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Stem Cells, Their Potential Therapeutic USES And Challenges In Low-Income Countries

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Abstract
Stem cells are defined as cells with the capacity for self-renewal, clonogenicity, and differentiation into a variety of cell lineages. Everyone has stem cells, from the earliest stages of human development to the end of life. The potential of stem cells to differentiate in different cell lines can be categorized into five main groups, totipotent, pluripotent, multipotent, oligopotent, and unipotent. Our brains, bones, muscles, nerves, blood, skin, and other organs all require them for proper growth, maintenance, and repair. Using stem cells to give consistent, reliable therapeutic interventions for life-altering medical disorders is known as stem cell therapy. Nigerians and other low-income countries are not spared from this effort, which is being waged by numerous researchers worldwide to find solutions to the problems this therapy presents. Many moral and scientific challenges are raised by stem cell research. Stem cell therapy, a prologue to an era of medical discovery of cell-based therapies that will one day restore function to those whose lives are now challenged every day, is still at the beginning of the road. Before stem cells may reach their full therapeutic potential, much more has to be studied about their biology, handling, and safety. Stem cells have immense potential in tissue regeneration and repair.

Keywords: *difficulties, tissue regeneration, cell-based therapeutics, and stem cells.*

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I. INTRODUCTION

Stem cells are regenerative, or repair networks found mostly in multicellular organisms such as human beings. They are simply defined as unspecialized biological cells which have the unique feature of unlimited self-renewal and differentiation into any cell of an organism (Zakrzewski et al., 2010). The attribute of "steaminess" in stem cells is greatly influenced by its niche or microenvironment which constitutes the signaling molecules, interaction between neighboring extracellular matrix and intercellular communication (Ramakrishna et al., 2011).

We all have them, from the beginning of human growth to the conclusion of life. They stand out for their capacity to renew through mitotic cell division and differentiate into a wide variety of specialized cell types. They are essential to the formation, expansion, upkeep, and repair of our bones, muscles, nerves, blood, skin, and other organs as well as our brains. The range of potential stem cell-based therapies has increased recently as a result of developments in stem cell research, even though stem cell-based therapies for some conditions, such as hematopoietic stem cell transplants for leukemia and epithelial stem cell-based therapies for burns and corneal disorders, have already been established as clinical standards of care. It has only recently become possible to explore growing stem cells for extended periods outside the body because scientists have improved their understanding of these cells. With that advancement, rigorous studies may be carried out, and it is now feasible to manipulate these cells to develop particular tissues (Kalra & Tomar 2014).

TYPES:

According to differentiation potential, stem cells are divided into 5 types: totipotent, pluripotent (which categorized into embryonic and induced pluripotent stem cell), multipotent, oligopotent and unipotent (*Hans R. 2007*).

Totipotent

Totipotent stem cells, also referred to as omnipotent cells, have the capacity to differentiate into extra-embryonic and embryonic cell types. Such cells have the capacity to create a whole, working organism (Schöler HR. 2007). These cells are produced when sperm and egg cells unite. The early divisions of the fertilized egg's cells result in the formation of totipotent cells (Mitalipov S. 2009). Totipotent cells are able to differentiate into

practically any form of a cell and are derived from pluripotent stem cells (Schöler HR. 2007).

Pluripotent

Pluripotent stem cells are the descendants of totipotent cells and can differentiate into nearly all cells *(Schöler HR. 2007).* Pluripotent cells got from the inner cell mass of the blastocyst formed during successive mitotic divisions of the zygote, a totipotent cell that results from the fertilization of an oocyte by a spermatozoon. Examples of matured cell types that originate from ESCs include adipocytes, muscle cells, chondrocytes, hepatocytes, enterocytes and neurons.

Pluripotent stem cells can be generated by integrating programming factors into adult differentiated cells these are called induced pluripotent stem cell. Induced pluripotent stem cells (iPSCs) are artificial stem cells produced from somatic cells through co-expression of defined pluripotency-associated factors *(Takahashi K et al., 2007).* Like embryonic stem cells (ESCs), they can typically proliferate and self-renew indefinitely in vitro and differentiate into derivatives of all three primary germ layers (i.e., ectoderm, mesoderm, and endoderm) as well as germ cells that give rise to the gametes. However, according to the strictest definition, genuine or bona fide iPSCs could develop into an entire embryo in conjunction with extra embryonic membranes. Since the full pluripotency of iPSCs has been demonstrated by several studies through the most stringent test of pluripotency, that is, tetraploid complementation, it is possible to derive truly pluripotent iPSCs from somatic cells *(Boland MJ.et al., 2009*) Because of these features, iPSCs have numerous biomedical applications in basic research, drug screening, toxicological studies, disease modeling, and cell therapy *(Shi Y. et al., 2017)* The ability to harness ESCs in vitro to generate specialized cells used for therapy is as a result of their pluripotency and unlimited expansive nature. The spontaneous differentiation trend of embryonic stem cells if not controlled or checked as a safety criterion may give rise to undesirable teratoma formation during therapy.

Multipotent

Multipotent stem cells can differentiate into a number of cell types, but only those of a closely related family of cells *(Schöler HR. 2007).* Examples include hematopoietic (adult) stem cells that can become red and white blood cells or platelets *(Kalra & Tomar 2014).*

Oligopotent

Having the capacity to differentiate into a small number of cells, such as adult lymphoid or myeloid stem cells (Kalra & Tomar 2014).

Unipotent

Possessing the self-renewal ability necessary to be classified as a stem cell but only having the capacity to create cells of the same type. Adult muscle stem cells are one example. By separating stem cells into two groups—early or embryonic and mature or adult—we can easily classify them. During about five days of development, a blastocyst's inner cell mass contains early stem cells, also known as embryonic stem cells. Certain adult bodily tissues, the umbilical cord, and the placenta after birth all contain mature stem cells (Jesse K. et al., 2009)

STEM CELLS THERAPEUTIC USES

The use of stem cells in stem cell therapy includes interventions for debilitating medical conditions like Alzheimer's disease, neurological disorders, diabetes, cardiovascular diseases, vision impairment, sexual dysfunction, burns, lost or damaged cells, tissues, and organs, as well as for treating or preventing diseases(Ramakrishna et al., 2018).Stem cell therapy procedures are in four stages. The processes include: extraction of cells from adipose tissues, bone marrow or umbilical cord through liposuction; concentration of harvested adult stem cells by centrifugation; activation of stem cells with a small dose of platelet rich plasma, which allows stem cells to grow in the new environment without any form of alterations in their biological structure; and then transplantation of activated stem cells into affected areas in patients using techniques such as X-rays and ultrasounds for maximum precision *(Miana et al., 2018*).

Stem cell therapy being naturally regenerative with no surgical complications is quicker, safer and requires lesser recovery time (about few weeks interval) unlike the conventional invasive approaches such as surgery *(O'Brien et al., 2009*)**.** Stem cell treatment may also provide knowledge for society to further stem cell understanding and future treatments (*Master Z. et al., 2007).*

Alzheimer's disease (AD)

Alzheimer's disease (AD) also referred to as senile dementia is an irreversible, progressive neurodegenerative disease that destroys memory and other important mental functions *(Cherubini et al., 2010).* Memory loss and confusion are the main symptoms for AD while the cause of the disease is still unknown though

it is assumed to be a combination of genetic, lifestyle and environmental factors. It accounts for between 60% to 80% of dementia cases worldwide *(Moghadam et al., 2009*). By the year 2018, 15,183 deaths were recorded while 318,000 prevalence was recorded in 2015. Stem cell therapy promises to be a unique approach to treating Alzheimer's disease. For instance, there was significant progress in behavioral disorder and memory with no sign of tumor as neural precursor cells derived from embryonic stem cells were injected in mice *(Moghadam et al., 2009*). In 2010, it was reported that apoptosis, markers of glial activity and oxidative stress were reduced in mouse brain as mesenchymal stem cells derived from human umbilical cord were injected into Alzheimer's mice. Likewise, cognitive abilities and learning memory in mice were returned *(Carter et al., 2010).*

Neurodegeneration

Brain degenerative diseases like Parkinson's, Amyotrophic lateral sclerosis, and Alzheimer's may be treated with stem cells. Neural stem cells, which proliferate to maintain general stem cell levels or become progenitor cells, are present in healthy adult brains. Progenitor cells migrate inside the brain of healthy adult animals and serve primarily to sustain populations of olfactory neurons (the sense of smell). In adult rats used as models for neurological disorders, pharmacological activation of endogenous neural stem cells has been shown to cause neuroprotection and behavioural recovery (Androutsellis *et al*, 2006)**.**

Diabetes

Diabetes affects millions of people in the world and is caused by the abnormal metabolism of insulin. Normally, insulin is produced and secreted by the cellular structures called the islets of Langerhans in the pancreas. Recently, insulin-expressing cells from mouse stem cells have been generated *(Kumar S. et al., 2006).* In addition, the cells self-assemble to form structures, which closely resemble normal pancreatic islets and produce insulin. Future research will need to investigate how to optimize conditions for insulin production with the aim of providing a stem cell-based therapy to treat diabetes to replace the constant need for insulin injections.

Cardiovascular diseases

Typically, autologous bone marrow stem cells are used in myocardial infarction stem cell therapy. Adipose-derived stem cells and other adult stem cell varieties could be employed (Paul A. et al., 2013). The production of heart muscle cells, stimulation of the development of new blood arteries to repair injured heart tissue, and growth factor secretion are examples of potential healing mechanisms. It's also possible that adult bone marrow cells can differentiate into heart muscle cells. After a cardiac injury, stem cell therapy has the ability to regenerate damaged cardiac tissue and stop the tissue loss that leads to heart failure (Giarratana. et al., 2005).

Blindness and vision impairment

Since 2003, researchers have successfully transplanted corneal stem cells into damaged eyes to restore vision. Sheets of retinal cells used by the team are harvested from aborted foetuses. When these sheets are transplanted over the damaged cornea, the stem cells stimulate renewed repair and help in restoring vision (Kelly, 2019).

Infertility

Culture of human embryonic stem cells in mitotically inactivated porcine ovarian fibroblasts (POF) causes differentiation into germ cells (precursor cells of oocytes and spermatozoa), as evidenced by gene expression analysis *(Richards M.et al., 2008*). It could potentially treat azoospermia. These cells have the potential to treat infertility.

Brain and spinal cord injury

Stroke and traumatic brain injury lead to cell death. It is characterized by loss of neurons and oligodendrocytes within the brain. A small clinical trial was underway in Scotland in 2013, in which stem cells were injected into the brains of stroke patients.(Rouf & Kamain, 2016)

Haematopoiesis (blood-cell formation)

Multipotent stem cells harvested from bone marrow have been used since the 1960's to treat leukemia, myeloma and lymphoma. Since cells there give rise to lymphocytes, megakaryocytes and erythrocytes, the value of these cells is easily understood in treating blood cancers. Recently, some progress has been reported in the use of cells derived from bone marrow to treat other diseases. For example, the ability to form whole joints in mouse models has been achieved starting with mesenchymal stem cells that give rise to bone and cartilage *(Singec et al., 2007).*

Baldness

Hair follicles also contain stem cells. These follicle stem cells may help in treating baldness through an activation of the stem cells progenitor cells. Baldness is treated by activating already existing stem cells on the scalp. Baldness treatments may be able to signal follicle stem cells to give off chemical signals to nearby follicle cells which have shrunk during the aging process. These follicles in turn respond to these signals by regenerating and once again making healthy hair.

Missing teeth

The tooth regeneration technology can be used to grow live teeth in human patients. Stem cells taken from the patient could be coaxed in the lab into turning into a tooth bud which can be implanted in the gums. It will give rise to a new tooth and would be expected to be grown in a time over three weeks (Singularity HUB). It will fuse with the jawbone and release chemicals that encourage nerves and blood vessels to connect with it. The process is similar to what happens when humans grow their original adult teeth.

Deafness

Heller has reported success in re-growing cochlea hair cells with the use of embryonic stem cells (Patil,2015).

Orthopedics

Mesenchymal stem cells play an important role in treatment of many orthopaedic conditions. It may increase cartilage and meniscus volume in individual human subjects *(Busse D. et al., 2008)*.Their results show adequate safety and minimal complications associated with mesenchymal cell transplantation *(Centeno CJ. et al., 2010).*

Wound healing

Stem cells can also be used to stimulate the growth of human tissues. In an adult, wounded tissue is replaced by scar tissue. The scar tissue is characterized in the skin by disorganized collagen structure, loss of hair follicles and irregular vascular structure. In the case of wounded foetal tissue, wounded tissue is replaced with normal tissue through the activity of stem cells *(Gurtner GC et al., 2007).* A possible method for tissue regeneration in adults is to place adult stem cell at the site of injured tissue and allow the stem cells to stimulate differentiation in the tissue bed cells. This method elicits a regenerative response more similar to fetal wound-healing than adult scar tissue formation *(Gurtner GC. et al., 2007)*

CHALLENGES OF STEM CELL THERAPY

To accelerate the development of stem cell treatment, a number of obstacles must be investigated. Among these are difficulties facing scientists worldwide, which call for a greater comprehension of technology and scientific growth, as well as major issues and difficulties in developing and low-income nations.

Manufacturing issues

This is the most important global issue now. A thorough analysis of the manufacturing process, as well as the characterization and formal safety assessment of the product, is required prior to the introduction of stem cells to a human subject. The manufacturing process must take production consistency into account. Preclinical testing experts are required to provide streamlined safety evaluations for stem cells and their products (Goldring et al., 2011). Yet, early collaboration between regulatory bodies, treatment developers, and drug safety scientists is also crucial in this area.

Genetic instability

Genetic instability in stem cells is a problem that stem-cell therapies encounter globally. It has been shown that hESCs and iPSCs have an innate genomic instability when grown in culture (Baker et al., 2007). According to Sareen et al. (2009) and Ueyama et al. (2010), adult stem cells are unstable in culture (2011). Consequently, before beginning any cell-based therapy, it is crucial to do a thorough genetic investigation, including chromosomal abnormality and genome karyotyping. A comprehensive analysis is required to determine acceptable levels of genetic alteration. The same goes for cell surface indicators, transcription factor expression, proliferation potential, and differentiation propensity, all of which should be assessed (Blum et al., 2009). Furthermore, it is crucial to evaluate a culture heterogeneity since the engraftment of improperly or undifferentiated cells may provide a significant risk of tumorigenesis or immune dysfunction for the recipient (Fairchild et al., 2010).

Stem cell culture condition

The FDA has expressed concerns, one of which being the requirement that the created cell product be fully described, anticipated, and free of contamination (Geronet al., 2009). Maintaining stem cells' genotypic and phenotypic activity in the correct condition in vitro is another part of stem cell therapy. There is an increased risk of chromosomal abnormalities when a stem cell line's number of passages rises (Hovatta et a., 2010).

Pharmacological issue

The difficulties that can't be solved using typical analytical processes created for low-molecular-weight medications or other biopharmaceuticals are another component of the difficulty that is being faced globally during the development of stem cell therapy. In reality, medications can seriously damage stem cells. Sometimes the provided stem cells are affected by medication given during or after transplant for several common goals, such as transplant rejection or decreased immunity at the time of transplant (Baxter et al., 2010). As a result, it is necessary to analyze preclinical research using a large animal model to take into account the actual pharmacokinetic behavior of stem cells.

Stem cell distribution after transplant

In animals with weakened immune systems, pluripotent stem cells can develop teratomas (Blum et al., 2009). Improper stem cell localization and dissemination following transplant is a significant issue. Thus, the capacity to track cell distribution within the host following treatment is essential. A good methodology must be used to track the behavior of transplanted cells, or else incorrect ectopic tissue formation or tumorigenicity may ensue. In reality, stem cells may be impossible to diffrentaite from host cells. GFP-labeled cells can be given to an animal model for this purpose, and the migration to organs other than the intended target can be tracked using qPCR, histological analysis, nuclear magnetic resonance (NMR), or magnetic resonance imaging (MRI) scans of the entire animal or fixed slices of tissue (Xiong et al., 2010).

Before administering stem cells into the host during stem cell therapy, immunological considerations must be made. To avoid immunological complications, cells are sufficiently defined by assessing their antigen and other cell surface indicators. To achieve appropriate resolution in human individuals, the host and graft cells should be monitored based on these immunological features (Okamura et al., 2007). More research is required to fully understand how the graft interacts with the host immune because the risk of immunotoxicity is still poorly understood.

CHALLENGES IN DEVELOPING COUNTRIES

In addition to global challenges to Stem cell therapy, Nigeria faces some peculiar challenges as follows;

Awareness

In a research on the utilization of BMT for the treatment of sickle cell anemia in tertiary health centers throughout certain states in Nigeria, 64.5% of the respondents knew that BMT might be used; nonetheless, this is low compared to reports from industrialized countries (Adediran et al., 2016). Donor acquisition is very difficult due to low awareness..

Beliefs

In Nigeria, stem cell applications are greatly hampered by cultural and religious beliefs. The human body has a certain amount of sacredness attached to it. This has an impact on the development of therapeutic research involving human organs, such as the umbilical cord, which is viewed as a disposable biological by-product. These cords could, however, be cut off at birth and stored in the cord blood bank for use in research and treatment (Olayanju et al., 2017).

Inconsistent Power Supply

The irregular and unstable electricity supply in Nigeria is one of the biggest problems that businesses, organizations, and the healthcare industry must deal with. For the purpose of maintaining and preserving cells in the bank, stem cell research and banking require a continuous electricity supply. Apheresis and cryopreservation procedures need to be carried out with an uninterrupted power supply for the SCT machines to function properly. It is impossible to store stem cells in a bank when there is no reliable power source. Electricity fluctuations are causing damage to electrical equipment that is in use. Private companies may choose to run their electrical generators on gas or fuel, which would result in higher costs (Nwagu et al., 2020).

Shortage of Trained Medical Personnel and Poor Funding

When compared to the population of Nigeria, the number of medical experts, such as Medical Laboratory scientists, doctors, nurses, and other medically linked professions, who are trained in stem cell technology, is

negligible. In spite of several vows to fund the health sector, Nigeria's statistics on health care growth are bad. Due to inadequate financing, medical research is progressing slowly in Nigeria. They may not have received appropriate money for their training since they are unable to pay for their education in this field of medicine (Nwant todi et al., 2014).

Inadequate Facilities and Building

Poor funding makes it difficult to afford the costly purchases and upkeep of the facilities required for stem cell technologies. Poor maintenance practices have an impact on the machines utilized in the majority of Nigerian hospitals and laboratories. In Nigeria, there are centers for stem cell research in Lagos and Abuja (Nwannadi et al., 2018). Due to the high transportation costs required to travel to either of these two states, the lack of suitable stem cell centers makes the assessment of stem cells all but impossible. In addition to investing in standard equipment, it's crucial to have spares on hand for SCT-related equipment (stem cell therapy). Also, it is crucial to check that the diagnostic unit of the facility is up to minimum standard, notably the laboratory and radiology departments.

Cost of Stem Cell Therapy

Lack of insurance coverage from public or private sources is a significant barrier to stem cell transplant accessibility in Nigeria (Mitchell et al., 2011). At the University of Benin Teaching Hospital (UBTH), Nigeria, noteworthy attempts were undertaken in 2011 to pioneer bone marrow transplantation (BMT). Due to a lack of political will on the part of the Nigerian government, this practice could not be maintained at the UBTC. At the moment, BMT costs about ten million nairas to perform in just one private hospital in Nigeria (10 million naira which is about 26000 USD). Drugs for SCT are very expensive to acquire in developing countries like Nigeria and the process of importing drugs from abroad has proven difficult throughout the years.

PROSPECTS AND WAY FORWARD

Notwithstanding the ethical, financial, social, political, and religious difficulties stem cell therapy in Nigeria faces, there is still hope for the country's health industry to overcome these obstacles in the years to come, but only if the welfare of citizens is given priority above the pursuit of profit. The treatment of infectious and non-infectious disorders should be a focus of future stem cell research in Nigeria, and it would be crucial whether the country's government can use stem cell research to strengthen its economy. It is crucial to invest in cord blood banking since the stem cells that can be extracted from it have hematological properties, can be employed for bone repair, and can act as immune modulatory cells in allogeneic transplantation. Cord blood banking and a donor registry will generate income that would help the Nigerian economy (Nwannadi et al., 2014).

The obstacle that traditional beliefs are placing on stem cell technologies in Nigeria can be removed with more awareness. This can be accomplished by educating everyone on stem cells and their technologies, especially those in rural areas and more populated areas like offices, marketplaces, hospitals, and schools. To properly advise patients, cell donors, and the general public in making informed decisions and voluntary contributions respectively based on their various life principles, Nigerian healthcare providers should be adequately equipped with first-hand knowledge of the biology of stem cells, relating ethical issues, research design, treatment procedures, benefits, and the full implications of the therapy (Agbedia et al., 2013). Also, it is anticipated that the Nigerian government will intensify its efforts to lower mortality and morbidity rates across the country by reorganizing and planning its health rules and policies to support stem cell therapy.

II. CONCLUSION

The drawbacks of stem cell therapy have prevented the average person from benefiting from stem cell transplants. In addition to research, the nation's social services need to be improved so that patients and their families are aware of the necessity to adhere to treatment during the post-transplant period. By 2030, stem cell research and therapy in the country are expected to have made significant strides, making this technology a viable treatment option for non-communicable disorders. With the implementation of all of the aforementioned suggestions, stem cell research and technology will rapidly advance throughout the nation, resulting in a decrease in morbidity and mortality from diseases that today appear to have no effective medical treatments.

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