Review Article

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STEM CELLS THERAPY IN HUMAN WELFARE AND DISEASE

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ABSTRACT

The study Global Burden of Disease (GBD) drew international healthcare community's attention to the burden of neurological disorders and many other chronic conditions. This study highlighted that the burden of neurological disorders was seriously underrated by traditional epidemiological and health statistical methods that prefer only mortality rates but not disability rates. There has recently been a great deal of interest in stem cells and the nervous system, in terms of their potential for deciphering developmental issues as well as their therapeutic potential. With the advancement in cell culture, isolation techniques, and molecular analyses, various types of stem cells have now been broadly classified, isolated, and characterized from different parts of the body, even from brain and heart. The concept of stem cell-based therapy provided new hope for the treatment of neurological diseases. In this review we will discuss about ongoing stem cell therapy for neurodegenerative disease.

KEYWORDS: Stem Cell, Stroke, Parkinson's disease, Alzheimer's disease.

INTRODUCTION

Stem cells (SCs) can be described as unspecialized cells i.e. they possess clonogenic and self-renewing ability and their specific role in the body is yet to decide. After differentiation, they mature into multiple cell lineages exhibiting characteristic morphologies with specified body functions, such as heart, skin, muscle and nerve cells. Starting from the premature developmental stages, SCs are established in almost all the higher animals and last till the end of life. In contrast to other cells of the body that have a definite life span, SCs are characterized by Self-renewal and totipotency properties. Although totipotency is the specific characteristic of stem cells that appears in the body for a very short period named 'embryonic stem cells (1), the adult stem cells exhibit multipotency and differential ingenuity which can be utilized for future therapeutic options (2). The term stem cell, for the very first time, works of eminent scientist Ernst Haeckel appeared in the scientific literature as early as 1868. Haeckel coined the word "Stammzelle" (stands for stem cell in German) for a single cell organism which he believed had evolved from the ancestor of all multicellular organisms (Haeckel, 1868-74). In 1981 researchers were able to stem cells from the embryos of mice named embryonic stem cells. Further, human embryonic stem cells isolated were successfully isolate in 1998 (3). In 2006, another breakthrough made in the field of stem cell research when specific conditions that can reprogramme the terminally differentiated cells into a stem-like state called iPSCs were developed. Today, almost every part of the body has known stem cells. (4).

The research in the area of adult stem cell accelerated more than 60 years ago when two types of stem cells in the bone marrow was discovered in the 1950s. Out of which, one population was responsible for the development of all types of blood cells in the body termed as hematopoietic stem cells. The second population, discovered after a few years later, was called bone marrow stromal stem cells or mesenchymal stem cells. These are non-hematopoietic stem cells that contribute to a small proportion of the bone marrow stromal cell population, and can produce bone, cartilage and fat cells that support blood and fibrous connective tissue formation. In the next decade i.e. in the 1960s, scientists involved in the studies of rat brain discovered that brain contained dividing cells ultimately developing into nerve cells. It was established in the 1990s that the brain contains stem cells that can generate astrocytes and oligodendrocytes, which are non-neuronal cells, and neurons, or nerve cells, from the three major cell types of the brain(5).

For decades, researchers have been investigating the biology of stem cells to adjudge the developmental process and to generate new methods for treating

health issues (6). Stem cells provide an opportunity for research into the mechanisms that regulate embryonic development, cell differentiation, and organ maintenance. The researchers and medical doctors are currently planning to make the renowned idea of regeneration a reality by creating therapies to recover missing, injured, or aging cells and tissues inside the human body (7). Given their capacity for proliferation and differentiation, stem cells have great potential to develop novel cell-based therapies (8-9). Neural stem cells (NSCs) along with other types of stem cells including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and mesenchymal stem/stromal cells (MSCs) are potential tools for transplantation in the treatment of neurological injuries and diseases (10).

In this review, we will discuss the categorization of stem cells based on origin and potency and finally discuss some pieces of evidence for the treatments of neurological diseases based on stem cell therapy.

Historical perspectives:

The concept of a stem cell was first proposed by Haeckel, Dantchakoff, Pappenheim, Ehrlich, Maximow working on the concept of the stem cell that is put forward for the first time in 1882. In the early 1900s, the first accurate stem cells were identified when it was found that few cells generate blood cells. In 1908, the Russian histologist Alexander Maksimov suggested the term "steme cell" for scientific use. In 1968, bone marrow transplant between two siblings treated SCID with fruitful outcome. Hematopoietic stem cells were discovered in human cord blood in 1978 (11). The first human embryonic stem cell line was established by James Thomson and coworkers at the University of Wisconsin–Madison in 1998 (12). Recently, in 2005, scientists were found another category of stem cells in Kingston University, England. These were named cord blood embryonic-like stem cells, which instigate in umbilical cord blood. Korean researcher Hwang Woo-Suk (2004-2005) purported to have created numerous human embryonic stem cell lines from unfertilized human oocytes (13). In October 2006 Scientists create the first-ever artificial liver cells using umbilical cord blood stem cells at Newcastle University in England. It is suggested that these stem cells can differentiate into more cell types than adult stem cells, opening up greater potential for cell-based therapies (14). In early 2007, a new type of stem cell had been isolated in amniotic fluid by Dr. Anthony Atala (15). This new stem cell could be a feasible option for the controversial use of embryonic stem cells (16). In 2007 a group of researchers (Mario Capecchi, Martin Evans, and Oliver Smithies) awarded by Nobel prize for their work on embryonic stem cells from mice using gene targeting strategies producing genetically engineered mice for gene research (17).

In 2008 the first published study of unbeaten cartilage regeneration in the human knee using autologous adult mesenchymal stem cells is published by clinicians from Regenerative Sciences (18). Embryonic stem cell secluded from a single human hair was reported in 2008 (19). Australian scientists (2009) have found a way to develop mouse muscles chemotherapy stem cell (20). Reported the creation of patient-specific "induced pluripotent stem cells" (iPSCs) from skin cells and they also claimed it as the 'ultimate solution for stem cell'. In another advance study, human embryonic stem cells were cultured in a completely artificial medium without using any animal substances, which is necessary for future clinical uses in 2010 (21).

Over recent years, stem cell research becomes the topic of debate among the public as well as religious groups. The national policymakers, government officials, and scientists have led to different laws and procedures regarding stem cell harvesting, development, and treatment for research or disease purposes. Such policies aim to safeguard the public from unethical stem cell research and use although continuing to endorse new developments in the area.

Stem cell

Stem cells are cells present in most multi-cellular organisms, if not in all. A stem cell is non-specialized, generic cells which are characterized by self-renewal and strength i.e. ability to regenerate themselves through the division of mitotic cells and to differentiate into a wide range of specific cell types (Fig. 1). They are essential for brain cells, bones, muscles, nerves, blood, skin, and other organs to develop, grow, maintain, and repair (22).

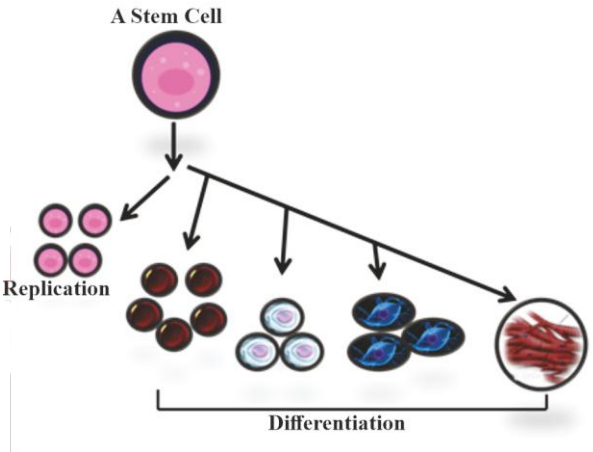

Fig 1: Characters of Stem Cell: Replication and Differentiation

The in vitro study of stem cells enables the researchers to discover the qualities of the cells make them distinct from specialized cell types. Currently, the use of stem cells for screening of novel drugs and development of model systems to study normal growth and recognize the causes of birth defects are in regular practice (23). Research on stem cells is continually augmenting our knowledge about the development of an organism from a single cell and the mechanism behind the rehabilitation of damaged cells in adult organisms. Stem cell research is one of the most promising fields in contemporary biology but, as with other growing fields in science, stem cell research as quickly as it produces new findings poses fundamental questions. In addition, during the last year, adult SCs have been used solely or in conjunction with other therapies to obtain major "health benefits" for patients in any human body tissue.

Classification of stem cells on the basis of potency:

Stem cells are categorized based on the strength that can differentiated into various types of cells. Such five primary classifications are totpotent, unipotent, multipotent, oligototent and pluritotent.

Totipotent:

A totipotent cell is a single cell that, with sufficient maternal support, may give rise to a new organism. This is the cell which gives rise to all of the extra embryonic tissues, as well as placenta's supporting extra-embryonic structures, all of the body's tissues and germ line. A single totipotent cell may replicate the entire organism by division in utero.

Pluripotent:

Pluripotency is the capability of a cell to differentiate into almost all types of cells. Examples are early embryonic stem cells and cells originating from the layers of mesoderms, endoderms, and ectoderms that are produced in the early stages of embryonic stem cell differentiation. The production of pluripotent stem cells would allow the testing of drugs for a wider range of cell types. Nevertheless, the conditions must be the same when comparing different drugs in order to test drugs effectively.

Multipotent:

A multipotent cell has the ability to distinguish between a closely related cell families. Types involve hematopoietic (adult) stem cells that can transform into cells or platelets of red and white blood. They have the ability to develop into the cell of more than one type.

Oligopotent:

It has the ability to differentiate between a few cells. Examples of oligopotent cells in an body are lymphoid or myeloid stem cells (adult). Oligopotent cell lines have the ability to transform into quite a limited number of other cell types, including myeloid cells, plasma cells, B cells, T cells, or lymphoid cells.

Unipotent:

A cell is called unipotent when it is able to generate only cells of their own kind, but has the property of self-renewal to be identified as a stem cell. Example includes (adult) muscle stem cells.

Classification of stem cells on the basis of their sources:

The best way to identify stem cells is to separate them into two different types: early or embryonic and adult or mature stem cells. Early stem cells, also known as embryonic stem cells, are found in the inner cell mass of a blastocyst after about five days of development. There are adult stem cells for various tissues of the body, as well as the umbilical cord and placenta after conception. On the basis of origin, stem cells can be of following types-

Embryonic stem cells:

Embryonic stem cells are pluripotent, theoretically immortal, self-replicating cells (24). They originate in a developmental stage from embryos until they usually occur in the uterus at the time of implantation (2). The embryos that contain human embryonic stem cells are naturally 4 to 5 days old and are referred to as the blastocyst, a hollow microscopic ball of cells.

Adult stem cells:

Adult stem cells are multipotent or totipotent undifferentiated cells that follow embryonic development throughout the body that multiply through cell division to restore dying cells and regenerate damaged tissues. The main roles of adult stem cells in a living organism are to maintain and repair the tissue within which they are found. The origin of adult stem cells is still under study in some mature tissues, unlike embryonic stem cells identified by their origin (25).

Stem cell culture:

Within the laboratory the proliferation and preservation of cells is called cell culture. Human embryonic stem cells (hESCs) are formed by moving cells from an embryo in the preimplantation stage to a plastic lab culture dish which retains a nutrient broth known as a culture medium (26). The cells divide and disperse across the dish's surface. Nevertheless, if the plated cells survive, divide and multiply enough, they are gently removed and plated into several fresh crop dishes for several times and for many months. Every cycle of subculture process is known as 'Passaging'. Once the cell line has been formed, millions of

embryonic stem cells are capitulated by the original cells. Embryonic stem cells that have proliferated without differentiation in cell culture for six months or more are pluripotent and tend to be genetically stable are known as embryonic stem cell lines. Batches of cells can be frozen at any stage of the process and transported for auxiliary culture and testing to other laboratories (27).

Stem cell lines

A stem cell line is the result of a single parent community of stem cells, a family of regularly dividing cells. These are derived from human or animal tissues and can be duplicated in vitro ("within glass" or, generally, "in the laboratory" in an artificial environment) for long periods of time (28). They are used frequently to examine the connection between embryonic stem cells or the cloning hole organism. When stem cells are able to divide and multiply in a controlled culture, a stem cell line is called the group of healthy, dividing, and undifferentiated cells (16).

Applications of stem cells:

The goal of any stem cell therapy is to repair a damaged tissue that is unable to heal itself. Continuous stem cell therapy studies give hope to patients who do not normally receive medication to cure their disease, but only to relieve their chronic disease symptoms. Stem cell therapies are more than just transplantation into the body of cells; they help them to grow new and healthy tissue also (29).

Possible treatments by stem cells:

At present a number of stem cell therapies have been developed, but most are expensive and/or experimental, except for bone marrow transplantation (Fig. 2). Medical researchers expect adult and embryonic stem cells to be able to treat cancer, type 1 diabetes mellitus, Parkinson's disease, Stroke, Alzheimer's disease, Huntington's disease, heart failure, muscle and neurological disorders, and lot more in the near future (30). However, more research is warranted to clarify stem cell activity after transplantation, as well as the mechanisms of stem cell interaction with the diseased/injured micro environment, before stem cell therapy can be implemented in the clinical setting. A well-known clinical method of stem cell transplantation is bone marrow transplants (BMT). After high doses of chemotherapy and/or radiotherapy, BMT will repopulate the marrow and restore all the various types of blood cells that were used by our main defense to get rid of endogenous cancer cells. The isolation of additional stem and progenitor cells is currently being developed for many other clinical applications for the cure of neurological diseases. Several of them are

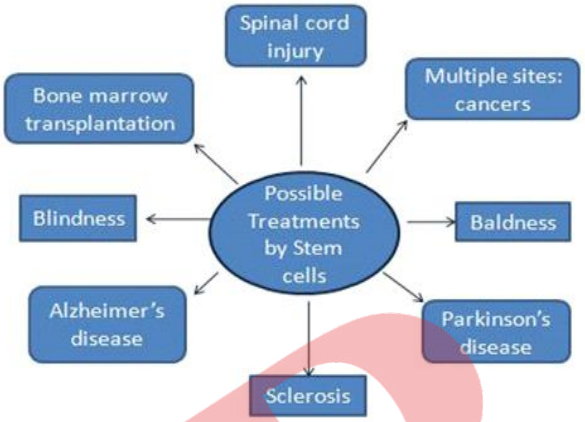

Fig 1: Characters of Stem Cell: Replication and Differentiation

listed below.

Parkinson's disease (PD):

Parkinson's disease is the second most severe neurodegenerative condition whose origin is still largely unknown. Parkinson's disease is a slow-onset neurodegenerative condition, with partial loss of substantial dopaminergic neurons and significant decrease of striatal dopamine, an organic compound of catecholamine and phenethylamine families (**31**). The incidence rate of PD in the population of 65 years of age or older rises with age to around 1 per cent. Drug therapies and surgery can't fix the problem entirely right now (32). Through having dopaminergic neurons and cell transplantation techniques, medical professionals are investigating treatment through restoring dopamine neurotransmitters as stem cells can supply dopamine. A double-blind study was conducted for the treatment of Parkinson's disease by transplantation of fetal cells exhibited survival and secretion of dopamine from the transplanted cells along with valuable improvement in clinical symptoms (33). However, in some patients side effects were observed suggesting that there was an over sensitization to or too much dopamine was released. Although further worsening of side effects were not anticipated and the experiment was assumed as successful and significant at the cellular level.

Stroke: Ischemic stroke is one of the world's most severe health conditions. The only anti-thrombotic drug approved by FDA for an acute ischemic stroke is the tissue plasminogen activator. The number of deaths associated with strokes is rising, and stroke remains one of the leading causes of death and disability worldwide (34). Drastic brain tissue damage following ischemic stroke entails not only destruction

of a population of a heterogeneous brain cell type but also major disruption of neuronal connections and vascular systems. Several types of stem/progenitor cells, such as embryonic stem cells (ESCs), neural stem/precursor cells (NSCs/NPCs), mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and induced neurons were assessed as possible stroke dependent cell therapy (35).

Alzheimer's disease: Alzheimer's disease (AD) is a clinically characterized neurodegenerative condition with memory loss and cognitive dysfunction. It is the most common type of neurodegenerative dementia, comprising 50–70 percent of these cases. The number of dementia patients globally was estimated at 46.8 million in 2015 and this figure is expected to exceed 131.5 million in 2050 (36). Alzheimer's disease is characterized pathologically by β-amyloid plaques and neurofibrillary tangles. Traditional treatment strategies using medications only reduce the symptoms without treating the disease which is a significant problem and affects patients and their caregivers' quality of life. Stem cell research has provided new developments in the treatment of neurodegenerative disorders in recent years. The major types of stem cells currently include NSCs, ESCs, MSCs and iPSCs. Often identify potential problems in the clinical implementation of stem cell transplantation and drug discovery as a cure for Alzheimer's disease (37).

Scientists and stem cell research:

Scientists claim that with the help of stem-cell research numerous diseases afflicting humans could be cured. However, anti-abortion groups, some religious groups, and conventional citizens say that using cells from embryos is unethical because it destroys life. However, recently the decision has been made that stem cell research should be supported and funded by the federal government, despite controversy over the use of human embryos (38).

CONCLUSION

Starting with the belief that the stem cells can only be isolated from embryos now it is well accepted that a human body contains stem cells in various tissues. They are present in dormant phase until they are required. The current research on stem cell therapies gives hope to patients who would generally not receive treatment to cure their diseases. Stem cells have a great future for the therapeutic world for stem cell therapy. We wish to see new therapeutics in the form of bone-marrow transplant, skin replacement, organ development, and replacement of lost tissue such as hairs, tooth, retina and cochlear cells.

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