Review Article

Stem Cell Therapy in Treatment of Non-Communicable Diseases: Possibilities and Challenges

Abstract

Over recent years stem cells have stood out as a promising tool for regenerative medicine, providing alternative therapeutic solutions for many non-communicable diseases. Many clinical trials using stem cells or induced pluripotent stem cells are focused on the refit and regeneration of various tissues and organs in degenerative diseases, whose current treatment only succeeds in delay down the progression of the disease. This review summarizes several current clinical and nonclinical information on the use of embryonic stem cells (ESCs), induced pluripotent stem cells (IPSCs) and mesenchymal stem cells (MSCs) in various diseases. The aim of this review was to expand on the background and therapeutic potential of ESCs, MSCs, and IPSCs whilst linking this to their use within disease therapy with a specific focus on diabetes, kidney disease, and cardiovascular disease with future possibilities and challenges. Also aimed to explain the benefits of transplantation with side effects shortly after transplant and later and interruptions, possibilities and challenges of transplantation.

Key words: Regenerative medicine, Stem cells, Stem cell therapy, Pluripotent stem cells, Embryonic stem cells, Mesenchymal stem cells.

Abbreviations

ESCs: Embryonic stem cells

IPSCs: Induced pluripotent stem cells

MSCs: Mesenchymal stem cells

DPSCs: Dental pulp stem cells

AVN: Avascular Necrosis

AdSCs: Adipose stem cells

HSCs: Hematopoietic stem cells

AFSCs: Amniotic fluid stem cells

RPs: Renal progenitors

CVD: Cardiovascular diseases

CHD: Coronary heart disease

GVHD: Graft-versus-host disease

Introduction

Stem cells are undifferentiated cells of a multicellular organism, that can turn into specific cells, as the body needs them. Stem cells have the potential to revolutionize tissue regeneration and engineering [1]. Cells in the body have specific purposes, but stem cells are cells that do not yet have a specific role and can become almost any cell that is required. There are three main types of stem cells depending on source: embryonic stem cells (ESCs), induced pluripotent stem cells (IPSCs) and mesenchymal stem cells (MSCs) [2].

For the first time in 1981, researchers could isolate stem cells from mouse embryos. More accurate studies on the biology of mouse stem cells led to discovery of methods for separation of stem cells from the human embryo in 1998. Another name of stem cell therapy is regenerative medicine, it's promotes the repair response of diseased, dysfunctional or injured tissue using stem cells or their derivatives [3]. The origin and function of these stem cells varies but they all hold diagnostic and therapeutic potential. A potential route of treatment is using stem cells that have the capability of differentiating into healthy tissue, replacing any lost through disease manifestation and thus justifying the avoidance of lifelong expensive treatments [4].

Stem cells provide new cells for the body as it grows and replace specialized cells that damaged or lost. They have two unique properties that, they can divide repeatedly to produce new cell, and they can change into the other types of cell that make up the body [5].

Classification based on potency

Stem cells can be classified based on potency, by the extent to which they can differentiate into different cell types. The four main classifications are totipotent, pluripotent, multipotent, or unipotent.

Totipotent: The ability to differentiate into all possible cell types. Examples are the zygote and the first few cells that result from the division of the zygote [5].

Pluripotent: The ability to differentiate into almost all cell types. Examples are embryonic stem cells and cells that are isolated from the mesoderm, endoderm, and ectoderm germ layers that are formed in the beginning stages of embryonic stem cell differentiation [6].

Multipotent: The ability to differentiate into a closely related family of cells. Examples include hematopoietic (adult) stem cells that can become red and white blood cells or platelets.

Unipotent: The ability to only produce cells of their own type. Examples include (adult) muscle stem cells [7].

Classification based on their sources

Embryonic stem cells: Embryonic stem cells are self-replicating cells that are potentially immortal [7]. They are derived from embryos at a developmental stage before the time of implantation occur in the uterus. They can change into any cell in the body, so these stem cells are said to be pluripotent [8].

Adult stem cells: Adult stem cells are undifferentiated totipotent or multipotent cells that are found in the body after embryonic development and multiply by dividing cells. The main role of adult stem cells in vivo is to preserve and improve the tissue in which they are found. They can replace blood stem cells (or “blood formation”) only with blood cells and various types of skin cells (or “epithelium”) [8]. There are a number of adult stem cell types have been isolated from dental tissues, known as dental pulp stem cells (DPSCs) [9] and these cells exhibited differentiation potential into odontoblastic, adipogenic and neural citotype; the same group isolated a similar citotype in deciduous teeth that have been called SHEDs (stem cells from human exfoliated deciduous) [10].

Induced pluripotent stem cells: Recently, a third type of stem cell has emerged that has properties like embryonic stem cells. Scientists have created these induced pluripotent stem cells (iPS cells)

by controlling the expression of specific genes and reprogramming somatic cells into pluripotency [11]. They are also pluripotent and can develop into cells of any type [12].

Applications of stem cell therapy

The goal of stem cell therapy is to treat damaged tissue that can't heal itself. Recent stem cell research often encourages patients who have not been treated for diseases in order to alleviate the symptoms of chronic diseases. Stem cell therapy involves more than just implanting cells into the body and growing new healthy tissue. It may also be possible to gratify stem cells already in the body to work overtime and produce new tissue [13]. The growth of stem cells after implantation into host tissues or organs is influenced with Several natural polymers employed as biologic scaffolds carry stem cells for tissue repair, including alginate, collagen, fibrin, albumin, hyaluronan, platelet-rich plasma, and gelatin [14].

Diseases and conditions where stem cell treatment is being investigated include: Non-union/Delayed Union Fracture, Osteonecrosis or Avascular Necrosis (AVN),Knee Cartilage Defect, Rheumatoid Arthritis (RA), Spinal Cord injury, Spinal Fusion Treatment, Cerebral Palsy, Autism, Motor Neuron Disease, Multiple Sclerosis, Parkinson's Disease, Alzheimer/Dementia disease, Cerebellar Atrophy, Cerebellar Ataxia, Spinal Muscular Atrophy, Down Syndrome, Optic Nerve Damage, Retinitis Pigmentosa, Macular Degeneration, Dystrophy Glaucoma Disease, Diabetes (Type 1 & 2), Acute/Chronic Liver Disease, Muscular Dystrophy, Acute/Chronic Kidney Disease, Peripheral Arterial Disease, Myocardial Infarction, Lung Disease, Erectile Dysfunction, Anti- Aging Treatment, Scleroderma Disease, Skin Replacement, Male Infertility, Female Infertility, Breast cancer, Scar, Colon cancer, etc. [15-17].

Possibilities in some most occurring non communicable diseases

Stem cell therapy for kidney disease

Kidney diseases are caused by damage to nephrons, which can be sudden and short lived called acute kidney disease or slow and progressive called chronic kidney disease. Chronic kidney disease can lead to renal failure and is fatal if not treated. Scientists are studying how the kidneys can be restored and the types of kidney cells involved in this process [18].

After variety of insults the kidney has the capacity for regeneration. The factors that caused kidney damage over the past few decades have been carefully studied. There is currently no FDA approved stem cell therapy for kidney disease [19]. However, clinical trials are being conducted to determine whether stem cell-based kidney therapy is safe and effective in humans. Scientists have already successfully created an artificial rat kidney that produces urine once transplanted into the animal, making artificial organ transplantation a highly possible reality for human kidney [17, 20].

Types of stem cells investigated to regenerate damaged tissue

Significant advances have been made in promoting stem cell products as a possible treatment of kidney disease, restoring various types of stem cells from renal function in preclinical models of acute and chronic renal failure [21]. Both preclinical reports and clinical trials of stem cells used for treatment kidney disease are increasing rapidly. Different types of stem cells, ranging from mesenchymal stem cells (MSCs), adipose stem cells (AdSCs), hematopoietic stem cells (HSCs), amniotic fluid stem cells (AFSCs), renal progenitors (RPs) and so forth, can stimulate renal repair in vivo in models of acute and chronic kidney failure [19].

The promise of stem cell therapies in pre-clinical models of kidney diseases is yet to be translated into more persuasive proof of clinical efficacy. Several clinical trials have confirmed the safety and tolerability of stem cells, and of MSC-based therapies, in patients with renal diseases and kidney transplants. However, long-term monitoring is recommended to rule out the potential risk of cancer and of developing anti-HLA antibodies [22].

Stem cell technology for the treatment of diabetes

Diabetes is a disease with high blood sugar. Most of the glucose comes from the food we eat. The hormone used to transport glucose to the cell as energy is insulin. When our body cannot produce insulin, it is called type 1 diabetes. In type 2, glucose is not available due to insulin resistance [23].

In the past, numerous diabetes treatment technologies have been used, including increased insulin delivery and glucose monitoring systems, new methods for the complete transplantation of the pancreas and graft, and the formation of B cells from the pancreatic ducts or stem cells. Now-a-days these two conditions of diabetes are treated by stem cell technology [24].

Types of stem cells investigated to regenerate damaged tissue

Stem-cell therapy means the replacement of diseased cell or missing cells from progeny of pluripotent or multipotent cells. Many groups of cells are used to turn into beta cells of the pancreas, which produce insulin during differentiation. Both embryonic stem cells (derived from the inner cell mass of a blastocyst) and adult stem cells (found in the postnatal organism) have been used to produce β-cells or otherwise restore the functioning of β-cell [25]. Embryonic stem cells (ESC): Stem cells follow appropriate developmental pathway in order become insulin producing cells by using embryonic stem cells transfusing with insulin promoter, resulting insulin producing cells in mouse ESC. Which permitted them to make insulin producing cells [24].

Induced pluripotent cells (IPSC): IPS has high reproducibility and pluripotency. These cells can be divided into cells that produce insulin. So, we can also make the pancreatic beta cells form these cells that can be used for the treatment of diabetes [25].

Mesenchymal stem cell (MSC) therapy: Stem Cell Therapy is an alternative to small islet cell transplantation in patients with type 2 diabetes. Mesenchymal stem cell (MSC) can be obtained from patients with autologous transplantation. However, autologous MSCs from diabetic patients are still remarkably different from ESCs, because of prolonged exposure to hyperglycemia [26].By using these different kinds of stem cell technologies, we can make the insulin producing cells that will be helpful in the cure of diabetes that is worldwide disease. Type 1 diabetes can successfully treated by using β cell from stem cells where type 2 diabetes is treated by using β cell in combination with drug therapy [27].

Stem cells and cardiac repair

Cardiovascular diseases (CVD), hypertension, coronary heart disease (CHD), stroke, and cardiac arrest (CHF) were the leading causes of death. Finally, stem cells can satisfy a large unmet clinical need and improve the quality of life of millions of people with cardiovascular diseases [28]. Reliable evidence suggests that stem cells promise to be a treatment for damaged myocardial regeneration. Ischemic heart failure occurs when there is a lack of oxygen in the tissues of the heart [29].

Types of stem cells investigated to regenerate damaged myocardial tissue

Adult and embryonic stem cells have been investigated to regenerate damaged myocardial tissue in animal models and in a limited number of clinical studies. Specific considerations for the application of various cell types will be discussed in the following sections [30]. Embryonic stem (ES) cells: Pluripotent ES cells can produce various types of cells that repair damaged myocardial tissue, including myocardial cells, endothelial cells and smooth muscle cells. For this purpose, it has been shown that mouse and human ES cells spontaneously differentiate in vivo to form endothelial muscle and smooth muscle cells in the body. Human ES cells differentiate into myocytes with the structural and functional properties of myocardial cells. Moreover, ES cells that were transplanted into is chemically injured myocardium in rats differentiated into normal myocardial cells that remained viable for up to four months suggesting that these cells may be candidates for regenerative therapy in humans [31].

Other diseases

Stroke

Stroke triggers the loss of neurons and glial cells in large numbers. In the treatment of this disease, cell therapy opens fresh horizons by facilitating the process of neuronal regeneration. Animal studies and several preclinical studies verify the effectiveness of cell therapy in post-stroke functional enhancement [3].

Spinal cord injury

Spinal cord injury is one of the serious neurological damage caused by neuronal tissue loss and consequently sensory and motor function loss. There is no therapy for this damage to be regenerated. This harm can be remedied by replacing stem or progenitor cells [32].

Inflammatory bowel disease

Crohn and ulcerative colitis were referred to as inflammatory diseases of the intestine. The precise cause of these illnesses is still unknown, but one of their causes is immune system dysfunction. Because stem cells are immunoregulatory cells, and also because of their capacity to transdifferentiate and fuse cells, they appear to have a beneficial impact on improving these illnesses [33].

Liver diseases

Stem cell transplantation has now been proposed in the therapy of cirrhosis as a novel technique. For this purpose, various types of stem cells such as embryonic stem cells, mesenchymal stem cells, annex stem cells and endothelial progenitor cells were used in laboratory studies. Also, laboratory studies have shown that primary hepatocytes can be replaced in liver, spleen, peritoneal cavity and other sites outside the liver [34].

Benefits of stem cell therapy

With so many treatment options out there, you may be surprised what benefits stem cell therapy provides. Some of the benefits include minimal risk, minimal recovery time and minimal worry. Here are 5 more specific benefits to be aware of- no need of surgery and avoid its risks and complications because it is an invasive, non-surgical procedure, required less post-procedural recovery time, does not require the use of general anesthesia, there is no risk of rejection because this therapy uses the biologics extracts from the patient, no risk of communicable disease transmission [35].

The potential growth of stem cells relies on effective recruitment of host stem or progenitor cells into the implanted biomaterial scaffolds and induction of the infiltrating cells into tissue-specific cell lineages for functional tissue regeneration [36]. Growth factors released from the scaffolds could remarkably prompt stem cell growth and differentiation, but most of these proteins cannot bind with scaffolds and so require a bridge to covalently crosslink scaffolds on one end and bind growth factors on another end. Heparin, one such element, has high levels of sulfated anionic glycosaminoglycans that contain a growth factor binding domain [37] which allows heparin to bind growth factors with high affinity while retaining its biological activity. Using heparin with growth factors controls their release keeps stem cells viable after transplantation into host tissues or organs [38].

Side effects of stem cell transplant

After the transplantation many of the side effects are happens to the patient shortly after the transplant and later. These side effects are briefly described below-

Shortly after the transplants

Many of the problems can happens shortly after the transplants this includes- mouth and throat pain, nausea and vomiting, infection, bleeding and transfusions, interstitial pneumonitis, other

lung problems, graft failure and graft-versus-host disease. When the body does not accept the new stem cells the graft fails. Graft failure is more common when the patient and donor are not well matched and when patients get stem cells that have had the T-cells removed. Graft failure can lead to serious bleeding and/or infection and graft-versus-host disease (GVHD) can happen in allogeneic transplants when the immune cells from the donor see the recipient's body as foreign. Doctors think of GVHD as acute or chronic. Acute GVHD starts immediately after transplant and lasts a short time. Chronic GVHD starts later and lasts a long time [39].

Acute GVHD

The average time is about 25 days, but acute GVHD may occur between 10 and 90 days after transplantation. Skin rash, redness of the skin, redness of the palm and initial signs. It can spread throughout your body. Other symptoms include nausea, vomiting, abdominal cramps, diarrhea (moisture, sometimes bleeding), loss of appetite, yellowing of the skin and eyes (jaundice), abdominal pain (abdominal pain) and weight loss [40].

Chronic GVHD

90 to 600 days after the stem cell transplant, chronic GVHD can start anywhere. Rash on the palms of the hands or the soles of the feet are the first signs. The rash can spread and is usually itchy and dry. In severe cases, the skin may blister and peel, like a bad sunburn. Other symptoms of chronic GVHD can include: enlarged liver, bloated abdomen (belly), pain in the upper right part of the abdomen (belly), increased levels of liver enzymes in the blood (seen on blood tests), the skin feels tight, dry burning eyes, dryness or painful sores in the mouth, burning sensations when eating acidic foods, bacterial infections, and blockages in the smaller airways of the lungs, etc. [41].

Problems that may show up later

Organ damage, Relapse (the cancer comes back), Secondary (new) cancers, Abnormal growth of lymph tissues, infertility (the inability to produce children), hormone changes, such as changes in the thyroid or pituitary gland, cataracts (clouding of the lens of the eye, which causes vision loss) [42].

Dietary concerns during stem cell transplant

Patients with stem cell transplantation are very sensitive to microorganisms that can be transmitted through food and beverages. To provide a more protected environment, transplant patients are maintained on a diet upon admission which is secure for the patient. The stem cell transplant diet restrictions continue until the patient's ANC (ANC: The absolute neutrophil count, the number of white blood cells (WBCs) that are neutrophils) is greater than 500 for three consecutive days and if graft vs. host disease is not present [43]. Patients who underwent autologous or allogeneic HSCT(hematopoietic stem cell therapy) had more pronounced changes in diet acceptance and longer hospital stays, as well as a greater delay from transplantation until engraftment because they are at increased nutritional risk due to the underlying disease, high metabolic demand and complications related to the conditioning regimen, which mostly affect the gastrointestinal tract, and are thus able to cause symptoms, such as nausea, vomiting, mucositis, odynophagia, diarrhea, abdominal pain and constipation, that make the ingestion of food and absorption of nutrients worse [44, 45]. When the appropriate transplantation occurs, the special diet is terminated. The special diet will be stopped when adequate engraftment occurs; however, it is a good idea to continue to use safe food handling and preparation even after the special diet restrictions have ended. Diet guidelines should be maintained before and after therapy [46].

Interruptions, challenges and prospects

Though stem cells offer breathtaking commitment for coming therapies, significant technical hurdles remain. One of the major interruptions is that mass proliferation of stem cells to generate enough quantities of tissue is required for useful transplant purposes. Secondly differentiated stem cells should be able to integrate into the surrounding tissue after transplantation and their functionality for the total duration of the patient's life is another area of concern along with the fears of immune rejection. Uses of autologous adult stem cells and lifelong immunosuppressive medicine can reduce the harmful side effects. Another major concern is the development of cancer after SCT due to self-renewal and uncontrolled proliferation capabilities of stem cells, in this way making them able to malignant transformation as CSCs. Another major complexity after allogeneic hematopoietic stem cell transplantation is graft-versus-host disease is due to donor T-cell recognition of recipient alloantigen's. Autologous hematopoietic stem cell transplantation

also exposes the development of a syndrome like allogeneic graft-versus-host disease causing serious disease in the GI tract [47].

Though this field is still in its primary stage, scientists are hopeful to use iPSCs in transplantation therapy. Use of retroviral vectors to initiate transcription factors for reprogramming objective can be harmful itself with a raise risk of cancer and viral disease development therefore researchers are currently investigating non-viral allotment techniques. Although the nature of the reprogramming method is still not surely clear and the developmental potential of iPSCs derived from various tissues using various methods is unknown. Another main challenge is to recognize adult or cancer stem cells in a tissue population [48].

Many preclinical studies regarding SCT have moved to clinical trials and translational stage. Such as to promote recovery of the damaged heart after myocardial infarction (MI), stem cells have been delivered by intracoronary infusion. Where, recent reviews of these clinical trials report that less than half of the trials found only small improvements in cardiac function. Significant tasks yet remain to enhance the usefulness of stem cell therapy for CVD including improved identification, recruitment, and in vitro growth of autologous stem cells, besides identification of mobilizing and homing agents, and development of novel culture conditions to improve stem cell survival and engraftment. Other clinical trials are planned to address treatment options for diabetes and kidney diseases [49].

To date (08/04/2019), over 880 MSC-based clinical trials, complete or ongoing, have been registered in the US National Institutes of Health database, including hematological diseases, graft versus host disease, diabetes, organ transplantation, inflammatory diseases, and diseases in the lung, liver, bone as well as cardiovascular, neurological and autoimmune diseases. Most of the above clinical trials are carried out in early phases (phase I–II), suggesting that the efficiency of SC treatment remains to be further investigated in the long-term [50].

Conclusion

There is a lot of research on investigating how stem cells can be used to treat different types of diseases. It is expected that; stem cell therapy might be used to develop for many types of diseases in future for which there are no effective treatments now. The obtained pluripotent stem cells and adult stem cells are important candidates for regenerative therapy because of the nature

of self-healing and the wide range of properties of pluripotency. Stem cells have been tested for use in various diseases, such as diabetes, kidney disease, spinal cord injuries, heart disease, stroke and Parkinson's disease, as well as various forms of blood diseases. Where kidney disease has been studied, there is no proven treatment for this disease with stem cells because of its complex structure. On the other hand, type 1 diabetes can successfully treated by using β cell from stem cells where type 2 diabetes is treated by using β cell in combination with drug therapy. And for the patient with different heart disease stem cell therapeutics are very promising. As stem cell therapy has many benefits for treating disease it also has some side effects too. Stem cells have a bright future for the therapeutic world according to different literature. We hope to see new horizon of 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 which will add new dimension to the treatment and healing process of ailing patients.

Acknowledgments

The authors acknowledge the support of Department of Food Technology & Nutrition Science, NSTU for the opportunity to conduct this research work.

Competing interests

The authors declare that they have no competing interests.

Authors contributions

Md Ruhul Kabir & Nahian Rahman conceptualized the idea, analyzed updated evidence, compared it, conducted the study and prepared the manuscript and drafting. Mussamat Mahbuba Sultana & Marium Sultana helped in drafting process and comparison. All other authors helped in manuscript preparation, drafting and submission.

Ethics declarations

Ethics approval: Not applicable.

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