Invited Review Article

Differentiating ability of Stem cells-A Mini Review

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Abstract

Stem cells possesses the calibre to differentiate/ transdifferentiate into any lineage under particular conditions, which makes them one of the important sources of treating several diseases/conditions especially in regenerative medicine. This review is focused on describing the uniqueness of stem cells and their types. Further, differentiation ability of stem cells to particular cells/tissue/organs and their role in preclinical and clinical studies are elaborated in detail. In addition, we also list the side effects of the treatment and future endeavours of stem cell therapy.

Keywords: *Stem cells, differentiation, transplantation, stem cell therapy, pre-clinical and clinical studies*

Introduction

In 1908, a famous histologist derived the term stem cells[1]. What makes stem cells different from rest of the cells in the body? Stem cell research have fascinated many scientists around the world due to its unlimited proliferation, self-renewal and multi-lineage capability and also makes it unique type of cell. Moreover, internally, it can repair the damaged tissues of a particular organ. Stem cell in general fall into two categories namely embryonic or induced pluripotent stem cells (iPSCs) and adult stem cells[2]. Embryonic stem cells (ESCs) and induced pluripotent stem cells are pluripotent in nature while the former is isolated from inner cell mass of blastocyst stage[3], the latter is obtained by reprogramming adult somatic cells by adding four pluripotency genes, Oct4, Sox2, Kl4-2 and c-Myc[4].Being multipotent in nature, adult stem cells are named depending on the source of tissue or organ. These adult stem cells are the greatest source of autologous transplantation and many research are carried out in this field. Although ESCs possess better potential than adult stem cells to differentiate into any lineage of the cells, they are more prone to form teratomas. Another concern owing to ESCS is ethical issues procuring the embryos. These two disadvantages hinder them to be employed in therapeutical purposes[5].

Stem cells comes from variety of sources like embryo, fetus, brain, liver, skin, hair, ovary, testis, heart, gut and muscles[6].Fetal blood are large sources of hematopoietic stem cells and Mesenchymal stem cells/ Mesenchymal stromal cells (MSCs)[7], which was first isolated by Friedenstein and his co-workers[8]. Other sources of MSCs are bone marrow, pancreas, Umbilical cord/blood, dental-pulp and adipose tissues[9,10,11,12,13,14,15]. The International Society of Cellular Therapy (ICST) has declared that MSCs, should adhere to plastic, Positive for cell surface markers CD90, CD 73 and CD 105 ($\geq$95% positive) and differentiate into adipocytes, osteocytes and chondrocytes under *invitro* conditions[16]. Trans differentiation capability and multipotential ability of adult stem cells make them

available for therapeutic purposes for treating many disorders like stroke, skin and tissue burns, injuries in spinal cord, and neurodegenerative disorders like Alzheimer's and Parkinson's[17,18]. In this mini review we would like to focus on various stem cells and their potency to differentiate into various lineages and how far they have travelled in preclinical and clinical research in treating numerous disorders (Fig 1).

The Term stem cell:

Till and McCulloch, (2012) transplanted hematopoietic stem cells derived from bone marrow (BM) into the mice system. After 10 days of transplantation, they noticed cellular colonies in the spleen of recipient mice and they exhibited two properties 1) their ability to form all blood lineages and 2) ability to self-Renew. These finding introduced the term Stem cell and which possess two properties namely multipotency and self-renewal. HSCs are the only cells in hematopoietic system to form functional blood cells with self-renewal properties[19].

In 1988, hematopoietic stem cells with stem cell potential from bone marrow was purified using multi-colour, fluorescence activated cell sorting. Spranrude and colleagues were able to prove that these HSCs from BM of mouse when transplanted into lethally irradiated mice were able to reconstitute the entire hematopoietic system[20].

Capability of stem cells to differentiate in to other lineages

Many early studies demonstrated the

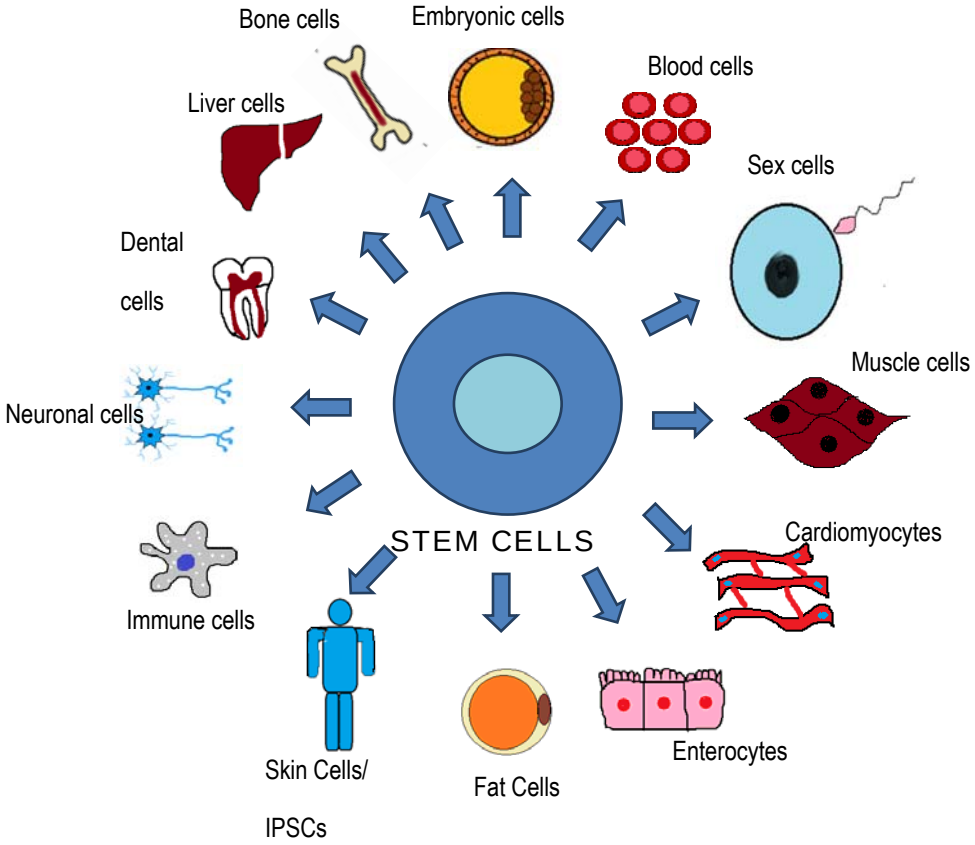

Fig1: Differentiating capability of Stem cells.

differentiation ability of stem cells to other lineages. In that case, HSCs apart from differentiating into lineage of blood, they have higher plasticity to differentiate into other lineages namely myocytes, hepatocytes, adipocytes, osteoblasts and as well as neurons[21,22,23]. HSCs of Peripheral- blood stem cells when transplanted into hematological cancer or breast cancer patients their liver, gastrointestinal (GI) tract and skin biopsy proved that circulating stem cell also differentiate into mature hepatocytes, epithelial cells of GI and skin[21]. Bone marrow stromal cells, an another source of stem cell was also able to differentiate into other cell lineages such as lungs, kidney and skin[24,25,26]. Apart from HSCs, many studies have proved that, MSCs being a mesodermal origin were able to differentiate into non-mesodermal lineages like hepatocytes and neurons[24, 27,28,29].

Mouse Embryonic stem cell lines/induced pluripotent stem cells from Mouse embryonic fibroblasts (MEFs) also possess the ability to switch lineages. iPSCs or ES cells differentiated into hematopoietic stem cells and their potency of differentiation was dependent on the source of origin used to derive iPSCs[30,31,32,33] and also differentiated into hepatocyte in the presence of FH1 molecule[34]. Further human ESCs and iPSCs also differentiated into cardiomyocytes, and pancreatic endocrine islets when treated KY02111 and sodium cromoglicate compounds respectively[(35, 36)].

Extracellular vesicles from stem cells

MSCs are said to exert their action against any inflammation through paracrine signalling, called as secretome. These secretome consists of protein fractions and vesicular fraction namely, extracellular vesicles (EVs). EVs are heterogeneous population consisting of secretory vesicles, exosomes and microvesicles and they come from a different cellular compartment. EVs aid in cellular communication, transfer of mRNAs, miRNAs, bioactive lipids and proteins between cells without direct contact. EVs are of therapeutic importance and their therapeutic potential had been demonstrated in various cell model and central nervous lesions. Several *in vitro* studies revealed that EVS obtained from different sources of MSCs played therapeutic role in decreasing the proteins that damage the neurons. Apoptosis of dopaminergic (DA) neurons in PD cell model, increase neprilysin enzyme by uptake of EVs by neuroblastoma cell line and decreasing amyloid-β (Aβ) levels intracellularly and extracellularly and EVs exerted neuroprotective role by decreasing ROS accumulation of hippocampal neurons in presence of AβO *via* catalase present in EVs[37,38]. Exosomes derived from MSCs are one of the important paracrine factors and aid in cell-cell communication. They have also an important role in normal physiology, wound healing and diseases like renal fibrosis, hepatic fibrosis and myofibrosis. Exosomes from UC-MSCs derived mi-RNA (uMSCs-EXO-MiRNA) and WJ-MSCs aided wound healing in skin defect nude mouse model and in rats promoted functional recovery in stroke and traumatic brain injury. Similar to MSCs, ESCs derived exosomes enhanced cardiac function and repaired infarction in mice[39].

Stem cells – pre-clinical and clinical study

ESCs/iPSCs

Human ESCs were also used to treat severe neurological disorders, like Parkinson's disease (PD)[40]. Transplantation of oligodendrocytes derived from hESCs proved to improve motor function in spinal cord injured patients after 7 days[41].

(NCT02239354-
https://www.clinicaltrials.gov/). In 2016, quadriplegic patient regained upper body motor function after 2 weeks and 90 days of transplantation of stem cells ($10*10^6$). In a particular study conducted in India, transplantation of hESCs to the patients suffering from Multiple Sclerosis (MS) and Lyme disease improved the physical strength, learning and motors kills[42]. In short duration transplantation of hESCs into MS patients improved the clinical symptoms and long duration study proved not only to be safe but also improved functional and cognitive ability of the MS patients[43].

Embryonic stem cells from mouse when microinjected in embryonic kidney and cultured in presence of nephrogenic factors (retinoic acid, Bmp7, activin A) resulted in lower expression *pax2* (early marker of kidney epithelial cells) and *wt1* (renal mesenchyme and epithelial cells and in podocytes), and increased expression of *cadherin-6* (early proximal tube marker), *gdnf*, *lim-1* and *eya-1*(early kidney mesenchyme)[44].

Many clinical trials have been conducted to prove the safety and efficacy of hESCs in treating cardio vascular diseases. Following preclinical study conducted in pigs, thin sheets of tissue derived from iPSCs were transplanted into the diseased human heart and repaired the human heart[45].

HSCs

The first human bone marrow transplant (HSC transplantation) was carried out in 1957 in monozygotic twins (syngeneic transplant) suffering from acute leukaemia. Later in 1968, first allogenic BMSCs was performed in paediatric patient suffering from combined immunodeficiency syndrome[46, 47]. In 2010 and 2013 Centre for international blood and marrow transplant research (CIBMTR), reported that HSCs were obtained from bone marrow (BM) as well as UC blood and was opted for patients suffering from blood and bone marrow disorders but further data was needed to analyse the impact of the changes. This study revealed that early allogenic transplantation of HSCs increased the survival rate to 50% and 13 out of 100 patients were free of leukemia after 1-4.5 years of follow up[48,49]. Later, it was discovered that allo-HSCT was more effective by sequentially administrating antigen specific or whole tumor cell vaccines, monoclonal antibodies and use of targeted drugs in combination with allo-HSCT[50,51,52]. Recent discovery in treating blood related disorders has shifted to CAR-T cell, combination of CAR-T and allo-HSCT therapy may be a promising therapy in future as they are still in pre-clinical trial[53,54].

In case of treating liver diseases, transplantation of bone marrow derived cells along with reduced size liver grafts enhanced the formation of new and regeneration of liver cells in animals and human. Hepatocyte proliferation, growth factors and cytokines such as hepatocyte growth factor (HGF), epidermal growth factor (EGF) and interleukin-6 (IL-6) are the factors responsible of liver regeneration[55,56].

It was also proved that peripheral stem cells or cord blood transplant increased the dosage of chemotherapy as it restored the bone marrow in the patients suffering from non-Hodgkin lymphoma[57,58].

There are only few results regarding HSCs in treating neurological disease, transplantation of hHSCs subcutaneously into the MS patients prolonged the progression of the disease compared to disease modifying therapy after 2 years was observed[59].

MSCs

MSCs potency to differentiate into hepatocytes, treated liver related disorder in human without any side effects. After autologous transplantation of bone marrow (BM), later in 2017 and 2019, allogenic BM and UC-MSCs when injected into the peripheral vein and spleen respectively of a patient suffering from liver related disorders improved liver function, survivability and histological score[60,61,62,63]. MSCs are proved to be safe in patients suffering from renal disease and kidney transplants. Combinations study was also conducted in patients suffering from Hepatitis B Virus-Related Acute-on-Chronic Liver Failure. This particular clinical trial was conducted in China by transplanting UC-MSCs (intravenous) and Plasma exchange. After 360 days, though did not improve the prognosis of the disease, but proved to be safe[63].

In case of treating heart diseases, MSCs exerts its therapeutic action through the following mechanisms: differentiation and homing ability, vasculogenesis and its paracrine effects Orlic and his colleagues, observed mycordial regeneration after transplantation of BM-MSCs into myocardial infarcted mice model. This study was further confirmed by the expression myocyte enhancer factor2 (MEF2), cardiac specific marker GATA-4 and early myocyte development marker Csx/Nkx2.5[23]. Clinical studies conducted on BM-MSCs proved to improve cardiac structure and function of patients suffering from acute myocardial infarction, ischemic and non-ischemic heart failure[64,65,66].

In case of treating neurodegenerative diseases like Alzheimer's (AD), PD and MS, transplantation of MSCs from various sources proved to be safe[67,68,69]. In addition transplantation of UC-MSCs intravenously to MS patients decreased the symptoms and improved the mental and physical functional ability[70,71]. Similarly, in addition to safety and tolerability, articulatory functions also improved in Amylotrophic Lateral Sclerosis (ALS) patients after transplantation of MSCs[7262]. In a stroke patient, Sonia Coontz, BM-MSCs was directly injected into the brain region near the area of the condition improved her physical function and speech[73]. In case of orthopaedic, Regenexx, a US company treated 30,000 patients suffering from various joint problems[74].

MSCs has not only been employed to treat life threatening disease, their role in field of cosmetics is also noticeable especially in case of hair loss and anti-aging. Till 2020 there has been 100 publications regarding hair loss and stem cells. In 2017, hair density increased after 23 weeks of injection with hair follicle stem cells into the fontal scalp region of male suffering from androgenetic alopecia[75]. Similarly, in 2017 allogenic transplantation of MSCs intravenously (20, 200 and 100 million cells) in patients in aging frailty proved to be safe after 1 month of follow-up[76].

Neural stem cells

Initially, there was a theory that, brain cells cease to divide or renew on its own and remain constant throughout adults' life. This concept was disproved by ^{3}H-tymidine and BrdU cell proliferation experiments and proved that neurogenesis take place throughout adulthood and formation of new neurons takes place in the brain regions[77]. Neurogenesis take place mainly in Subventricular zone (SVZ) and the hippocampal dentate gyrus (DG) and majority of NSCs reside in SVZ region and olfactory bulb (OB) remain the place for mature neurons. In addition to their ability to differentiate into neurons, astrocytes and glial

cells[78], they also differentiate into other cell lineages such as hepatocytes, myocytes (MyoD, Myf5, myogenin and myosin heavy chain was observed when NSCs from mice and human embryonic neural stem cells cocultured with C2C12 (myoblast cell line) myogenic cells after transplantation into transgenic mice) and hematopoietic stem cells[80,81]. Apart from their pre-clinical study in treating or improving the conditions of AD, PD, HD and ALS mouse/Rat models. In supporting to the information above some examples are explained. Human PSCs derived NSCs when transplanted into Spinal cord injured rats expressed NF-70 (axonal marker), TUJ-1 DCX, NeuN, β-III tubulin (neuronal markers), NG2 (Oligodendrocyte marker) and adenomatous Polyposis Coli (APC-mature oligodendrocyte mature marker) after 3 – 6 months and also functional recovery was also observed[82]. In another case, intrathecal transplantation of NSCs in SMA mice model maintained NSC marker Nestin and minimal percentage differentiated into TUJ-1 (neuronal marker) and glial fibrillary acidic protein (GFAP) (astrocyte marker) and also reduced disease condition, muscular and motor neurons degeneration[83]. Induced PSCs derived NSCs exerts neuroprotection and reduces macro/microglia in ALS mice model thereby extending their survival period and reduced motor neurons and axonal loss, further assay also reveals the expression of nestin, Neun and GFP positive cells[(84)]. In a PD rat model, after unilateral administration of human neural progenitor cells (hNPCs), cell survival, proliferation, immunomodulation and antiapotosis activity of NPCs secretome enhanced the Tyrosine Hydroxylase+ cells, survival rate of rat and motor function [(85)]. In an AD mouse model transplantation of hNSCs improves spatial memory, reduced microgliosis, astrogliosis, tau phosphorylation and Aβ42 levels via increasing TRK dependent Akt/GSK3β and decreasing BACE1 expression and further decreasing the inflammation respectively [(86)]. Clinical study also showed to be safe in PD and ALS patients, further improved the functional ability in MS patients [(87,88,89,90)].

Hair follicle stem cells

Early in 2006 Yu et al proved hair follicle stem cells can differentiate into neuron, smooth muscle cell and melanocyte lineage in the presence of induction medium[(91)].

Conclusion:

Stem cell has set its foot in therapeutical purpose due to its ability to differentiate / transdifferentiate into different cell lineages. Scientists all over the world should be able to successfully choose right kind of stem cells, proliferate for longer duration of period, differentiate into desired cell type precursors cells. Later, when transplanted as differentiated cells / undifferentiated cells / precursor cells they should integrate successfully into the host system without any immune rejection and function properly for required life span. Due to its differentiation capability patients own cells or autologous transplantation is also possible which reduces the risk of immune rejection as opposed to allogenic transplantation. MSCs are immune privileged cells and scientist claim that allogenic transplantation is also possible to treat several diseases. On the other hand, iPSCs serve as a platform for disease modelling, drug testing, to develop organ/ organoids and also aid in drug testing for several diseases. All these advantages make stem cells great therapeutic option.

Though it claims to treat several conditions, its survival, replication,

integration and duration of its effects under *in vivo* remains in dark. Another evidence claims that they can give rise to cancerous cells as they are the source of mutant cells[92]. In case of treating type 1 diabetes mellitus using hESCs their ethical and scientific concerns hampers hESCs in clinical trial surrounding ESCs. Apart from ethical considerations, they also exhibit technical limitations[93,94]. *Bmi-1* is involved in hematopoietic stem cell development and cancer cell development and more detailed study should be made on its role in normal cell and cancer cell developments[95]. Disease modelling need to be further enhanced in mimicking the human diseases and long-term clinical studies should be conducted to elucidate the detailed study of its side effects. Keeping the disadvantages in mind scientists should pay great attention towards the side effects presented by stem cells and take necessary scientific steps to remove the side effects posed by them.

Scientific contributions towards stem cells in treating various diseases are tremendous, each step is validated scientifically (gene, protein and functional studies) for transforming from preclinical to clinical side. Various advanced scientific developments and studies hope in future employ stem cells in combination with other conventional treatment to cure particular disease and make human life better to live.

List of Abbrevations

OC T-4 = Octamer-binding transcription factor 4

KL4-2 = Kruppel- like factor-2

SOX-2 = SRY-Box Transcription Factor 2

KY02111 = WNT signalling inhibitor, promotes differentiation of hPSCs to cardiomyocytes

FH1 = Functional hit 1

BMP 7 = Bone morphogenic protein 7

Pax 2 = Paired-Box containing genes 2

Lim-1 = homeobox transcription factor

gdnf = glial cell line derived neurotrophic factor

eya-1 = eyes absent 1

CAR-T = Chimeric antigen receptor T cells

Csx/Nkx2.5 = Cardiac specific transcription factor/natural killer homeobox gene family

GATA-4 = GATA binding protein 4

MyoD = Myoblast determination protein 1

Myf5 = Myogenic factor 5

NF-70 = Neuralfilament 70

NG2 = Nerve/glial antigen 2

DCX = Doublecortin

TUJ-1 = Neuronal specific class III beta tubulin

AKT/GSK3β = proteinase Kinase B/glycogen synthase kinase 3 β

TRK = Tyrosine kinase receptprs

BACE1 = β-secretase enzyme 1

Ethical Interest

None.

Competing Interest

None.

Consent for Publication

Not Applicable.

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Conflict of Interest

Author declares no conflict of interest

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