricted by their potential barrier and proved the opposite. There are observations which state that cells from bone marrow can be used to generate various tissues including the brain tissue. If adult stem cells turn out to have the same potential as embryonic stem cells, then this can help in overcoming some of the ethical issues surrounding embryonic stem cells.[7] Adult stem cells can be obtained from the mesodermal tissues such as bone marrow, muscle, adipose tissue, synovium and periosteum. Stem cells have been also isolated from the tissues

of endodermal lineages such as intestine and from the ectodermal tissues including skin, deciduous teeth and nerve tissue.[3]

4.1. Mesenchymal stem cells

Adult stem cells are primarily unipotent cells, under certain conditions they show a plasticity that leads to differentiation into other cell types within the same tissue. This capacity occurs from transdifferentiation when there is presence of favorable conditions and adequate factors as occurs in mesenchymal stem cells, which are able to differentiate into cells of an ectodermal (neurons and skin) and endodermal (hepatocytes, lung and intestinal cells) or from the process of cell fusion, such as in vitro fusion of mesenchymal stem cells with neural progenitors or in vivo fusion with hepatocytes in the liver, Purkinje neurons in the brain, and cardiac muscle cells in the heart. This is the major reason why one of the cell types most widely used to date in cell therapy are mesenchymal stem cells (MSCs).[11]

MSCs are basically obtained from bone marrow, but they have been isolated from multiple other tissues, such as adipose tissue, periosteum, synovial membrane, synovial fluid (SF), muscle, dermis, deciduous teeth, pericytes, trabecular bone, infrapatellar fat pad, and articular cartilage. They are generally restricted to form only mesodermal specific cell types such as adiposities, osteoblasts, myocytes and chondrocytes, but several MSCs are capable to differentiate. Several studies report the differentiation of MSCs into various tissue lineages in vitro and the repair or "engraftment" of the damaged organs in vivo, they are even able to differentiate in endothelial cells and contribute to revascularization of the ischemic tissue. In particular, recent studies show that cultured MSCs secrete various bioactive molecules which have got anti-apoptotic, immune modulatory, angiogenic, antiscarring and chemo-attractant properties, providing a basis for their use as tools to provide and cultivate local regenerative environments in vivo.[3] Recent studies have also shown that MSCs support hematopoiesis and immune response regulation. They also represent an optimum tool in cell therapy because of their easy in vitro isolation and expansion and their high capacity to accumulate in sites of tissue damage, inflammation, and neoplasia. MSCs are therefore said to be useful in regenerative therapy, in graft-versus-host disease and in Crohn's disease, or in cancer therapy. The development in the future of an optimum methodology for genetic manipulation of MSCs may even increase their relevant role in cell and gene therapy.[11] Adult stem cells with which we have experience resides within the bone marrow of humans and many other species. Bone marrow is a complex tissue composed of the hematopoietic system and the

bone marrow stroma, two distinct but interdependent biologic cell populations.[7] There are total of 15 types of mesenchymal stem cells named and cultivated on basis of their anatomical origin, they are as follows.

1. Adipose-derived MSCs.
2. Amniotic fluid (AF) and amniotic membrane (AM) derived MSCs.
3. Bone marrow (BM) MSCs.
4. Dental pulp MSCs.
5. Endometrial MSCs.
6. Limb-bud-derived MSCs.
7. Menstrual-blood-derived MSCs.
8. Muscle- and periosteum-derived MSCs.
9. Peripheral-blood-derived MSCs.
10. Placenta- and fetal-membrane-derived MS.
11. Salivary-gland-derived MSCs.
12. Skin- and foreskin-derived MSCs.
13. Sub-amniotic human umbilical cord lining membrane derived MNCs.
14. Synovial fluid MSCs.
15. Wharton's jelly (WJ) derived MSCs.

This classification gives a clear idea on list of anatomical origins from where mesenchymal stem cells can be cultivated.[12]

4.2. Human skeletal muscle derived stem cells

Earlier skeletal muscle stem cells were thought to regenerate only muscle fibers when a muscle experiences muscle trauma. But then further study says that skeletal muscle tissue contains progenitors also called pluripotent stem cells that are able to generate and differentiate in to several other phenotypes.[13] In skeletal muscle, the stem cells are called satellite cells, they are in latent state and are activated by muscle tissue injury to proliferate and differentiate in to muscle tissue, and these cells have greater ability for muscle regeneration. Cardiac progenitor cells are known to me multipotent and may differentiate both in vitro and in vivo in to cardiomyocytes, smooth muscle cells and vascular endothelial cells.[11] There are 2 types of skeletal muscle stem cells based on morphology, a) spindle type of satellite cells, b) rounded cells. It was proven that some of the skeletal muscle stem cell cultures can be preserved for up to 6 months. There are different hypothesis but out of which 2 were selected , a) during embryonic development, some neuroectodermal precursors are

confined in extraneural areas such as muscle and its done under particular culture and isolated conditions and this could be used to induce the expression of neurogenic potential. 2) Muscle derived fibroblast and meningeal cells secrete stomal cell derived factor 1(SDF1).[13]

4.3. Neutral stem cells

The discovery and development done in finding NSC is a major step in the field of regenerative medicine.[14] Human Neural Stem Cells are the duplicate form of neural cells of the CNS and can differentiate so in to many forms. These cells are collected from the fetal, neonatal, adult brain, or from differentiated IPSC. These cells can be cultivated in vitro as aggregates, called neurospheres which contain all types of neurological cells observed in a living organism in the presence of growth factors like bFGF and EGF. In general, hNSCs (non- modified) present lower risk of tumor formation than pluripotent cells.[15]

Neural stem cells are present in the adult mammalian brain throughout life and generate functional neurons. The proliferation and differentiation of the neural progenitors is governed by multiple signaling mechanisms provided by the specialized microenvironment of the niche. The striking regenerative capacity of NSCs raises hopes for therapy for multiple degenerative disorders such as stroke, Parkinsonism, Huntington's and Alzheimer's disease. Generation and manipulation of specific neuronal subtypes require extensive understanding of the identity of different neural progenitor populations and the signals that govern their fate. It is although the presence of NSCs is accepted, whether a single population of aNSCs exists in vivo, or multiple functionally distinct populations constitute the endogenous pool remains to be substantiated. It is, however, of critical importance to elucidate the lineage potential of NSCs using in vivo experimental paradigms.[14]

4.4.Neutral crest stem cells

Neural crest stem cells (NCSCs) are born during vertebrate embryogenesis within the dorsal margins or the closing neural folds. Firstly they are integrated within the neuroepithelium where they are morphologically or structurally indistinguishable from the other neural epithelial cells. Post induction, NCSCs are delaminated through an epithelial tomesenchymal transition and they start migrating extensively to several different locations in the embryo where they contribute, according to microenvironment , into a variety of cell types including cartilage, bone, connective tissue, endocrine cells as well as neurons and glia. Since these cells are generated transiently within the embryo, it is considered that it may be more appropriate to describe the majority of NCSCs as progenitor cells, with a more limited

potential to self-renew and differentiate compared to that of true stem cells, it is said irrespective of that, NCSCs continue to attract the interest of the scientists because of their importance in vertebrate development and their potential application in modern regenerative medicine. The advantages of the use of NCSCs as compared to hESCs are both related to the no need to supply immunosuppressive medication since it can be used the patient's own cells and that their usage is not ethically problematic. In addition, compared to hiPSCs, there is no need for genetic manipulation. NCSCs can be found in different adult tissues including dermis, hair follicles, heart, cornea or gut.[15]

4.5. Human epidermal neutral crest stem cells (hEPI-NCSCs)

NCSCs have been successfully isolated from murine and human epidermis. These cells were designed like epidermal NC stem cells (EPI-NCSCs). This discovery has led to therapeutically significant findings of the last few years in the field of adult NCSCs. Skin being the most accessible tissue of the body, and for that reason is a good candidate to be used in autologous cell replacement therapies and regenerative medicine. EPINCSCs are multipotent stem cells, which are derived from the embryonic neural crest and are located in the bulge of hair follicles. Therefore they are readily accessible in the hairy skin by minimal invasive procedure. They are able to generate all major neural crest derivatives, including bone/cartilage cells, myofibroblasts, melanocytes and neurons. It has been observed that EPI NCSCs transplanted in spinal cord injury animal models, integrate and are able to differentiate into gabaergic neurons and myelinating oligodendrocytes, with no tumour or teratoma formation. The recovery mechanism seems to be related to the expression of neurotrophic and angiogenic factors by EPI-NSC's. Also hEPI-NCSCs can be isolated reproducibly, with high yield; they can be purified and expanded "ex vivo" into millions of stem cells that remain multipotent.[15]

4.6. Neural preginator stem cells.

Neural progenitor cells (NPC), like stem cells, have a tendency to differentiate into a specific type of cell, particularly their "target" cell. Transplantation of NPC for neurological diseases has been studied by a number of researchers. Transplantation of adult brain-derived NPC into the injured spinal cord of adult rats at 2 and 8 weeks after injury was done by few researchers. It was found that a substantial number of surviving NPC in the injured spinal cord up to 10 weeks after transplantation, at the sub acute stage of SCI, and the surviving NPC integrated principally along white matter tracts and displayed close contact with the host

axons and glial cells. It was also observed by them that injured rats receiving NPC transplants had improved functional recovery. The first clinical application of ESC-derived tissue in CNS is likely to consist of oligodendrocytes for the treatment of SCI. Most preclinical studies of cell replacement in SCI examine thoracic injury models. More than half of all human SCI occur at the cervical level. Remarkable differences between cervical and thoracic injury were enlarged neuronal pools, proximity of descending axons to their cell bodies and at level neuronal mediation of limb movement. It was noted that the transplanted NPC survived and differentiated, and animals that underwent transplantation had reduced infarct size and improved outcome on behavioral tests of sensorimotor and cognitive function.[17]

4.7. Hemopoeitic stem cells

Hematopoietic stem cells together with mesenchymal stem cells, the so-called "side population", and multipotent adult progenitor cells (MAPCs), are the stem cells forming bone marrow.33 Their role is maintenance and turnover of blood cells and immune system. The high rate of regeneration of the liver, as compared to other tissues such as brain tissue, is due to proliferation of two types of liver cells, hepatocytes, and oval cells (stem cells). In response to acute liver injuries (hepatectomy or hepatotoxin exposure), hepatocytes regenerate damaged tissue, while oval cells are activated in pathological conditions where hepatocytes are not able to divide, proliferate and converting into functional hepatocytes.[11]

Another potential source of multipotent stem cells for cell transplantation are hematopoietic stem cells (HSCs), which are functionally defined by their unique capacity to self renew and to differentiate in producing all mature blood types. HSCs have the potential to repopulate the removed bone marrow, a characteristic feature demonstrating their multiplying capacity. They can differentiate into erytroid, lymphoid and myeloid lineages. Isolation or selection of HSCs is done on the basis of cell surface marker phenotypes representing different stages of differentiation. The first cell-surface marker used to enrich human HSCs was CD34, a ligand for L-selectin that is expressed by a small percentage of blood or bone marrow cells. HSCs can be obtained from different anatomical regions like bone marrow, peripheral blood, or umbilical cord blood. The biggest difference in obtaining HSCs from different sources is the quantity of cells generated. Human umbilical cord blood (HUCB) may be a viable source of HSCs; very few HSCs can be obtained, thereby limiting use to children and not in adults. Bone marrow offers the best viable option for autologous HSCs administration and better yields; however this procedure is painful and may. Peripheral blood also contains circulating

HSCs. In the last few years evidence has emerged that granulocyte-colony stimulating factor (GCSF) can have a therapeutic potential in neurological disorders such as stroke. It has been shown to exhibit neuro protective and regenerative activity in experimental stroke models. Recent data support the notion that human HSCs play key regulatory roles in the maintenance of homeostasis and the repair of nervous system. For instance, systemic administration of human CD34+ cells to mice previously exposed to stroke 48 h earlier induces neovascularization in the ischemic zone there by creating a permissive microenvironment for survival of exogenous grafts and endogenous stem cells, essential for neural regeneration.[15]

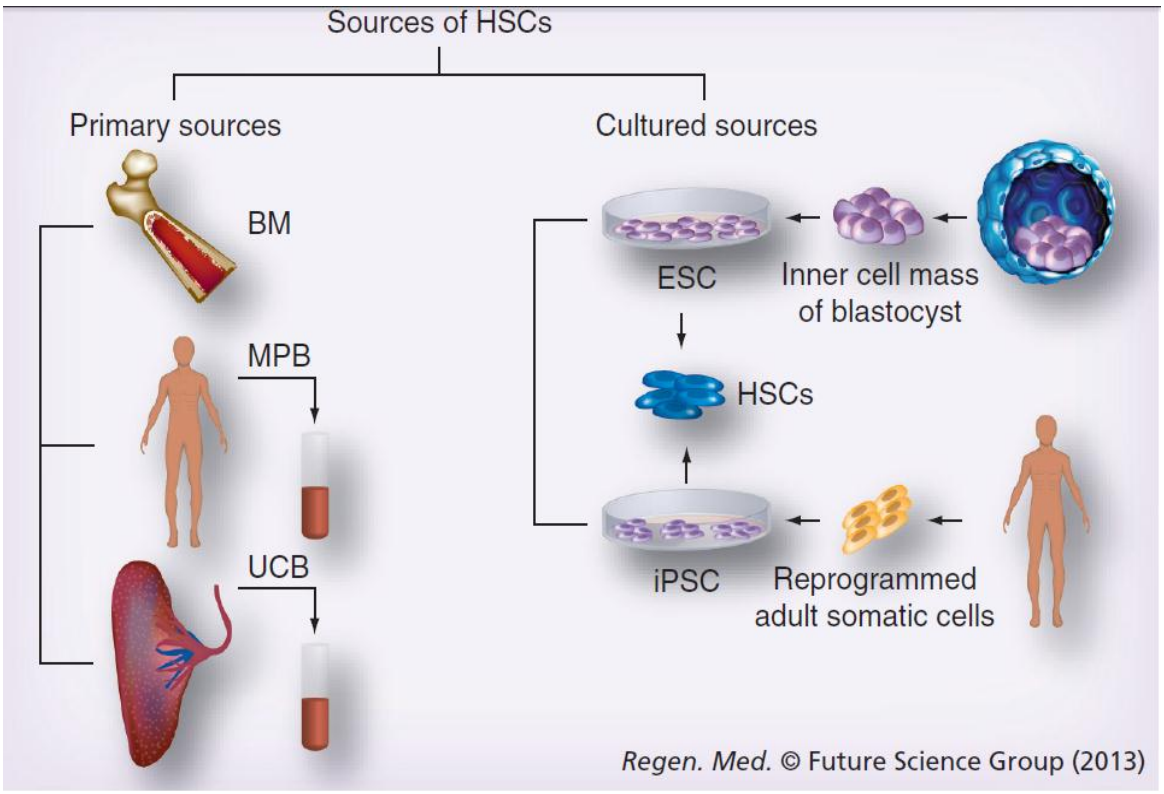

Fig. 3: Sources of hematopoietic stem cells.

HSCs can be obtained from primary tissue sources, such as BM, MPB and UCB, or from cultured cell sources, such as ESCs and iPSCs. Generating ESCs from 5–7-day-old embryos, and iPSCs from adult somatic tissues, is also shown. These established cell lines can be further differentiated to HSCs *in vitro*.

BM: Bone marrow; ESC: Embryonic stem cell; HSC: Hematopoietic stem cell;
iPSC: Induced pluripotent stem cell; MPB: Mobilized peripheral blood;
UCB: Umbilical cord blood.[21]

4.8. Bone marrow stromal cells

Bone marrow stromal cells (BMSC) gives rise to bone, cartilage and mesenchymal cells. Studies have shown that BMSC can differentiate into neural cells, including glial cells and neurons. BMSC have been studied for their effectiveness as transplants for the treatment of neurological disorders. Research in recent years, BMSC transplantation has emerged as a potential therapy for SCI and has been under rigorous experimentation in animal models. Undifferentiated BMSC were injected into the injured spinal cord, and different tests were conducted several weeks after transplantation. It was seen that BMSC transplantation into lesions of SCI had markedly therapeutic effects on tissue repair and axonal outgrowth, leading to elevated functional recovery. With developments in cell therapy research and regenerative medicine, BM-BMSC transplantation has been accepted widely as treatment for neurological disorders, including stroke, AD, HD and multiple sclerosis. No serious adverse events were seen to occur after stem cell transplantation in research projects these patients, suggesting that the protocol is safe.[17]

4.9. Olfactory enheathing cells

Olfactory ensheathing cells (OECs) are glial cells that help in enveloping bundles of olfactory axons, both peripherally in the olfactory nerve and within the olfactory nerve layer of the olfactory bulb as well as in the nasal olfactory mucosa. The OECs guide growing axons from the neurons of the nasal cavity of the olfactory mucosa to the olfactory bulb to form synapses in the brain. These cells are found in a fairly accessible portion of the brain and can be removed from a person without causing any harm, they have been considered as a attractive non embryonic source of cells with potential for transplantation based therapy in neurological diseases and degenerative disorders. A number of studies have shown that transplantation if the OEC's into the demyelinated spinal cord, can repair the defective myelin, restore conductance in remyelinated axons and improve of motor behavior. The particular mechanisms underlying functional improvement after OECs transplantation are not fully understood, human trials have been carried out to analyze the therapeutic effect of OECs transplantation on spinal cord injury and other CNS diseases including amyotrophic lateral sclerosis, multiple sclerosis and ataxia. The results showed that the transplant was safe and there were no adverse effects, however sensory improvement was modest. These results suggest a possible clinical benefit of hOECs after autologous transplantation in stroke patients.[15]

4.10. Dental stem cells

Dental SCs have been found in several tissues and can be classified into dental mesenchymal stem cells (MSCs) and dental epithelial stem cells. MSCs from human dental tissues include dental pulp stem cells (DPSCs) in human permanent teeth, stem cells from human exfoliated deciduous teeth (SHEDs), periodontal ligament stem cells (PDLSCs), and dental follicle stem cells (DFSCs) from human third molars. Dental epithelial stem cells have also been found in continuously growing incisors in molars in various mammalian species.[4]

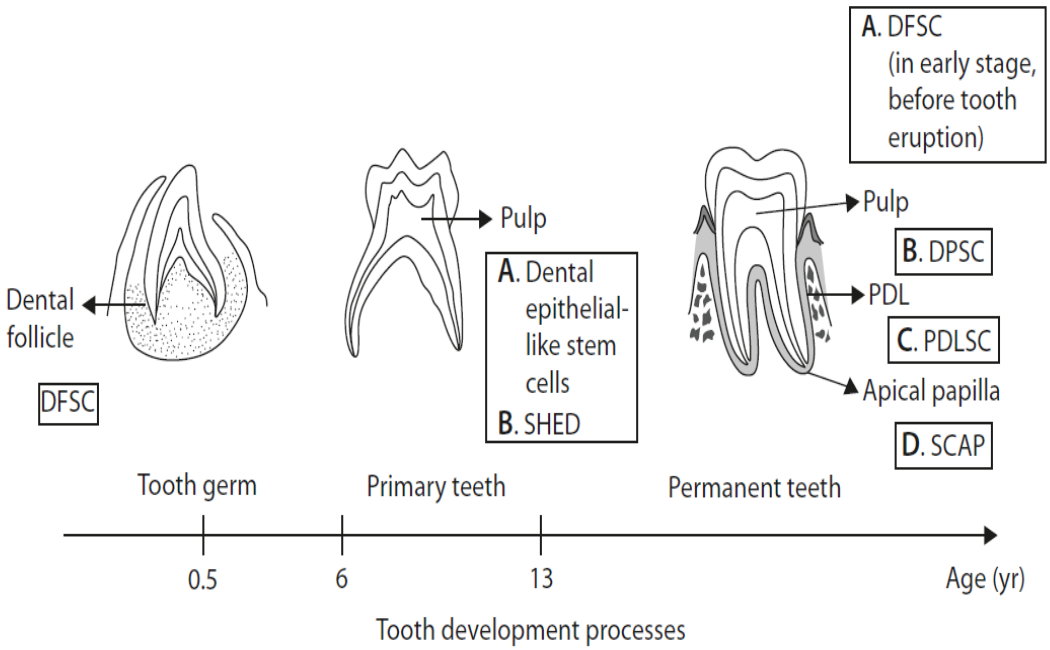

Fig. 4: Tooth developmental stages and the derivation of dental derived stem cells. DFSC = dental follicle stem cells; SHED = stem cells from human primary exfoliated deciduous teeth; DPSC = dental pulp stem cells; PDLSC = periodontal ligament stem cells; SCAP = stem cells from apical papilla.

4.10.1. SHED (Stem Cells from Human Exfoliated Deciduous Teeth).

SHED are immature, unspecialized cells in the teeth that are able to grow into specialized cell types by a process known as "differentiation." SHED appear at the 6th week during the embryonic stage of human development. Scientists believe that these stem cells behave in a different way than the post-natal (adult) stem cells. SHED cells multiply rapidly and grow much faster than adult stem cells, they are less mature, so they have the potential to develop into a wider variety of tissue types.[2]

SHEDs are multiple stem cells found in the pulp tissue of human exfoliated deciduous teeth. They were originally found as a population of extensively proliferative clonogenic cells, and can differentiate plastically into neuronal cells, adipocytes and odontoblasts. In addition, SHEDs show higher proliferation rates than DPSCs, and can form significant amounts of alveolar and orofacial bone for tissue regeneration.[4]

- Types of Stem Cells in Human Exfoliated Deciduous teeth

❖ Adipocytes: Adipocytes have successfully been used to repair damage to the heart muscle caused by severe heart attack. There is also preliminary data to say that they can be used to treat cardiovascular disease, spine and orthopedic conditions, congestive heart failure, Crohn's disease, and to be used in plastic surgery.

❖ Chondrocytes and Osteoblasts: Chondrocytes and Osteoblasts have successfully been used to grow bone and cartilage which would be suitable for transplant.

❖ Mesenchymal: Mesenchymal stem cells have successfully been used to repair spinal cord injury and to restore feeling and movement in paralyzed human patients. Since they can form neuronal clusters, mesenchymal stem cells also have the potential to treat neuronal degenerative disorders as Alzheimer's and Parkinson's diseases, cerebral palsy, and other disorders. Mesenchymal stem cells have more therapeutic potential than other type of adult stem cells.[4]

4.10.2. Stem cells from apical papilla

SCAP looks to be a different population of stem cells from dental pulp stem cells. In developing teeth, root formation starts as the epithelial cells from the cervical loop proliferate apically, and monitor the differentiation of odontoblasts from undifferentiated mesenchymal cells and cementoblasts from follicle mesenchyme. Dental papilla contributes to tooth formation and converts to pulp tissue as time prolongs. The root continues to develop after the bell stage; the location of the dental papilla becomes apical to the pulp tissue. SCAP show a two- to threefold higher proliferation rate than DPSC after the BrdU incorporation. SCAP, similar to DPSC, are more committed to osteo/dentinogenicity. Their adipogenic aspect of the multi potentiality was also confirmed. SCAP exhibit a heterogeneous nature by showing co expression of STRO-1 with a variety of osteo/dentinogenic markers and a low percentage of STRO-1–positive cells, while most of cells positive with osteo/dentinogenic markers in cultures.[1]

4.10.3. Peridontal ligament stem cells

As periodontal tissues are able to regenerate after mild trauma, researchers in the early 1970s Proposed a theory that PDLSCs might play an important role in periodontal repair.12 PDLSCs were first isolated, and were found to be capable of differentiating and multiplying into cementoblast-like cells, adipocytes and collagen forming cells.[4]

The periodontal ligament (PDL) is a specialized connective tissue derived from the dental follicle and originates from neural crest cells. The PDL connects the cementum to the alveolar bone, and functions primarily to support the tooth in the alveolar socket. A report identified stem cells in human PDL and found that PDLSC implanted into nude mice generated cementum/PDL-like structures that resemble the native PDL as a thin layer of cementum that interfaced with dense collagen fibers, same as to Sharpey's fibers. These cells can also differentiate into adipocytes, odontoblasts, myotubes, NFM-positive neuron-like cells, GFAP positive astrocyte-like cells, and CNPase-positive oligodendrocyte-like cells.[1]

4.10.4. Dental follicle progenitor cells:

DFPC are localized in the dental follicle, a mesenchymal tissue that surrounds the tooth germ and can be easily isolated after wisdom tooth extraction. These cells are available only from patients during wisdom tooth eruption. Human DFPC have the ability to differentiate toward alveolar osteoblasts, PDL fibroblasts, cementoblasts, adipocytes, and neuron-like cells. Long-term cultures of DFPC with dexamethasone have known to produce compact calcified nodules or which appeared to be as plain membrane structures of different dimensions consisting of a connective tissue–like matrix encapsulated by a mesothelium-like cellular structure. DFPC differentially express osteocalcin and bone sialoprotein after transplantation in immune compromised mice, but without any symptom of cementum or bone formation. DFPC are fibroblast like, colony-forming, and plastic-adherent cells.[1]

4.10.5. Dental mesenchymal stem cells

Human third molar tooth isolated DPSCs were differentiated into functionally active neurons and further shown to embrace the expression of nestin and GFAP under neural inductive conditions. DPSCs from human exfoliated deciduous teeth (SHED) were able to differentiate into neural cells by using growth factors such as Shh, FGF8, GDNF and forskolin. It was a two-step induction process (a) to form neurosphere like aggregates and (b) differentiation towards dopaminergic phenotype. Its therapeutic efficacy had been investigated in a Parkinsonian model. Increase of dopamine content in the striatum was noted to be observed

along with behavioral recovery. Neural cells could also be isolated directly from the dental pulp and found to be effective in cerebral stroke models. It has been reported that adult rat dental pulp cells have the ability to form neurospheres when cultured in serum-free culture medium on super-hydrophilic plates. Another group had showed the neuronal differentiation of DPSCs by using three-step protocol involving epigenetic reprogramming, which was followed by simultaneous PKC/PKA activation and then by incubation with neurotrophic medium resulting in robust neuronal differentiation.[12]

4.10.6. Dental epithelial stem cells

Tooth enamel, is the most mineralized tissue of the body, is the first formed in the crown stage of dental development. Before the tooth erupts into the mouth, the ameloblasts are broken down.

4.11. Human induced pluripotent stem cell

Human pluripotent stem cells holds great promise for basic research and regenerative medicine due to their inherent property to propagate infinitely, while still maintaining the potential to differentiate into any given cell type of the human body.[18] Embryonic stem cells like pluripotent stem cells can be generated by the simultaneous introduction of several factors, into somatic cells, yielding induced pluripotent stem (iPS) cells. This technology allows us to generate human pluripotent stem cells without human embryo.[19]

Generation of iPS cells does not require the destruction of a blastocyst (or an egg donor), and iPS cells are 'equivalent' to human ESCs. iPS cells are increasingly easy to generate, with the application of various methods to increase the efficiency of reprogramming, and with commercial reprogramming kits available, accessing these pluripotent cells should not be a major issue and further makes it even more easy.[20] ESCs and iPSCs are the more recent sources for obtaining HSCs, however, their potential use for human stem cell therapy is still under investigation. Complete in vitro differentiation of ESCs and iPSCs to RBCs, capable of maturation up to enucleated RBCs, and platelets from ESCs, has been demonstrated. Improvements in these protocols are required to scale up the cell numbers and prove their safety and efficacy.[21] These were first created in 2006 from adult somatic cells by a simple molecular genetic trick, induced pluripotent stem cells (iPS) system is the latest platform in stem cell research. Induced pluripotent stem cells are produced by nuclear reprogramming technology and they resemble embryonic stem cells (ES) in key elements, which give them the potentiality to differentiate in to any type of cell in our body.[22] which ultimately proves

that induced pluripotent stem cells can the future of both genetic, molecular and regenerative modification.

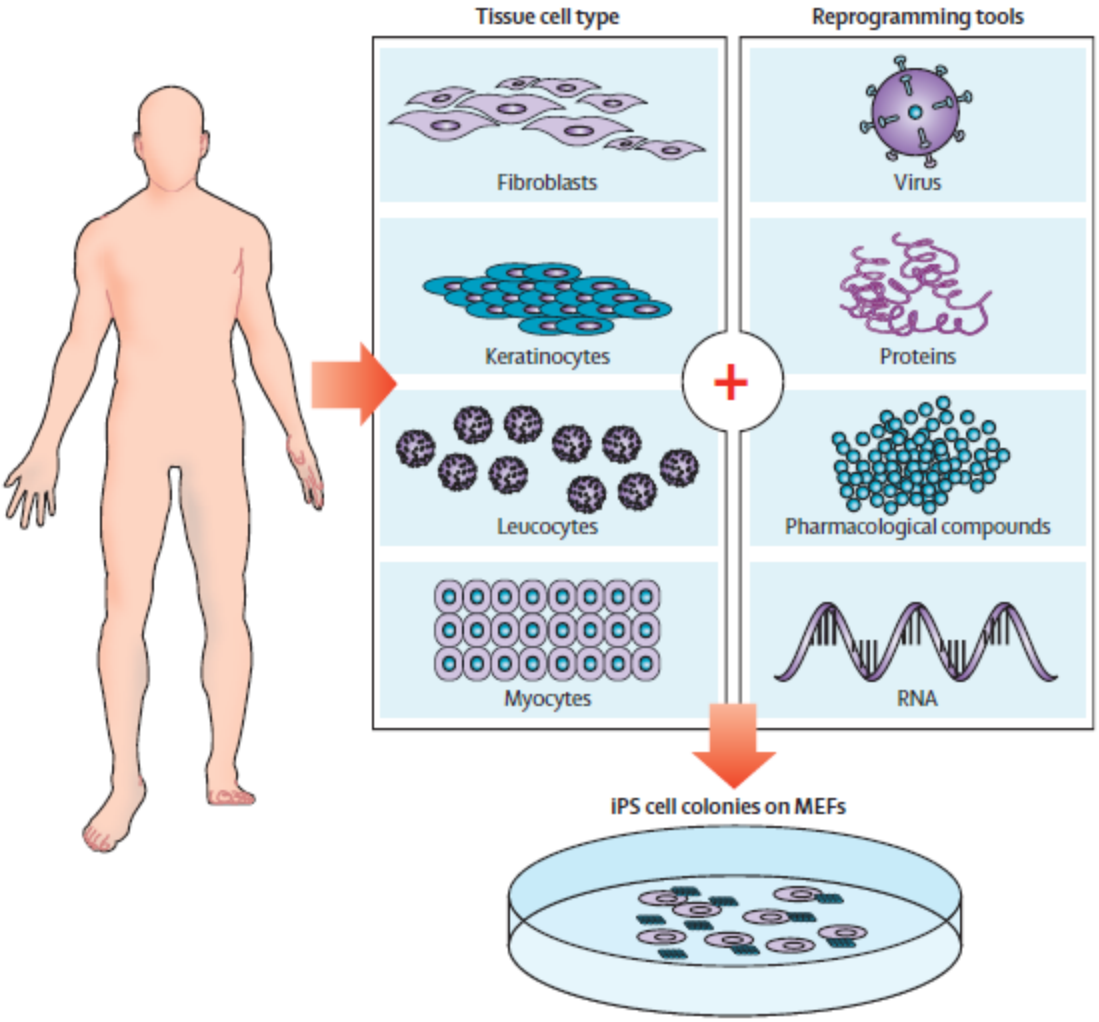

Fig. 5: Generation of iPS cells.

Somatic cells (eg, fibroblasts, keratinocytes, leucocytes, or myocytes) are recovered from biopsy samples taken from a patient, and are reprogrammed to a pluripotent state. Reprogramming can be accomplished by use of a virus to transduce pluripotency genes, or with a combination of proteins, messenger RNAs, or various small molecules. Once reprogrammed, the cells are seeded on to MEFs (pink cells) and form colonies (blue cells). iPS=induced pluripotent stem. MEFs=mouse embryonic fibroblasts.[23]

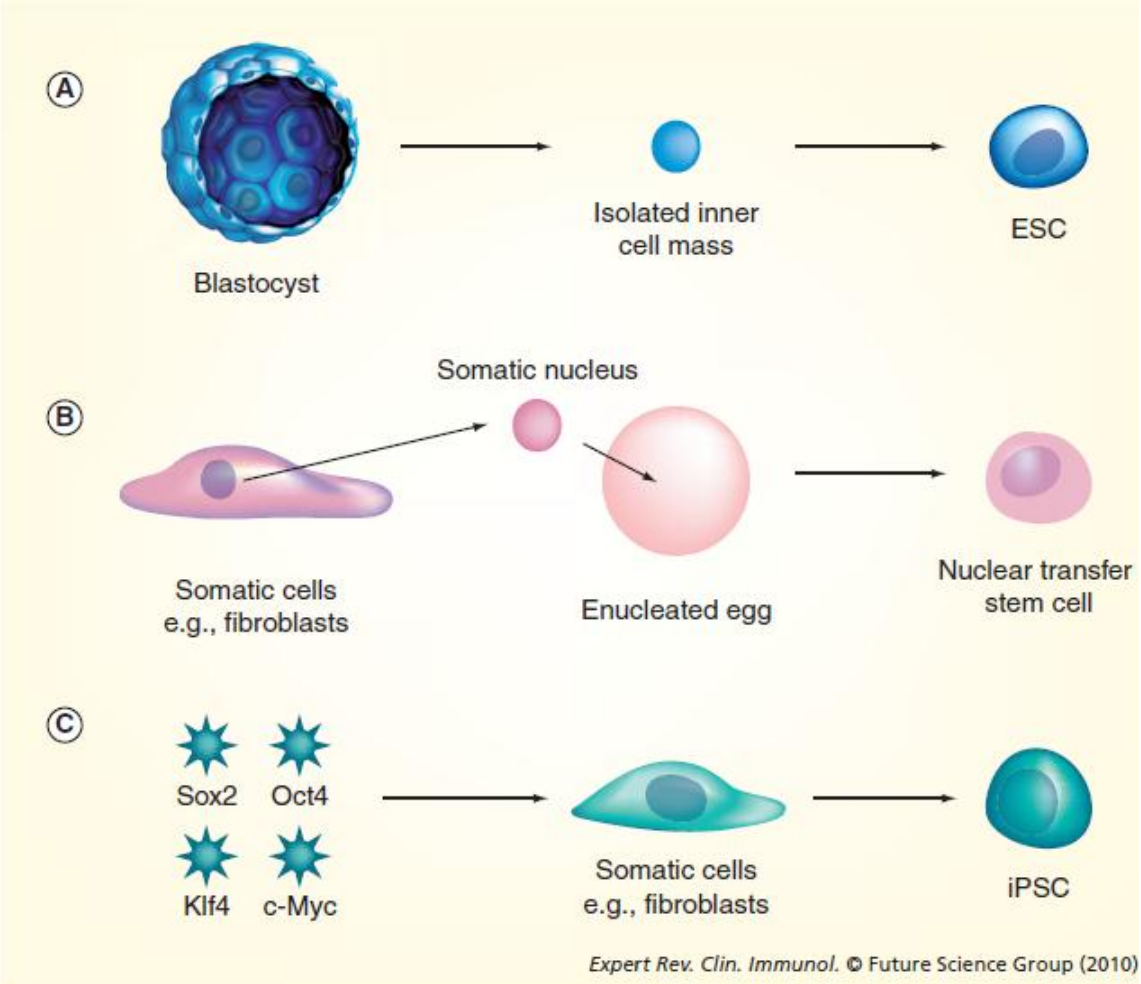

Fig. 6: Methods to isolate or generate pluripotent stem cells. (A) Isolation of ESCs from a newly fertilized preimplantation blastocyst. (B) Somatic cell nuclear transfer or therapeutic cloning, the method used to create 'Dolly' the sheep, wherein a somatic cell nucleus is inserted into an enucleated egg to generate a clone. (C) Cellular reprogramming to generate iPSCs, depicted here using retroviruses encoding the four original transcription factor reprogramming cocktail Klf4, Oct4, Sox2 and c-Myc. ESC: Embryonic stem cell; iPSC: Induced pluripotent stem cell; Klf4: Kruppel-like factor 4; Oct4: Octamer-binding transcription factor 4; Sox2: SRY-related high mobility group-box protein 2.[24]

Our knowledge of pluripotent cell differentiation, cellular reprogramming, human brain development, and neurological diseases is rapidly expanding. Neurological diseases may be among the most challenging to treat with cell-based cell therapies as a result of the extraordinary complexity of the nervous system, but may also afford the greatest therapeutic opportunity given that adult neurogenesis is limited or nonexistent in most regions of the CNS.[25]

CONCLUSION

Stem cells are the future of personalized medicine and posses many applications in real life treatment. Stem cells are classified based on their origin and their properties. They posses multiple differential properties based on their origin and time of collection and kind of preservation.

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