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Stem Cell and its Applications in Medical Biotechnology

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Stem cells are undifferentiated cells in multicellular organisms that can be specialized into many types of cells and multiply into different types of cells. Stem cells can be produced from many sources in the body such as early embryos, embryonic tissue, foetal membranes *i e*; chorion and amnion, umbilical cord, and amniotic fluid. Stem cells are also present in organs of adult organisms like blood, skin, skeletal muscle, bone marrow, etc., Stem cells can be totipotent, pluripotent, multipotent, and unipotent. Stem cells are used to regenerate injured cells in the body, and repair the cells due to any kind of disease. From all types of cells, totipotent stem cells can generate any

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kind of cells in the body so they are the most important type of cells. Along with this, pluripotent stem cells also produce all types of cells, except the placenta or embryonic cells. These cells can be isolated from the body from the late embryonic stage after 1 week of the birth of a child, from the miscarriage of 12 weeks, and also from the umbilical cord of the child. These can be stored for another 2 decades. Another type is multipotent stem cells, which can generate a limited number of cells in a specific type; the last fourth type is unipotent stem cells, which can only produce cells of their own type. Diagnosis with stem cells is a useful technique to treat patients with many blood-related diseases for example blood cancer, thalassemia, etc., It also cures diseases like diabetes, liver disease, bone and cartilage, and organ transplantation.

Keywords: Stem cell; totipotent; pluripotent; multipotent; regenerative medicine.

1. INTRODUCTION

1.1 Stem Cell

Stem cells, which typically originate from a single cell (clonal), proliferate extensively (self-replicate), differentiate into numerous cell and tissue types, and are composed of undifferentiated cells. Stem cells originate from diverse sources and possess unique characteristics. Pluripotent cells, as well as pluripotent stem cells generated through induction, are produced by reprogramming somatic stem cells, which are derived from interior embryonic cells of the blastocysts. All three embryonic layers' tissues are capable of dividing from pluripotent cells: ectoderm, mesoderm, and endoderm. A single lineage of pluripotent stem cells is capable of differentiating into numerous tissues, including cartilage-forming mesenchymal cells, adipose tissue, and bone cells. Tissue-dependent cells are oligopotent because they undergo a diverse array of cellular differentiation within distinct tissues. For the regeneration of organs or the replacement of damaged cells, stem cells may be utilized in cell therapy. In addition, stem cells contribute to our comprehension and awareness of the pathogenesis of disease and development [1].

The fusion of sperm and egg results in fertilization, leading to the formation of the blastocyst. The tissue is enveloped by embryonic stem cells, which are a particular type of stem cell. Two main cell types make up the blastocyst. These are the inner cell mass (ICM) and the trophectoderm (TE), which develop in the ectoderm and trigger fetal development. The blastocyst is responsible for regulating the ICM microenvironment.TEs continue their development and produce many extraembryonic support structures that are necessary for the development of the embryo, such as the placenta. placenta. Once TEs begin to develop specific promotors, Inner giant cells continue to proliferate, remain pluripotent, and lack differentiation. Stem cell pluripotency enables them to differentiate from a single cell within the organism. Different types of stem cells are described in Fig. 1.

1.2 Origin

The initial discovery of stem cells occurred in 1961, when Dr. James A. Till and Ernest A. McCulloch of the University of Toronto, Canada, reported on the matter. It was noted that stem cells from the bone marrow of rodents exhibited a propensity for multipotentiation, hence the name pluripotent stem cells (PSCs). Later on, in 1966, Keith Campbell, Lan Wilmut, and other associates at the Roslin Institute of the University of Edinburgh in Scotland cloned Dolly the sheep to demonstrate the effectiveness of somatic cell nuclear transfer (SCNT). James Thomson subsequently isolated the initial human embryonic stem cells (hESC) in the United States in 1998. From reprogrammed adult cells, inducible PSCs (iPSCs) were isolated in 2006 using only four out of twenty-four essential mutations. John Gurdon (Gordon Institute, Cambridge, UK) and Shinya Yamanaka (Kyoto University, Japan and Gladstone Institute, USA) were honoured in 2012 for their research demonstrating that mature cells can regenerate into a pluripotent state [2].

2. CLASSIFICATION

2.1 Based on their Differentiation Potential

One of the important features of stem cells is their ability to form different cell lineages. However, this ability is not the same across all stem cells and there are abilities across stem cells. A fertilized egg that can produce an entire

embryo and part of the placenta is a sample of a totipotent cell. The cells of the giant cell are considered pluripotent, and most cells that arise from the third layer of the organism may arise from giant cells, but the products of the placenta do not include body cells in the body. Most tissue-specific cells are pluripotent and tend to differentiate into two, three, or more different specific cell categories that manifest the functional attributes of the tissue in which they are situated.

Totipotent stem cells can undergo rapid cell division and specialize into many cell types across the entire organism. Totipotency refers to the highest level of cell division capacity, enabling cells to form both embryonic and certain extraembryonic structures. The Zygote, which forms when the sperm fertilizes the egg, is a great example of a totipotent cell. These cells can turn into the placenta or one of the three germ layers. Approximately four days later, the inner cell of the blastocyst acquires pluripotency. The generated structure serves as the source of pluripotent cells. Induced totipotent stem cells can be broken down into two different types. Induced totipotent stem cells can be broken down into two different types. The cells that have been activated are expanded stem cells (EPSC) and two cell-like cells (2CLC). Both cell types exhibit resemblances to totipotent stem cells. The cells divide into lines of embryonic and extraembryonic cells and merge with the host The cells divide into lines of embryonic and extraembryonic cells and merge with the host blastocyst to create the Inner giant cell and trophectoderm but their ability to grow is limited. (Lu and Zhang, 2015; Genet and Torres-Padilla, 2020). Injecting or transplanting morula and blastocysts with externally generated totipotent cells into the uterus has yielded varying outcomes. (Riveiro and Brickman, 2020). After transfer, EPSCs can stimulate the Trophectoderm and ICM of embryos, but cells in the TE express OCT4, there is a decrease in CDX2 and ELF5, and transferred embryos can grow up to 4.5 DPC [3].

Pluripotent stem cells (PSCs) can produce cells in all layers of tissue, except extraembryonic tissues for example the placenta. Embryonic stem cells (ESCs) serve as a prime illustration. ESCs are separated from the bulk of preimplantation embryo cells. Another illustration is making induced pluripotent stem cells (iPSCs) from the ectoderm of embryos that have been transplanted. Their ability to differentiate into many cell types is a progressive phenomenon, beginning with fully pluripotent cells (such as ESCs and iPSCs) and concluding with cells that have limited potency (oligopotent, pluripotent, or unipotent cells). Teratoma testing is a method used to assess the activity and spectrum. Induced pluripotent stem cells, often known as iPSCs, are pluripotent stem cells that are produced from somatic cells and have comparable functionalities to pluripotent stem cells (PSCs) [1].

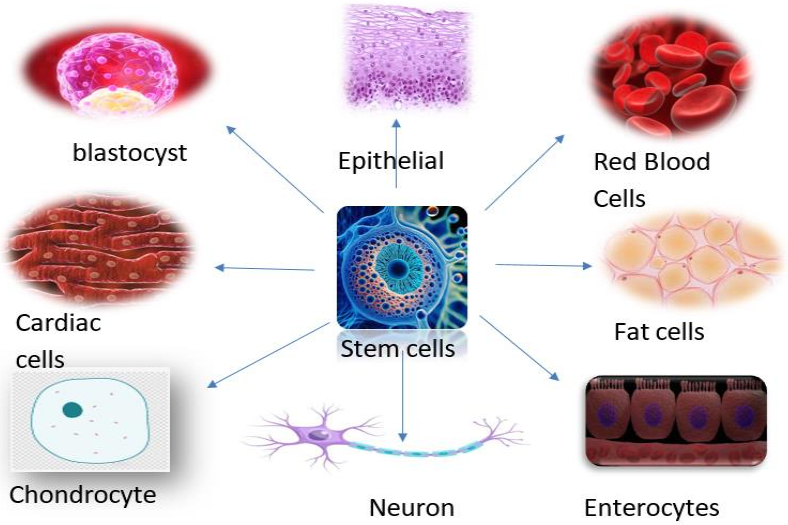

Fig. 1. Stem cells are differentiated cells and they can be of various types according to the division in the body for example blastocyst, cardiac cells, chondrocytes, epithelial cells, neuron cells, red blood cells, fat cells and enterocytes

They have been cultivated extremely effectively and are employed in regenerative medicine both currently and in the future. Pluripotent stem cells have a narrower lineage and are more capable of differentiating from PSCs, but they may be specialized cells that discriminate between certain diseases. Hematopoietic stem cells (HSCs) are one example; they are capable of differentiating into various blood cells. Their ability to proliferate is then limited to the cells of their progeny. However, some cells can divide into undifferentiated cells, suggesting that they are pluripotent cells. Different forms of pluripotent cells are defined in Fig. 2.

The bone marrow is an instance where oligopotent stem cells differentiate into white blood cells (WBC) but not red blood cells (RBC), showcasing their capacity to differentiate into many cell lineages.

Unipotent stem cells possess a restricted capacity to undergo differentiation into a particular cell type and possess a distinctive redistributive feature. Their ability to redistribute resources makes them promising candidates for regenerative therapy. These unipotent cells can mainly produce a single type of cell, such as skin cells.

Multipotent stem cells (MSCs) have important properties similar to other stem cells. Like other stem cells, over an extensive length of time, pluripotent stem cells have the remarkable capacity to undergo self-renewal and undergo cellular differentiation into a diverse array of specialized cells, each possessing its distinct repertoire of functions [4]. MSCs can differentiate in different lineages and self-renew. Mesenchymal stem cells (MSCs) have a significant role in promoting growth, facilitating tissue repair, and providing protection in biological processes [5]. Stem cell acquisition for diagnosing many disorders, including neurological and cardiovascular conditions, has gained significant recognition in recent years. This field holds immense potential for the advancement of medicine. A wide variety of cell types may be differentiated from these stem cells., although their capacity to specialize is limited. For instance, mesenchymal stem cells can undergo differentiation into nerve cells and glial cells. On the other hand, hematopoietic stem cells can divide and give rise to numerous varieties of red blood cells, however, they can't generate enough cells for the brain. MSCs, or mesenchymal stem cells, are responsible for the are widely recognized as a prominent subset of mesenchymal stem cells, being capable of differentiating into numerous cell types. Multiple studies have substantiated the ability of these specialized cells to undergo differentiation into various tissues, including cartilage, muscle, bone, fat, and other types of tissues. Mesenchymal stem cells can generate specialized cells. The stem cells mentioned are different from pluripotent stem cells, which can divide and transform into almost any type of cell, and totipotent stem cells, which can divide and transform into only one type of cell. Pluripotent stem cells are essential in the formation of mesenchymal stem cells, which are primitive cells responsible for generating specialized cells with distinct activities [6].

2.2 Based on their Origin

The four primary types of stem cells are early stem cells (ESCs), foetal stem cells (FSs), adult stem cells (ASCs), and induced pluripotent stem cells (iPSCs). These stem cells are classified based on their specific area of origin. Adult stem cells often exhibit either oligopotent or unipotent characteristics, while ESCs and iPSCs possess pluripotent properties due to their ability to differentiate into several cell types.

2.3 Embryonic Stem Cells

ESC can be identified by the presence of certain transcription factors, including Nanog and Oct 4. The presence of these substances sustains the undifferentiated state of stem cells and enables them to undergo self-renewal. An ESC line is produced when undifferentiated ESCs are cultured without any genetic defects. These cells can undergo cryopreservation and subsequent thawing for use in other cultures and research. The preservation of embryonic stem cells in an undifferentiated condition is highly dependent on the cultural environment. The nutrient layer of embryonic fibroblast cells (MEFC) or media containing the anti-differentiation cytokine leukemia inhibitory factor (LIF) is included. Embryonic stem cells (ESCs) passing through the feeder layer result in the formation of "germ bodies" that contain all three germ layers (endoderm, mesoderm, and ectoderm). (Zwaka & Thomson, 2005).

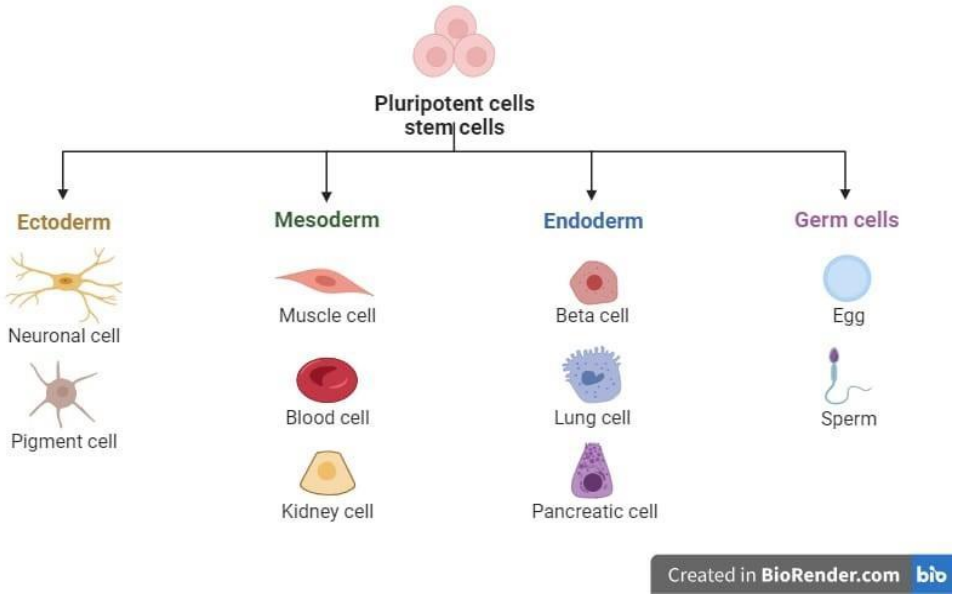

Fig. 2. Pluripotent stem cells are of different types based on their origin form ectoderm, mesoderm, endoderm, and germ cells in the form of neuronal cells, muscle cells, blood cells, kidney cells, lung cells, pancreatic cells, and egg, sperm cells

Table1. Difference between various types of stem cells totipotent, pluripotent, and oligopotent stem cells Du and Wu, [7]

Cell type	Origin	Characteristics	Application
Totipotent	All three embryonic germ layers and extra-embryonic tissue	It can create a complete organism for example zygote.	It can differentiate into 200 or more types of cells in the body for growth.
Pluripotent	All three embryonic germ layers	It can divide into most cell types but cannot make complete organisms for example embryonic stem cells and induced PSC.	It can produce any cell and tissue that the body needs for repair.
Oligopotent	WBC (White blood cells)	It can differentiate into a few types of cells.	It is used in defence as WBC are produced by this stem cell.

The cells that make up adult stem cells originate from adult tissue. Examples include human amniotic epithelial cells, which are stem cells taken from placental tissue, in addition to MSCs. These cells seem to have anti-inflammatory properties and promote the healing of animal injury models. Although these cells exhibited the ability to differentiate when germ cells are cultured into tissue from multiple layers in a laboratory, their ability to differentiate is limited. Adult stem cells are advocated due to their autologous nature, which eliminates ethical controversy and fears of refusal.

In addition to the placenta, adult stem cells can be extracted from all three germ layers of tissues. Numerous scientific investigations have demonstrated that the transplantation of these stem cells can restore damaged organs in living organisms. This includes the process of revascularizing ischemic heart tissues and repairing bone tissue by differentiating stem cells and generating new, specialized cells. Additional studies have illustrated that grown adult stem cells produce a range of chemical mediators that have angiogenic, immunomodulatory, anti-

apoptotic, and some chemoattractant properties, which aid in the process of restoration [8].

2.4 Tissue-Resident Stem Cells

Tissue stem cells are essential for the process of regenerating and repairing specific tissues and organs in adults by producing specialized cells that are specific to those tissues. According to studies, these cells form throughout ontogeny and remain resting unless they are stimulated locally to undergo growth, differentiation, or relocation. The "stem cell niche" is where tissue-resident stem cells remain. The milieu that controls these cells' ability to convert and self-renew is known as the stem cell niche. Numerous indications suggest that the microenvironment and external signals have a significant impact on stem cell activity; hence, the niche is essential for both tissue healing and stem cell homeostasis [9].

Although most tissue-resident stem cells remain inactive, they are stimulated by specific signals when there is an injury or need for repair. The mechanisms underlying the dormancy of tissue-resident strain cells are not well understood; nevertheless, it is anticipated to influence a distinct ecological habitat. This feature is essential for preserving a population of cells that solely produce tissue-specific cells during the repair process. The niche environment consists of many signals that are facilitated by the extracellular matrix and soluble mediators. These mediators regulate the expression of genes and the signaling between cells, hence governing the processes of stem cell growth, movement, specialization, and programmed cell death. The mechanisms by which stem cells shift from a state of self-renewal and proliferation to differentiation, or the unique signals required for this transition in distinct tissues, remain to be comprehended.

Additionally, the sort of cell division that stem cells undergo to control the cells that the cell type produces. When a stem cell splits a cell symmetrically, it produces identical daughter cells that produce new cells for healing injured cells. It is vital to remember that while stem cell depletion would impede organ repair, unchecked stem cell differentiation expansion could result in excessive growth of stem cells and/or the development of cancer; hence, it is essential to maintain a balance in stem cell homeostasis.

When a stem cell produces both a second differentiated daughter cell and a comparable daughter cell, this is known as asymmetric division. This process maintains the stem population cells while enabling organ repair and regeneration [10].

2.5 Induced Pluripotent Stem Cell

iPSCs originate from these somatic adult cells. They have been subjected to genetic reprogramming, resulting in the acquisition of "ESC-like states." Takahashi and Yamanaka created the first mouse-induced pluripotent stem cells (iPSCs) in 2006 by introducing four genes that encode the transcription factors SOX2, OCT3/4, KLF4, and c-MYC into mouse fibroblasts using a process called transduction. In 2007, Yamanaka and his colleagues reported the utilization of adult human dermal fibroblasts and four specific factors (Oct3/4, Klf4, Sox2, and c-Myc) to produce human induced pluripotent stem cells (hiPSCs) [11].

The ability of these cells to grow into human ESCs outside of the body, as well as their surface antigens, morphology, proliferation, epigenetic status, gene expression, and telomerase activity of genes specific to pluripotent cells, were all shown. Currently, induced pluripotent stem cells (iPSCs) are valued resources for conducting pharmaceutical research, disease modeling, and regenerative medicine. Nevertheless, while iPSCs and ESCs demonstrate pluripotent stem cell characteristics, it remains uncertain whether they will exhibit notable distinctions in therapeutic application. Induced pluripotent stem cells (iPSCs) are utilised in a therapeutic experiment is constrained by the employment of retroviral vectors, which deliver reprogramming factors into mature cells, as well as oncogenes such as c-Myc. The vectors employed for the delivery of transcription factors into mature cells can potentially lead to the development of cancer.

Researchers are currently investigating novel methods for creating genome-free iPSC modification that ensures safety. Various mouse breeds and adult somatic human cells have been used to illustrate the latest technologies. To inhibit the utilization of c-MYC and KLF4 oncoproteins, either OCT3/4 or KLF4 alone, or a combination of other factors, together with non-retroviral vector strategies, including plasmids, chemical compounds, adenoviruses, and transposons, were utilized. This innovative discovery has resulted in the development of an optimal method to revert cells to earlier undifferentiated stages and generate induced

pluripotent stem cells (iPSCs) that exhibit complete genetic compatibility with the donor cells. This particular method successfully bypasses the issue of rejection, regardless of the existence of significant safety concerns [12].

Tissue resident stem cells rely on a complex interplay of signals from their surrounding environment, called the niche, to regulate their function. These signals become especially important when there's an injury or a need for repair. some key signaling pathways involved are:

1. Niche-derived signals

- **Growth factors:** Following injury, cells in the damaged tissue release growth factors like epidermal growth factor (EGF) and fibroblast growth factor (FGF) which stimulate stem cell proliferation and differentiation [13].
- **Wnt signaling:** This pathway plays a crucial role in stem cell self-renewal and differentiation. Activation of Wnt signaling by niche cells promotes stem cell proliferation after injury [14].
- **Notch signaling:** This pathway helps maintain the balance between stem cells and their progeny. For instance, Notch signaling from stem cells can influence the fate of neighboring cells, promoting their maintenance (Chacon *et al*; 2018).

2. Signals from the extracellular matrix (ECM)

- **Stiffness and composition:** The stiffness and composition of the ECM surrounding the stem cells can influence their behavior. For instance, stiffer matrices associated with injury can trigger stem cell activation [13].

3. Self-signaling

- **Stem cells can also communicate with themselves through signaling pathways:** This can create feedback loops that regulate their response to injury cues [15].

Tissue-resident stem cells (TSCs) often exist in a dormant state, conserving energy and minimizing wear and tear until needed for repair or regeneration. Here's a breakdown of the mechanisms underlying this dormancy and how it influences their ecological niche:

2.6 Mechanisms of Dormancy

1. **Cell Cycle Regulation:** Dormant TSCs often exhibit low expression of cell cycle proteins, keeping them in a quiescent (resting) state. This can involve factors like p21 and p27, which inhibit cell cycle progression (Urban *et al*;2021).
2. **Metabolic Reprogramming:** Dormant TSCs tend to have lower metabolic activity compared to actively dividing cells. They rely more on oxidative phosphorylation for energy production, generating fewer reactive oxygen species (ROS) which can damage cellular components [16].

3. **Niche Signals:** The stem cell niche, composed of surrounding cells and the extracellular matrix (ECM), plays a crucial role. Dormant TSCs often receive signals from the niche that promote quiescence. These can include factors like Transforming Growth Factor-beta (TGF-β) and Bone Morphogenetic Proteins (BMPs) (Chacon *et al*; 2018).

2.7 Influence on Ecological Niche

The ability to enter and maintain dormancy allows TSCs to thrive in their distinct ecological habitat within the tissue:

- **Preservation of Stem Cell Pool:** Dormancy helps to conserve the pool of stem cells, preventing them from being depleted through unnecessary divisions. This is crucial for long-term tissue maintenance and repair capacity [17].
- **Reduced Vulnerability:** By staying dormant, TSCs are less susceptible to damage from factors like ROS or toxins in the tissue microenvironment. This ensures their survival for when they are truly needed [16].
- **Response to Specific Cues:** Dormancy allows TSCs to remain responsive to specific signals released during injury or stress. This ensures a targeted and efficient repair process when needed [18].

Stem cell differentiation from self-renewal and proliferation into distinct tissues is a complex process orchestrated by a unique interplay of signals. These signals can be broadly categorized as:

1. Niche-derived factors

- **Growth factors:** Specific growth factors like bone morphogenetic proteins (BMPs) for bone formation, Wnt signaling for neural development, and Sonic Hedgehog (Shh) for limb development play crucial roles in directing differentiation towards specific lineages [19,20,21].
- **Notch signaling:** This pathway helps regulate cell fate decisions. For example, activation of Notch signaling in a pool of stem cells can promote the development of certain cell types while inhibiting others [22].

These signals often work in a combinatorial fashion, with multiple factors acting together to determine the specific differentiation pathway a stem cell will take. The uniqueness of these signals lies in their:

- **Specificity:** Different tissues require distinct combinations of signals for proper development and regeneration.
- **Spatial and temporal control:** The timing and location of these signals are crucial for directing differentiation towards the correct cell type in the right place at the right time.

3. APPLICATION OF STEM CELLS IN MEDICAL BIOTECHNOLOGY

3.1 Application of Stem Cells in Cancer

Cancer, an intricate and diverse ailment distinguished by unregulated cellular proliferation, has consistently been a significant health issue. Despite notable progress in conventional treatments such as surgery, radiation, and chemotherapy, cancer continues to be a prominent cause of mortality worldwide. However, recent years have witnessed a burgeoning interest in stem cell therapy with the potential to revolutionize and revolutionize the field in the fight against cancer. Stem cells, by their remarkable self-regeneration and differentiation capabilities, hold immense promise in cancer treatment. Their potential applications can be broadly categorized into three main areas:

1. Targeting Tumour Cells

- Direct Cytotoxic Effect: Stem cells can be engineered genetically to generate particular chemicals that target and eliminate cancer cells selectively. The method employed, referred to as chimeric antigen receptor (CAR) T-cell therapy, T-cell extraction is involved from a patient, their modification with CARs that target certain cancer antigens, and their subsequent reintroduction into the patient. The therapeutic efficacy of CAR T-cell therapy of specific hematologic malignancies has been exceptionally promising, providing a glimmer of hope for patients with few therapeutic alternatives.
- Immunomodulatory Effects: To improve the capacity of the immune system to recognize and eliminate malignant cells, stem cells can also be utilized to modify it. Mesenchymal stem cells (MSCs), for instance, have shown promise in suppressing tumor growth and promoting anti-tumor immune responses.

2. Tissue Regeneration

- Cancer Treatment Adverse Effects: Cancer therapies such as radiation and chemotherapy can result in substantial harm to normal tissues. Stem cells offer a promising avenue for regenerating damaged tissues and promoting healing. For example, hematopoietic stem cells can be used to restore bone marrow function after chemotherapy, while stem cells derived from adipose tissue can be used to reconstruct breasts after mastectomy.
- Stem Cell Transplantation: Stem cells can be used to support bone marrow function in patients undergoing high-dose chemotherapy, allowing for more intensive treatment regimens with reduced risk of complications.
- Regenerating organs or replacing stem cells: Stem cells (SCs), which can multiply endlessly and have a great potential for differentiating into a wide range of cells.Prior to being transplanted into the patient to replace necrotic or degenerated cells, stem cells can be made to develop into particular cells or tissue types in vitro. Moreover, SCs have the ability to produce cytokines, exosomes, and anti-inflammatory substances to lessen inflammation and enhance the damaged area's microenvironment, which in turn controls cell division and proliferation [23].

3. Drug Discovery and Development

- Cancer Drug Testing: It is possible to generate tumor models from patients by

using their stem cells, which provide a more accurate platform for testing new cancer drugs than traditional animal models. This allows researchers to identify more effective drugs with fewer side effects.

- Personalised Medicine: Stem cells have the potential to generate personalized treatment plans for cancer patients. By analyzing individual patients' tumors, researchers can identify specific genetic mutations and tailor their treatment accordingly. This personalized approach can lead to more effective and targeted therapies [24].

3.2 Application of Stem Cells in Neurodegenerative Disease

Neurodegenerative diseases, a group of progressive disorders affecting the brain and nervous system, are a growing global health concern. Diseases like Alzheimer's, Parkinson's, and Huntington's disease lead to a gradual decline in cognitive function, movement, and other essential abilities, significantly impacting the lives of patients and their families. While current treatments offer some symptom relief, they do not address the underlying disease process or offer a cure. However, a new ray of hope emerges from the realm of stem cell research. Stem cells have the remarkable ability to differentiate into many cell types and to self-renew, making them highly promising for the treatment of neurodegenerative disorders. Their potential applications can be broadly categorized into three main areas:

1. Cell Replacement Therapy

- Replacing Damaged Cells: In neurodegenerative diseases, specific populations of neurons degenerate and die, leading to the observed symptoms. Stem cells can be differentiated into specific neuronal subtypes and transplanted into the affected brain areas. This approach aims to replace lost neurons and restore lost functions.
- Stem Cell-Derived Neural Progenitors: Stem cells can undergo differentiation and transform into neural progenitor cells, which are precursor cells that can further differentiate into various neuronal subtypes. This approach offers a more flexible and potentially scalable solution for cell replacement therapy.

2. Neuroprotection and Immunomodulation

- Supporting Neuronal Survival: Stem cells can release various factors that support the survival and function of existing neurons. These factors can protect neurons from damage and promote their repair, potentially slowing down disease progression.
- Modulating the Immune System: Neuroinflammation is a crucial factor in the advancement of neurodegenerative disorders. Stem cells possess the ability to regulate the immune response, thereby diminishing inflammation and safeguarding neurons against harm [41].

3. Modelling of Diseases and Drug Discovery:

- Patient-Derived Cell Models: Stem cells can be obtained from individuals afflicted with neurodegenerative disorders, thereby enabling scientists to fabricate individualized cell models that mimic the pathological state. It is possible to utilize these models to investigate disease mechanisms and evaluate potential therapeutic pharmaceuticals.
- High-Throughput Drug Screening: Stem cell-based models can be used for high-throughput screening of potential drugs, accelerating the discovery process for new treatments.

Stem cell therapy for neurodegenerative diseases is still in its early stages, but several promising clinical trials are underway. Some notable examples include CAR T-cell therapy for Alzheimer's disease. This therapy aims to eliminate harmful proteins in the brain that contribute to the disease. The therapeutic application of mesenchymal stem cells for the treatment of Parkinson's illness aims to protect dopaminergic neurons that are essential for movement control. Stem cell therapy for spinal cord injury aims to promote regeneration of damaged spinal cord tissue [25].

3.3 Application of Stem Cells in Gene Therapy

Gene therapy is a dynamic field that involves the transfer of genetic material into cells to treat genetic illnesses. It has great promise for therapeutic applications. Stem cells play a crucial part in the progress of gene therapy applications because of their unique ability to renew

themselves and transform into various types of cells.

1. Cellular Carriers for Gene Delivery: Genomic modification is an option for stem cells to carry therapeutic genes, acting as vehicles for delivering them to specific target tissues.

- Mesenchymal stem cells (MSCs): Due to their capacity to migrate to various tissues and their immunomodulatory properties, MSCs are promising carriers for delivering genes to treat inflammatory and autoimmune diseases.
- Hematopoietic stem cells (HSCs): These proliferating blood progenitor cells can be modified to carry genes for treating blood disorders like sickle cell anemia and beta-thalassemia.

2. Long-Term Expression: Stem cells' capacity for self-regeneration and differentiation allows for the long-term expression of therapeutic genes.This enables the maintenance of therapeutic effects over an extended period, hence minimizing the necessity for recurrent treatments.

3. Gene Correction and Editing: Stem cells can be used for gene editing using tools like CRISPR-Cas9. This enables the rectification of precise genetic mutations, providing a prospective remedy for genetic disorders [26].

4. Personalized Medicine: Stem cells can be obtained from specific patients, allowing for the creation of customized gene therapy methods. This enables customization of the therapy based on the individual patient's distinct genetic composition, which has the potential to result in therapies that are more efficient and less risky.

5. Drug Discovery and Disease Modelling: Stem cells have the potential to generate disease models that are particular to individual patients, enabling researchers to investigate the underlying causes of genetic illnesses and devise novel gene therapy approaches. These models can also be used for high-throughput drug screening to identify potential therapeutic candidates [27].

3.4 Examples of Promising Stem Cell-Based Gene therapy Applications Include

- Gene therapy for cystic fibrosis: Using lentiviral vectors to deliver a functional CFTR gene to lung epithelial cells derived from patient stem cells.
- Gene therapy for X-linked severe combined immunodeficiency (SCID): Replacing the defective IL2RG gene in HSCs of SCID patients using retroviral vectors [42].
- Gene therapy for Duchenne muscular dystrophy (DMD): Editing the dystrophin gene in muscle stem cells using CRISPR-Cas9 technology [28,52].

3.5 Application of Stem Cells in Diabetes

Stem cell research holds significant promise for the treatment of diabetes., as it allows for the exploration of the condition, the creation of innovative treatments, and the possibility of finding a solution. An important use involves converting stem cells into beta cells that produce insulin, to replace or regenerate the malfunctioning or damaged pancreatic beta cells that are characteristic of diabetes. Pluripotent stem cells, such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), are being investigated as a sustainable option for creating functional beta cells that can produce insulin in response to glucose levels [46,47]. Scientists have made significant progress in transforming stem cells into beta-like cells that display glucose-responsive insulin production, replicating the activity of natural beta cells. This method exhibits significant promise for cell replacement therapy, wherein these produced beta cells might be implanted into individuals with diabetes to reinstate regular insulin secretion and control blood glucose levels. Moreover, stem cells are pivotal in disease modelling and drug discovery for diabetes [45]. Patient-specific iPSCs derived from individuals with diabetes enable researchers to create disease models, studying the underlying mechanisms of the disease and testing potential therapeutic interventions in a personalized manner. These models not only aid in understanding disease progression but also facilitate the screening of new drugs and therapies for their efficacy and safety. However, challenges persist in translating stem cell-based therapies into viable treatments for diabetes. Issues such as immune rejection, the need for long-term functionality and safety of transplanted cells, and the scalability of producing large quantities of functional beta cells pose significant hurdles [29,30]. Furthermore, the ongoing study is centered around improving techniques to ensure effective and consistent

differentiation of stem cells into fully developed and functioning beta cells. In conclusion, stem cell research offers promising avenues in diabetes treatment by providing opportunities for generating functional beta cells, modelling the disease, and advancing drug discovery. While significant progress has been made, continued research efforts aimed at overcoming challenges related to safety, functionality, and scalability are crucial in realizing the complete potential of stem cell- based diabetes therapies.

3.6 Applications of Stem Cells in Cardiovascular Disease

Stem cell-based therapies have become a hopeful approach in the field of cardiovascular disease, providing prospective methods for repairing injured heart tissue, enhancing heart performance, and treating different heart disorders. An important application involves the utilization of many categories of stem cells, such as mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), and cardiac stem cells (CSCs), for regenerative purposes in heart diseases [43]. MSCs are recognized for their immunomodulatory and regenerative attributes as they have shown promise in repairing damaged heart tissue post-myocardial infarction (MI) through the regulation of the immune system, reduction of inflammation, and stimulation of tissue regeneration [31,32]. Similarly, iPSC-derived cardiomyocytes hold the potential for modelling cardiac diseases and drug testing, aiding in understanding disease mechanisms and identifying potential therapeutics [33]. Furthermore, cardiac progenitor or stem cells isolated from the heart tissue itself, known as CSCs, have been investigated for their regenerative potential in repairing injured myocardium. The cells can develop into various kinds of cardiac cells. and potentially regenerate damaged heart tissue [34]. In addition to their regenerative potential, stem cells are being explored for their paracrine effects, secreting factors that promote tissue repair and angiogenesis. The secretion of growth factors, cytokines, and extracellular vesicles by stem cells contributes to the regeneration of blood vessels and heart tissue, enhancing cardiac function post-injury [48]. Despite promising preclinical results, challenges persist in translating stem cell therapies into routine clinical practice for cardiovascular diseases. Issues such as optimal cell delivery methods, cell survival and integration within the host tissue, long-term safety, and the potential for arrhythmias require further investigation [35].

Stem cell therapy holds promise for cancer treatment, but it's still under development and carries potential risks and side effects. Here's a breakdown of some key concerns:

1. Graft-versus-Host Disease (GVHD)

This is a serious complication that can occur in allogeneic stem cell transplants, where stem cells come from a donor. In GVHD, the donated stem cells recognize the recipient's body as foreign and attack healthy tissues. Symptoms can range from mild skin rash to life-threatening organ damage [36].

2. Relapse of Cancer

There's a risk that the original cancer cells may not be completely eliminated by the treatment, and the cancer can return [38].

3. Tumor Formation

In some cases, the infused stem cells themselves have a small chance of developing into tumors. This risk is especially concerning with certain types of stem cells like embryonic stem cells [39].

4. Infection

Stem cell transplant recipients are more susceptible to infections due to the suppression of their immune system during the procedure.

Stem cell replacement therapy for neurodegenerative diseases holds immense promise, but there are significant limitations hindering its widespread use. Here's a breakdown of some key challenges:

1. Delivery and Targeting

- Delivering stem cells effectively to the specific regions of the damaged brain is a major hurdle. The blood-brain barrier, a protective layer surrounding the brain, can impede access [41].
- Once delivered, ensuring the stem cells migrate and differentiate into the desired functional neurons is another challenge.

2. Source of Stem Cells

- **Embryonic stem cells (ESCs):** These cells have the highest differentiation

potential but raise ethical concerns and carry a risk of tumor formation [37,39].

- **Adult stem cells:** These are readily available but have a more limited differentiation capacity [40].
- **Induced pluripotent stem cells (iPSCs):** These patient-derived stem cells can potentially overcome rejection issues but are still under development, and there are safety concerns regarding their potential to form tumors [50].

3. Understanding Disease Mechanisms

- Our understanding of the underlying causes of many neurodegenerative diseases, like Alzheimer's and Parkinson's, remains incomplete. This makes it difficult to design optimal stem cell therapies that target the root cause [44,45].

4. Ethical Considerations

- The use of embryonic stem cells raises ethical concerns due to the destruction of embryos [53].
- There are also ethical considerations surrounding informed consent, especially for patients with progressive neurodegenerative diseases affecting cognitive function [49].

5. Long-Term Effects

- The long-term effects of stem cell therapy in the brain are still unknown. There is a risk of unintended side effects or tumor formation years after transplantation [49].

6. Factors Affecting Availability

- **Clinical Trial Progress:** Successful completion of large-scale clinical trials demonstrating safety and efficacy is crucial for regulatory approval by bodies like the FDA.
- **Manufacturing Challenges:** Developing efficient and standardized methods for producing large quantities of high-quality stem cells is important for wider accessibility [51].
- **Cost Reduction:** Stem cell therapies are currently expensive due to complex procedures and manufacturing processes. Bringing down the cost is essential for broader patient access [36].

4. CONCLUSION

Stem cell-based therapies offer a spectrum of potential applications in addressing cardiovascular diseases, from repairing damaged cardiac tissue to understanding disease mechanisms and drug testing. While ongoing research continues to elucidate their mechanisms and optimize their efficacy, additional clinical trials are required to ascertain the safety and enduring efficacy of stem cell-based therapies in the field of cardiovascular medicine. Several stem cell therapies are already undergoing clinical trials for various cancers and neurodegenerative diseases. Research is ongoing to address limitations like delivery methods, stem cell source optimization, and cost reduction.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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