IJRM
INTERNATIONAL JOURNAL OF RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Review Article
Vol.:1, Issue:2

Stem Cell Therapy: An Overview

IJRM
INTERNATIONAL JOURNAL OF RESEARCH METHODOLOGY
An Official Publication of Human Journals

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HUMAN JOURNALS

www.ijrm.humanjournals.com

Keywords: Stem cell therapy, Types of stem cell, Application in different diseases

ABSTRACT

In recent year, research advancement in stem cell therapy has been rapid. Accordingly, general clinical, scientific and public attention to the application of stem cell therapy has been substantial. Promises are great, mostly notably with regard to the application of stem cell therapy for disease that are currently difficult to treat or incurable such as Parkinson disease or diabetes mellitus. It is in the best interest of patient care for diagnostic and interventional radiologists to be actively involved in the development of these therapies, both at the bench and at the bedside in clinical studies (2). There has a rapid surge in the clinical trial involving stem cell therapies over the last two to three years and those trials are establishing the clinical pathway for emerging new medicine (1). This review article discusses how to treat different types of diseases by stem cell (SC) therapy and we get knowledge about different types of stem cell.

INTRODUCTION

Stem cell (SC) therapy is not a new concept. In aftermath of bombing of Hiroshima and Nagasaki in 1945, researchers discovered the bone marrow (BM) transplanted into irradiated mice produced haematopoiesis (3,13). Hematopoietic stem cells (HSCs) were first identified in 1961 and their ability to migrate and differentiate into multiple cells was documented (3,14). Radiology may play a pivotal role in stem cell delivery, stem cell engraftment monitoring through imaginary and, potentially, improvement of engraftment condition with use of minimally invasive procedures (2).

Stem cell has the ability to divide and self-renew indefinitely as well as to differentiate into one or more cell types (2,15). It relevant to differentiate between embryonic stem cells, which are obtained from the inner cell mass of blastocyst, and adult stem cell which are found in adult somatic tissue. The only type of stem cell that are pluripotent (i.e. may differentiate into any cell type) are embryonic stem cell. Embryonic stem cells subsequently develop into partially differentiated stem cell that may in turn give rise to several different cell lines, but these cells can no longer become any type of cell (i.e. They are multipotent stem cells). Adult stem cells are multipotent cell as well and result of further lineage progression. They are of more limited differentiation ability and destined to develop into a cell of specific organ, tissue or organ system with the ability to fulfil the corresponding function. Adult stem cell can be harvested from bone marrow, adipose tissue, umbilical cord blood (2).

Mostly Stem cell (SC) therapy is used for following diseases:

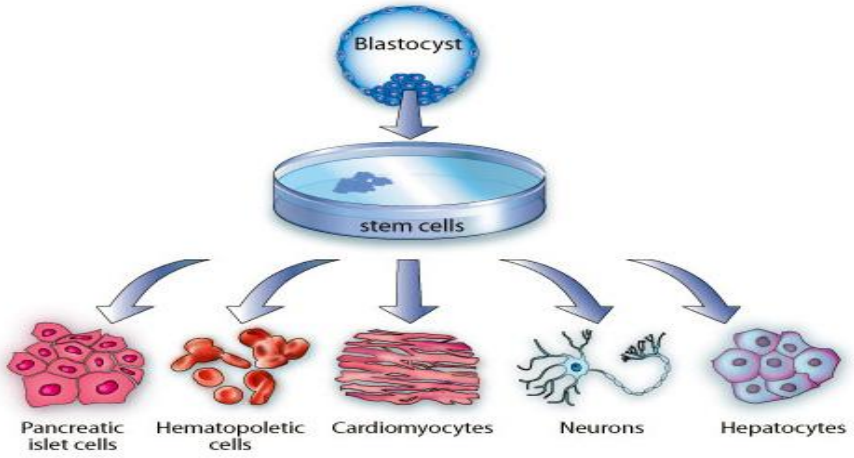

Figure: 1 (58)

Stem cell therapy for Retinal Disease:

Age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy are three most common causes of visual impairment and legal blindness in developed countries (3,16,17). One common denominator of this condition is a progressive loss of neural cell of eye – photoreceptor, interneuron and retinal ganglion cell or RGS- and essential supporting cell such as retinal pigment epithelium (RPE). Retinal dystrophies – retinitis pigmentosa (RP), Stargardt disease, Best disease, Leber congenital amaurosis and so on all evolve with early loss of photoreceptor and subsequent loss of RGC (3). The neuroretina is a complex structure whose health depend on blood vessels and retinal pigment epithelium (RPE), each of which is affected differently in spectrum of retinal disease. Therefore, three distinct cell types are conceivable target for future cell therapy in the retina: the neuroretina, bipolar cell, ganglion cell (4). Depending on the type of retina disease, different cell replacement strategies need to be developed (4).

❖ **Source of stem cell for cell therapy in retinal disease**

Bone marrow- derived Stem Cell:

Bone marrow (BM) derived stem cells (SCs) as a potential source for regeneration medicine (3,18,19). This is based on the assumption that hematopoietic stem cell isolates from bone marrow plastic and are able to "transdifferentiate" into tissue committed SCs for other organ e.g. heart, liver or brain (3). The identification of very small, embryonic-like SCs in BM supports the notion that the tissue contains a population of primitive SCs, which, if transplanted together with HSCs, would be able to regenerate damaged tissue in certain experimental setting. Cell from BM are easily and safely aspirated (3).

Retinal Stem Cell:

These cells can be isolated, expanded and differentiated into retinal neuron by culturing them in the presence of growth factor, such as epidermal growth factor and fibroblast growth factor (4,20,21). Of interest, when RBCs were transplanted into subretinal spaced of the degenerating retina in an animal model, they exhibited preferential expansion and glial cell (4).

❖ **Route of transplantation**

Routes that were tested for cell therapy for the retinal disease are systemic administration (intravenous), intravitreal injection and subretinal injection (3). Intravenous injection is much less invasive and easier to perform (4).

Subretinal injection techniques: 1) injection of cell suspension

2) injection of cell adhered to a matrix (3,22,23).

Stem cell for Parkinson's Disease:

Parkinson's disease neurodegenerative condition that tends to present late in life. This condition characterized by the presence of bradykinesia, a resting tremor and rigidity (5). It is associated with extending loss of dopaminergic (DA) neuron in the substantia nigra compacta (SNc) resulting in a severe deficiency of DA in striatum required for motor control (6). Patient can be effectively treated with a drug that target the dopaminergic nigro striatal pathway but over time efficacy of these medicines is limited by the development of profound motor fluctuations and dyskinesia (5,24).

There is the large variety of stem cells including embryonic stem cells (ESC), fetal neural cells (fetal NSC), and induced pluripotent stem cells (IPSC) (6). The use of cell-based therapy is based on two different strategies; exogenous and endogenous (6).

❖ **Stem cells as source of dopaminergic neuron for cell replacement**

On the basis, stem cell can be broadly classified as being totipotent, pluripotent or multipotent (6).

Embryonic Stem Cells (ESCs):

ESCs are pluripotent and are highly proliferative, they were deemed to have the greatest potential to be used in the clinical setting in Parkinson disease as they can give rise to any type of cell in the body including the dopaminergic neuron. The fact that they can be engineered *in vitro* means that ESCs possess many of necessary characteristics required for an optimal cell source

for cell transplantation therapies (6,26,27,28). However, progress with using ESCs as a viable option for disease therapy has been hindered by the risk of adverse reaction such as tumor formation (6,29,30) and immune reaction (6,31).

Fetal Neural Stem Cell (NSCs):

NSCs have been found to exist in the various regions of fetal and also the adult brain (6,32,33). NSCs that can be harvested from the embryo around embryonic day (E) 14- e15 in rodents (6,34,35) or 13 weeks post-fertilization in human (6,36,37) are multipotent cells that have the ability to regenerate and also to give rise to neuron, oligodendrocytes and astrocytes that represent the three major cell lineages of the CNS (6,38).

The most widely used form of treatment is levodopa (L-DOPA), which produce clinical benefit for some years by providing an exogenous source of dopaminergic to striatum (6,25).

There are two key approaches to stem cell therapy that can be applied in Parkinson's disease 1) The exogenous cell replacement strategy involves the transplantation of relevant stem cells (i.e. embryonic stem cell, induced pluripotent stem cell and adult stem cells) or fetal VM tissue that is able to generate therapeutic efficacy (i.e. by differentiating into dopaminergic neuron or the trigger of dopaminergic release etc.);

2) The endogenous regeneration approach involves the stimulation of lost brain stem cell to proliferate, differentiate into the dopaminergic neuron, and then to migrate to relevant regions such as the SNc and the striatal areas (6).

Stem cell in cancer therapy:

In the world, cancer remains a major cause of mortality. Despite great progress have been made in understanding the molecular basis of cancer. The progress in cancer despite great improvement has been made in therapies. The current treatment regimens for cancer shown limited survival benefits when used for most advanced stage cancers, because this treatment primarily target tumour bulk but not cancer stem cell (7,39,40). Indeed, conventional cancer therapies target neoplastic cell that are largely fast growing, suggestion that cancer stem cell may survive due to their high resistance to drug and slower proliferation rate (7,41).

❖ **Source of stem cell for cancer therapy**

Ideally, embryonic stem cells (ESCs) would be the source of stem cell for therapeutic purpose due to higher totipotency and indefinite life span compared to adult stem cells (ADCs) with lower totipotency and restricted lifespan (8). Due to legal and ethical reasons, use of ESCs in restricted in research and clinical field and ASCs remain the main supplement for stem cell. ASCs are acquired from bone marrow and peripheral blood (8).

Cancer Stem cell:

Cancer stem cells can be defined as cell in the tumour growth with tumour initiating potential. Compared to normal stem cell, the cancer stem cell is believed to have no control on the cell number. Cancer stem cell form very small number in whole tumour growth and they are said to be responsible for the growth of tumour cell (8). It is often considered to be associated with chemo-resistance and radio-resistance that lead to failure of traditional therapy (7,42). The first cancer stem cell was identified in human acute myeloid leukemia (ALM), showed that a rare malignant cell with the ability to repopulate the entire original disease over several transplantation, implying self-renewal and capacity to differentiate, was only found within the immature $CD34^{+}CD38^{-}$, but not the $CD34^{+}CD38^{-}$subpopulation (7,43). The cancer stem cell has been shown to have not only self-renewal capability but also generation wide spectrum of progeny like normal stem cell (8).

❖ **Differentiation therapy**

Differentiation therapy is an approach to the treatment of advanced or aggressive malignancies so that they can resume the process of maturation and differentiation into mature cell. It aims to force the cancer cell to resume the process of maturation. This therapy may use either known differentiation including agent /newly designed differentiation inducing agent (7).

❖ **Implication for cancer treatment**

The cancer treatment is targeted at its proliferation potential and its ability to metastasis and hence majority of treatment are targeted at rapidly dividing cell and at molecular target that

represent the bulk of tumour (8). Although current treatment can shrink the size of the tumour, this effect is transient and usually do not improve patients survive outcome (8,44).

Stem cell in treatment of coronary heart disease

Acute myocardial infarction (AMI) is the leading cause of death worldwide. Advance in treatment for the patient after AMI has led to decreasing in early mortality but, as a result, there is a higher incidence of heart failure (HF) among survivors (9,45). Cell therapy can improve the recovery of cardiac function in patient after acute myocardial infarction (AMI) (9).

❖ **Source of stem cell in cardiac transplantation**

The two main sources of stem cells are adult stem and Embryonic stem (ES) cells (10).

Embryonic cell:

ES cells are derived from the inner mass of developing embryo during the blastocyte stage. Feature of this ES cells includes their ability to differentiate into a wide variety of cell type including cardiac myocytes (10,46).

Adult stem cell: Resident Cardiac Stem cell

It has been recently reported that this cells can be harvested from cardiac biopsies. Injecting these cells in the setting of myocardial infarction can promote cardiomyocyte formation with associated improvement in systolic function (10,47).

❖ **Method of stem cell delivery**

Major role of cardiac stem cell therapy is transplant enough cell into the myocardium a site of injury or infraction to maximize restoration function (10).

Transvascular Route:

A transvascular approach is particularly well suited to treat the patient with acutely infarcted and reperfused myocardium. Stem cell can be infused directly into the coronary arteries and have a

greater likelihood of remaining in the injured myocardium as a result of activation of adhesion molecules and chemokines (10,48).

Direct Injection Into the Ventricular wall:

Direct injection of stem cell is used in patient presenting with established cardiac dysfunction in whom a transvascular approach may not be possible because of total occlusion or poor flow within the vessel of affected territory (10).

Stem cell therapy in Diabetes

Diabetes is one of top 10 leading causes of morbidity and mortality, affecting nearly 350 million people worldwide. B-cell replacement represent an attractive prospect for diabetes therapy but treatment option remains quite limited (12). Both type 1 and type 2 diabetes are characterized by a market deficit in beta-cell mass causing insufficient insulin secretion (11). Type 1 diabetes caused by autoimmune- mediated de-structure of beta cell (11,49,50). Type 2 diabetes is also characterized by an ~65% decrease in beta cell mass (11,51), associated with a ~10- fold increase in beta-cell apoptosis (11,52). The most effective protocol thus far have produced cell that express insulin and have molecular characteristics that closely resemble genuine insulin secretion cell (12).

❖ **Source of Stem Cells**

Human embryonic Stem Cells (hESCs):

Human embryonic cells are derived from the inner cell layer of the blastocyst (11,53). Human ESCs have the ability to form cell derived from all three germ layers (12,54). These cells subsequently give rise to all differentiated cells in adult through a series of cell fate choices that involve self- renewal and differentiation (11,55).

Islet beta cell:

Adult pancreatic islet has a complex architecture, with the beta cells being more preferentially located in the islet core and another cell type, such as alpha-, delta- and pp-cells, more abundant in the islet periphery (11,56,57). The main vascular supply of islet from an arteriole that enter the

islet from beta-cell enriched core from where the blood is being passed to the islet periphery (11,57).

CONCLUSION

Many people fall victim to various diseases like diabetes, cardiac failure, cancer, Parkinson's disease etc. The key to cure and treat these death causing diseases through research and by unlocking the hidden mystery of stem cells. The use of stem cells is limitless because of their ability to renew, differentiate themselves into any other type of cell.

Thus, we discuss an overview on stem cell derived from the various source and their application in the field of medicine.

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