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Stem Cell Development: Recent Improvements

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Abstract

In the early stages of life and growth, stem cells possess the remarkable ability to differentiate into a wide variety of cell types found in the body. Understanding the biochemical and metabolic processes, as well as the feedback linked to various stem cell responses, has advanced significantly. Limited cell survival, senescence-induced genetic instability or loss of function, and immune-mediated rejection are some of the difficulties associated with transplanted embryonic and Mesenchymal Stem Cells (MSCs). This study provides an overview of the most current knowledge and developments on stem cell development. Currently, research on stem cell treatment is being conducted for almost all human body tissues and organ types. Professionals with expertise in cell harvesting, culture, expansion, transplantation, and polymer design are crucial for the effective use of stem cell technology, as it currently encompasses the domains of engineering, materials science, and transplantation. Varying stem cell treatments are in varying phases of development; some are in preclinical studies, others are in clinical usage, and some are still in the discovery phase. Recent developments indicate that stem cell treatment may eventually have broader clinical relevance since it offers a promising therapeutic alternative for patients with a variety of degenerative diseases who need the replacement of lost tissue and cells. The discipline of regenerative medicine is a comprehensive scientific subject that has emerged more recently because of significant advancements in stem cell biology, tissue engineering, and nuclear transfer procedures. However, before initiating therapeutic uses, a deeper comprehension of the biology, manipulation, and safety of stem cells in tissue regeneration and repair is necessary.

Keywords: Embryonic stem cell, Mesenchymal stem cell, Regenerative.

1 | Introduction

Current therapies are primarily symptomatic for some degenerative diseases, including Alzheimer's, Parkinson's, motor neuron disease, multiple sclerosis, diabetes, kidney, liver, and heart diseases, as well as several cancers. For some diseases, full recovery necessitates organ transplantation [1]. Humans have been

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shown to benefit from several stem cell uses in tried-and-true treatments, ranging from bone marrow transplants to more recent developments in skin and corneal healing [2]. Stem cell transplantation would likely need to happen within the window of time that separates the irreversible loss of neurons from the initial indication of damage [3].

Current progress indicates that stem cell therapy, which includes the transplantation and reprogramming of Mesenchymal Stem Cells (MSCs), Embryonic Stem Cells (ESCs), and Induced Pluripotent Stem Cells (iPSCs), represents an intriguing and as of yet unresolved field of study with promising outcomes for numerous diseases [2]. Previously, the generation of human induced pluripotent stem cells necessitated the use of genome-integrating vectors, which may result in mutations and restrict the cells' usefulness for research and therapeutic purposes [4]. Over the past ten years, the application of stem cells in medicine has grown exponentially. This growth has been fueled by differing degrees of success in clinical trials as well as advances in our knowledge of the processes by which stem cells produce their apparent benefits.

In general, stem cells fall into one of two categories: adult or embryonic [5]. Adult tissues' stem and progenitor cells have great potential for the treatment of certain clinical disorders [6]. Many studies are being conducted on stem cell transplantation as a possible treatment for cardiac disorders linked to cell death [7].

Many problems regarding cell treatment remain unresolved as a result of this quick translation into clinical investigations [7]. An increasing body of research indicates that stem cells release a range of growth factors, cytokines, chemokines, and bioactive lipids that regulate their biology in an autocrine or paracrine fashion and coordinate their interactions with the surrounding milieu [8].

Cellular treatment is seeing a boom in the twenty-first century. Stem cell technology is showing promise as a tool for natural selection-driven evolution as well as for the formation and regeneration of diverse tissue and organ systems [9]. As of late, stem cell therapies are thought to be secure and efficient medical interventions. Clinical experiments are even looking into the potential uses of stem cells, such as treating solid-organ or blood malignancies or using them to repair injured heart, skin, bone, spinal cord, liver, pancreas, and corneal tissue [10]. Therefore, stem cell research is a relatively new subject that is developing at an astounding rate, with new findings being published all over the world.

For many years, researchers have been exploring the possibility of using stem cells to repair sick or damaged tissues and cells. Newspapers and the media are reporting on the wonders of using stem cells to treat terminal illnesses [11]. Hematopoietic Stem Cells (HSCs), MSCs, neural stem cells, epidermal stem cells, endothelial progenitor cells, limbal stem cells, ESCs, and induced pluripotent stem cells are among the stem cell types that have been employed in clinical trials thus far [12]. The ability of stem cells to perpetually renew themselves and transform from their original undifferentiated state into cells of several lineages is one of their primary characteristics [13].

According to [14]. Heart Failure (HF) is a major cause of mortality and disability in the US, resulting in over 50,000 deaths, one million hospital admissions, and almost $35 billion in medical expenses annually. Although the use of stem cells in cardiology is often described as a means of producing new myocytes, the process is far more intricate than that. Heart failure, whether global or segmental, often has a particular cause that needs to be eliminated before any reconstructive procedure may be successful. Similarly, the act of merely creating new vessels (by vasculogenesis or angiogenesis) [15].

What's more, the elementary myocardial functional units are myocardial cells integrated into a multicellular assembly of myofibers, not isolated cardiomyocytes like the progenitor cells utilized in bone marrow transplants. These cells are orientated in particular orientations; myofiber disarray is a disease state unto itself, and implanted cell treatment should not cause it. Thus, compared to bone marrow transplantation for bone marrow failure and blood transfusion for anemia, which are the only clinically effective cellular therapies to date, the hurdles associated with stem cell therapy for the heart are significantly more complex [14].

Heart transplantation is still the gold standard for treating heart failure, but it is expensive and does not include patients with co-morbidities or those for whom a donor organ is not available. As a result, stem cell therapy represents the first practical approach to reversing the effects of what was previously thought to be terminal heart damage [16]. Accordingly, in this review, we tried to summarize the current state of the field, present the available evidence, and highlight the potential benefits as well as the risks associated with stem cell therapy.

2 | Current Status of Stem Cell

2.1 | Embryonic Stem Cell

Human Embryonic Stem Cell (HESC) lines have been in high demand as study subjects ever since they were first generated in 1998. HESCs' nearly infinite capacity for self-replication and their capacity to differentiate into most, if not all, of the cell types seen in the human body have piqued scientific curiosity. These special talents enable the exploration of several intriguing research avenues that hold promise for advancing our knowledge of human cellular biology and maybe producing treatments for a wide range of illnesses [17]. The totipotent cells of the early mammalian embryo are the source of Embryonic Stem (ES) cells, which may proliferate endlessly and undifferentiated in vitro. To differentiate these pluripotent cells formed from embryos from pluripotent Embryonal Carcinoma (EC) cells derived from terato-carcinomas, the name "ES cell" was coined [4].

Derivation of HESCs

The Inner Cell Mass (ICM) of preimplantation stage blastocysts, both high and low quality, that have been given for study and would otherwise be discarded is the standard source of HESC lines. HESC lines can also be generated from late-stage blastocysts (7-8 days) or morula-stage embryos. However, every HESC line generated globally expresses distinct pluripotency markers [18]. There are a lot of changes across the lines that could have more to do with the variety of culture conditions that are now being used than with the genetic variants that were present in the embryos from which HESC were produced in the first place [19].

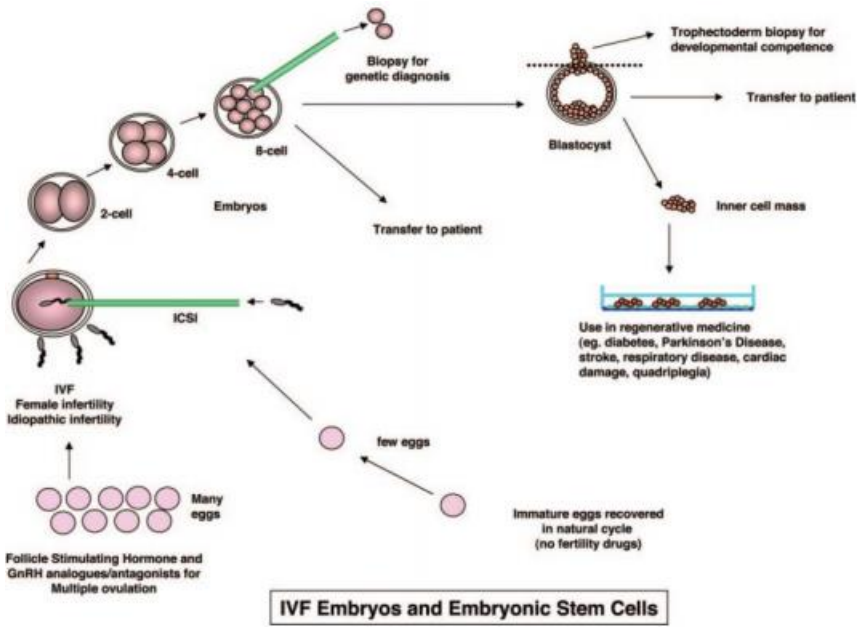


Fig. 1. Derivation of HESC Adapted from [20].

HESC colonies are distinct from ICM colonies in several aspects. First, the dorsal-ventral, anterior-posterior, and left-right axes are memories that ICM cells hold onto. This memory helps developing cells to have position connections that direct the differentiation, expansion, and integration of cell types needed to produce an organism. It is commonly accepted that ESCs are derived from epiblasts or even a kind of germ stem cell that may be cultured as immortal and pluripotent cell types in the presence of secretory products from adult

or embryonic somatic cells under rigorous laboratory conditions. Crucially, the Wnt family signaling pathway and most likely other pathways, including TGF-β and Basic Fibroblast Growth Factor (BFGF), are involved in the self-renewal of HESCs [20].

The effective generation of HESCs from preimplantation human embryos was initially reported by Thomson [4]. The article was the result of [18] comprehensive research on the generation of rhesus and marmoset ESCs. The research group in Singapore researched whole blastocysts and mechanically extracted ICMs cultivated on mouse embryonic fibroblasts (STO cells) from 1994 to 1996. These cultures produced cell lines that differentiated after many in vitro passages [21]. Reubinoff [22] described the techniques that were ultimately employed to create HESC lines effectively. Cowan [23] reported similar techniques, except that they included isolating ICM clusters from human blastocysts using immunosurgery and co-culturing them with mitotically inactivated Murine Embryonic Fibroblasts (MEFs).

The HESCs develop into normal undifferentiated cell colonies that require passage every week or, more frequently, as manually dissected colonies of ten or more cells. Similar techniques have been used to produce other HESC lines. Recently, cell-free lysates of MEFs have also been used to generate HESCs without the need for feeders [24]. The final success rates for the development of HESCs will depend on the selection criteria applied when selecting human embryos for HESC derivation. Reubinoff [25] employed a small number of blastocyst-stage embryos cultured in co-culture with human oviductal epithelial cells to develop six HESC lines following initial trials involving about thirty embryos [26]. The 12 blastocysts are the source of the six HESC lines.

This extremely high HESC production success rate may be contrasted with other researchers' utilization of many more embryos (blastocysts). Given the likelihood that around 50% of human embryos include chromosomal defects, it stands to reason that these genetic mistakes would lower the success rate of HESC creation. Establishing HESCs from monosomic or trisomic embryos is similarly challenging; fewer than 10% are produced from human embryos that have been identified as aneuploid. Remarkably, two HESC lines derived from trisomic embryos went for a revision to diploidy, suggesting that the embryos were likely mosaics [27].

Some IVF facilities have generated a high number of HESC lines from extra human IVF embryos; Kukharenko [28] reported 46 novel HESC lines derived from morulae, blastocysts, and ICMs extracted from blastocysts [27]. The ability of preimplantation human embryos to produce HESC lines seemed to be similar throughout all stages. To derive new HESC lines, a more recent comparison between plating whole blastocysts and mechanically isolating ICMs revealed that mechanical isolation is more effective. It is not ideal to employ antiserum that has been produced in animals for immunosurgery to isolate ICMs [29].

Genetic manipulation of HESCs

HESC clonal derivation is challenging and has a very poor efficiency [30]. It is feasible to transfect HESCs with DNA constructs, though, and this is crucial for understanding how transcription factors function in HESC renewal and differentiation. The monitoring of HESC derivatives in mixed cell cultures or upon transplantation into animal models is made possible by the identification of particular gene expression by reporter genes, which also permits the isolation of cells of interest in differentiation cultures. Both lentiviral and conventional transfection techniques have been effective [31]. Since HESCs cannot be cloned, it isn't easy to integrate reporter genes into the regulating regions of particular genes or to apply the gene knock-out or knock-in strategy used for functional genomics.

Nonetheless, [32] have demonstrated that homologous recombination of HESC colony pieces may be accomplished using electroporation of HESCs. Using short inhibitory RNAs [33] to regulate apoptosis, differentiation, renewal, and other processes involved in cell function and response to internal and external stimuli may be a more acceptable way to ascertain gene function in HESCs.

Markers of HESCs

According to Sperger [34], HESCs, human embryonal cancer cells, and seminomas all share 330 highly expressed genes by microarray research. Among these were FLJ10713, a homolog that is substantially expressed in mESCs, and POU5F1 (Oct4). DNA methylase (DNMT3B), which is involved in early embryogenesis, and Foxd3, a transcription factor belonging to the forkhead family that interacts with Oct4, which is crucial for the maintenance of mouse primitive ectoderm, were two of the genes that were only highly expressed in HESCs and human embryonal carcinoma cells [35].

Additionally, strongly expressed and known to have a role in pluripotentiality is Sox2. For instance, The extraction of neural progenitor cells from human Embryonic Stem (ES) cells is useful for studying human neurogenesis at an early stage as well as for providing an endless supply of donor cells for the treatment of brain transplantation. Here, we describe the production of proliferating neural progenitors from human ES cells that are both enriched and expandable. In vitro, the neural progenitors exhibited the ability to develop into three distinct neural lineages: oligodendrocytes, mature neurons, and astrocytes. Upon transplanting human neural progenitors into the ventricles of neonatal mice brains, a significant proportion of the progenitors integrated into the host brain parenchyma exhibited broad distribution and underwent differentiation into offspring of the three neural lineages [36].

Similar to Embryonic Germ (EG) cells, Embryonic Stem (ES) cells are cells formed from the early embryo that can proliferate endlessly in the primordial undifferentiated state while maintaining their pluripotency. [37] and [22] reported on a Serial Analysis Of Gene Expression (SAGE), which was compared to certain cancer SAGE libraries. While the quantity of Oct4, Nanog, and Sox2 transcripts is predicted, there were variations in the abundance of other transcripts (such as Rex-1) amongst HESCs.

Patient-specific stem cells: nuclear transfer methods are being used to inject somatic cell nuclei into enucleated oocytes to produce patient-specific stem cells [26]. The potential creation of immune-compatible cell derivatives for transplantation is the rationale for the creation of HESCs for specific patients. The development of novel disease-specific stem cells from patients suffering from cancer, neurological illnesses including Parkinson's, Alzheimer's, multiple sclerosis, and motor neuron disease, as well as illnesses with unclear causes or multigenic origins, is crucial. Restoring pristine HESCs that can be differentiated into cells that will express the disease phenotype in the lab could be a very useful resource for finding molecules that disrupt the disease phenotype and finding potential medications or molecular pathways that could open up entirely new therapeutic avenues for these patients. Using mESCs, this strategy has previously been shown to be effective [37].

Mesenchymal Stem Cells (MSCs)

Human adult bone marrow has many progenitor cells. MSCs are one kind of multipotent adult progenitor (MSCs). These cells have a well-established ability to differentiate into a range of connective tissues, including bone, cartilage, muscle, marrow stroma, tendon and ligament, fat, and many more [38]. Similar to bone marrow-derived HSCs, MSC development is mediated by many cell lineages that are regulated by bioactive substances present in the surrounding microenvironment or added to the culture medium of ex vivo cultured cells. Because it includes a sequential process that may be altered in terms of both time and end-stage consequence, this controlled differentiation scheme was chosen via evolution. A multi-step route enables the application of several regulatory components to protect the outcome [39].

MSCs have shown great promise for application in therapeutic settings. They are also known as multipotent mesenchymal stromal cells or connective tissue progenitor cells. To repair damaged tissue and manage inflammation brought on by heart disease, Myocardial Infarction (MI), brain and spinal cord injury, bone and cartilage damage, Crohn's disease, and Graft-Versus-Host Disease (GVHD) following bone marrow transplantation, a range of novel therapeutics has focused on MSCs [40]. According to Sakai [41], the minimal criteria for human MSCs include adhering to tissue culture plastic, being positive for CD105, CD73, and

CD90; negative for CD45, CD34, CD14 or CD11b, CD79a, or CD19, as well as HLA-DR. Additionally, the cells must be able to differentiate into osteoblasts, adipocytes, and chondroblasts under standard in vitro differentiating conditions.

Tissue sources of Mesenchymal Stem Cells (MSC)

The native concentration and reported MSC frequency (as determined by CFU-F) from some adult human tissues are reported. With recent discoveries indicating that the majority of MSCs, if not all of them, are of perivascular origin, the relative abundance of MSCs throughout the body makes sense. Moreover, MSC frequency and blood vessel density in stromal vascularized tissue are directly correlated [42]. The phenotypic surface indicators platelet-derived growth factor receptor and melanoma cell adhesion molecule (CD146) are shared by MSCs and pericytes.

The in vivo source of MSCs is thought to be pericytes, whose cellular components protrude into the blood vessel endothelial lumen to monitor and respond to systemic signals. The capacity of MSCs to respond to damage by detecting and secreting chemokines locally in response to injury, infection, or illness [42] in all vascularized tissues of the body would be explained by the extensive distribution of perivascular precursors for MSCs [20].

Capacity of Mesenchymal Stem Cells (MSC)

Trophic properties of MSC: the production of growth factors and other chemokines to promote angiogenesis and cell proliferation is the main trophic characteristic of MSCs. To promote fibroblast, epithelial, and endothelial cell division, MSCs express mitogenic proteins such as transforming growth factor-alpha (TGF-α), TGF-β, Hepatocyte Growth Factor (HGF), Epithelial Growth Factor (EGF), basic fibroblast growth factor (FGF-2), and Insulin-Like Growth Factor-1 (IGF-1). To attract endothelial lineage cells and start the vascularization process, endothelial growth factor (VEGF), IGF-1, EGF, and angiopoietin-1 are produced [43].

Anti-inflammatory and immunomodulatory properties of MSC: by using paracrine processes, MSCs maintain stability and alter the regenerative milieu through immunomodulatory and anti-inflammatory processes. MSCs secrete a variety of growth factors and anti-inflammatory proteins with intricate feedback mechanisms among the various types of immune cells in response to inflammatory molecules such as interleukin-1 (IL-1), IL-2, IL-12, tumor necrosis factor-a (TNF-a), and interferon-gamma (INF-g) [20]. The main immunomodulatory cytokines include prostaglandin 2, soluble tumor necrosis factor-a receptor, TGF-b1, HGF, SDF-1, nitrous oxide, indoleamine 2, 3-dioxygenase, IL-4, IL-6, IL-10, and IL-1 receptor antagonist. MSCs inhibit the growth and activity of several inflammatory immune cells, such as dendritic cells, T cells, B cells, natural killer cells, monocytes, and macrophages [44].

Antiapoptotic properties of MSC: the first anticipated result of administering MSCs to treat acute wounds is a decrease in the degree of cell death; this has been seen in co-culture studies and animal models of tissue damage. According to Togel et al., in a model of acute kidney damage, infused MSCs adhere to the renal micro-vascular circulation and reduce the death of nearby cells. These authors analyzed the MSC-conditioned medium and confirmed the presence of vascular endothelial growth factor (VEGF), Hepatocyte Growth Factor (HGF), and insulin-like growth factor 1 (IGF-1), factors that promote endothelial cell growth and survival to clarify the factors responsible for the observed renoprotective effect [42].

These and other antiapoptotic molecules were discovered to be present in an MSC-conditioned medium by [45]. Interestingly, they also demonstrated that 71% of the rats experimentally subjected to fulminant hepatic failure survived when an MSC-containing bioreactor was connected to their bloodstream, compared to 14% in the control group. MSCs have been discovered to have an antiapoptotic impact on UV-irradiated fibroblasts and lung epithelial carcinoma cells cultivated under low pH and hypoxia. This effect is at least partially attributed to the up-regulation and release of stanniocalcin-1 [46].

HGF, VEGF, Transforming Growth Factor Beta (TGF-β), basic fibroblast growth factor (bFGF, also known as FGF2), and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) have also been demonstrated to be expressed by adipose tissue-derived MSCs. Furthermore, it has been observed that these molecules express themselves more when cultured under hypoxic conditions; in particular, VEGF is upregulated under hypoxic conditions more so than other factors [47].

Since hypoxia occurs during the early stages of tissue injury, MSCs' secretion of antiapoptotic factors during this time reduces the amount of cell death in the tissues surrounding the injured areas. For this reason, it was further shown in the latter study that injecting mice with hind limb ischemia experimentally with cultured, adipose-derived MSCs improved perfusion and reduced necrosis. Researchers speculate that this antiapoptotic action may help to restrict the area of damage under in vivo conditions [47].

Antimicrobial properties of MSC: CFU was used to measure how well MSCs or its Conditioned Media (CM) inhibited bacterial growth directly. To put it briefly, 300 CFU of E. coli or S. aureus were added to MSCs in 24-well plates (2 × 105 cells per well) in RPMI supplemented with 5% FBS. The cells were then incubated for 6 hours in a humidified CO2 incubator. Following this, aliquots of the culture medium were taken from each well, serially diluted with sterile PBS, and plated on LB-agar plates (Teknova, Hollister, CA). Colonies were tallied during a 37°C overnight incubation period. A microdilution susceptibility test was used to evaluate the antimicrobial activity of MSC CM, also known as synthetic LL-37 [48].

By secreting antimicrobial peptides, the researcher who examined human MSCs may have demonstrated direct antibacterial action. They investigated how human MSCs affected the in vitro development of bacteria. Using immunohistochemistry, Enzyme-Linked Immunosorbent Assay (ELISA), and Reverse Transcription Polymerase Chain Reaction (RT-PCR), the expression of several antimicrobial peptides was examined. Human MSCs were stimulated with live E. coli, and one potential antimicrobial peptide was generated in response: LL-37. This peptide was later discovered to be the source of antimicrobial action in vitro.

They examined BM-derived human MSCs in a mouse model of E. coli pneumonia to see if the production of LL-37 by MSCs would change bacterial clearance in vivo. Four hours later, treatment with human MSCs led to a substantial decrease in the number of E. coli Colony-Forming Units (CFU) in the Bronchoalveolar Lavage (BAL) fluids and Lung Homogenates (LHs). A neutralizing antibody to LL-37 was able to prevent the effect, indicating that human MSCs have antibacterial activity. This is partially explained by LL-37's release [49].

Phenotypic characterization of MSCs: scientists sought a way to proactively identify progenitor cells from bulk populations based on positive or negative selection of CD markers produced by the cells following the discovery and early characterization of MSCs. Without a doubt, the first markers found on MSCs were CD73 (SH-3/4) and CD105 (endoglin or SH-2), which were followed by CD90 (Thy-1) and CD44. Since then, it has been found that the CD90ξ/CD105þ/CD73þ/CD44 quadruple-positive population [50], [51]. It is exclusive to fibroblasts and stromal cells and is only useful in differentiating them from hematopoietic cell types.

In the interim, much MSC phenotypic characterization has been published; regrettably, the field is still unable to come to a tight consensus [52]. A minimal set of standards for characterizing MSCs was created in 2006 by the International Society of Stem Cell Research as:

I. Plastic-adherent cells.

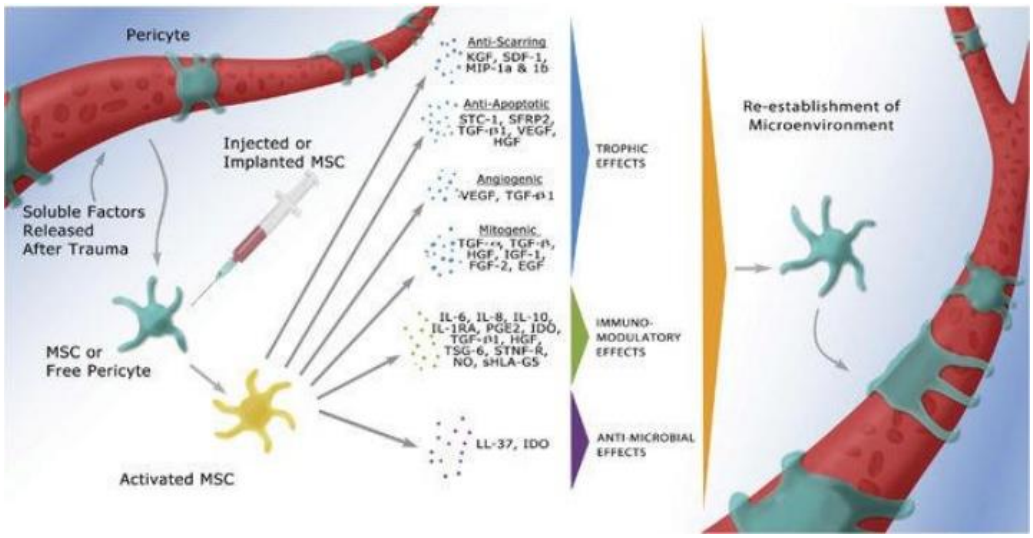
II. Capable of tri-lineage (bone, cartilage, and fat) differentiation.

III. Phenotypically positive for CD105, CD73 and CD90.

IV. Negative for CD45, CD34, CD11b, CD14, CD79a and HLA-DR [53].

The natural in vivo phenotype is not covered by these criteria, which are based on the characterization of in vitro cultivated cells. In BM aspirate, for instance, CD34 is thought to be a marker for endothelial progenitors

and HSCs but not for MSCs [54]. To become activated, MSCs, soluble growth factors, and chemokines stimulate pericytes. These MSCs then secrete trophic (mitogenic, angiogenic, antiapoptotic, or scar reduction), immunomodulatory, or antimicrobial substances in response to the microenvironment. Following the



restoration of the microenvironment, MSCs attach themselves to blood vessels and revert to their original pericyte condition [48].

Fig. 2. Phenotypic characterization of MSC.

3 | Clinical Translation of Stem Cell Therapies

Mesenchymal Stem Cells (MSC) in the treatment of cardiovascular therapies Cardiac: the ischemic event that causes MI is a complex insult to the cardiovascular system; the size of the original infarcted area determines the degree of damage and eventual heart illness [55]. It is typified by a disturbance in the blood flow to the heart muscle cells, resulting in cardiomyocyte death or MI.

The majority of treatment for Acute Myocardial Infarction (AMI) nowadays is reperfusion therapy, or the restoration of blood flow by thrombolytic therapy, bypass surgery, or Percutaneous Coronary Intervention (PCI), which is accountable for the notable decline in AMI mortality. Those with severe AMI who would not otherwise survive have a higher chance of survival thanks to the effectiveness of reperfusion treatment. But within 30 days, a large number of these survivors (23%) develop catastrophic heart failure. An ever-growing epidemic of heart failure is a result of the phenomenon of an increasing proportion of survivors with severe AMI [56].

Anti-inflammatory drugs may be used to reduce the harmful tissue remodeling that results from MI, according to Mckay's [57] proposal. There is currently no agreement on the best mode of administration or cell type for MSCs, despite some clinical research looking into their usage for this purpose. Cell therapy patients experienced a decrease in summed stress score and an increase in Left Ventricular (LV) ejection fraction at three and six months (both statistically significant) in a randomized, placebo-controlled study of patients with chronic MI who received intramyocardial injections of autologous BM-derived mononuclear cells [57], [58].

Subsequent research with 87 individuals with severe left ventricular failure showed no statistically significant variations in the extent of the infarct or LV ejection fraction between autologous BMNC infusion and placebo [59]. In a much smaller trial, it was shown that both enlarged BM MSCs and autologous BM MNCs produced a 3-month reduction in cardiac scarring, suggesting advantageous tissue remodeling [60]. Comparing allogeneic and autologous MSCs in 30 patients with ischemic cardiomyopathy through a randomized trial, the percutaneous stem cell injection delivery effects on neomyogenesis (Poseidon) trial revealed improved functional capacity, quality-of-life, and ventricular remodeling following both types of cell therapy [61]. The

most recent study found that injecting autologous, expanded BM MSCs directly into the heart improved angina attack frequency, exercise capacity, Canadian Cardiovascular Scale (CCS) class score, and nitroglycerin intake for up to a year after the intervention [62].

Opportunities and limitations of stem cell therapy

The intrinsic difficulty of cultivating particular cell types in sufficient amounts has been one of the barriers to using cell-based regenerative medicine strategies toward organ replacement [63]. The possible immunological response to a tissue transplant formed from ES and MSC cells, immune-mediated rejection, senescence-induced genetic instability or loss of function, and restricted cell survival are additional challenges that need more research. The inability of T cell-deficient nude mice to produce a rejection response in response to an allogeneic skin transplant serves as evidence for this. Hematopoietic chimerism presents an intriguing possibility for inducing immunological tolerance due to ES cells' exceptional capacity to generate HSC [64].

The development of regeneration service lines is based on clinical-grade biotherapies that are efficient and suited for standardization, scaling up, and deployment. Product delivery that satisfies patient demands and quality-controlled production is necessary for a sustainable supply chain. Patient variables, including age, sex, morbidities, and concurrent therapy impact regenerative fitness. Additionally, factors related to procurement, manufacture, and/or delivery may have an impact on cell performance. As it happens, not every person possesses stem cells that are equally capable of healing [65].

4 | Clinical Future Perspectives

The last ten years have brought us closer to understanding the formation of the cardiovascular system and stem cell biology. To create sophisticated stem cell therapies to restore or regenerate damaged heart disease, however, a deeper comprehension of cardiac myogenesis would be necessary [66]. The future will likely include:

I. The human CM lineage tree should be further investigated;

II. Methods to isolate specific cardiac progenitor pools or specialize CM subtypes should be developed;

III. Strategies to ensure transplanted cells survive, integrate functionally with the host myocardium, and avoid immune rejection should be developed;

IV. Technologies to accurately assess integration should be developed;

V. Parameters that optimized engraftment, such as delivery method, timing of transplantation post-MI, and cell preparations, should be determined and

VI. Large animal models of heart failure that closely resemble human cardiovascular physiology and disease should be developed to assess cell engraftment, host immune response, and myocardial function [67].

Treatment for people with Alzheimer's disease and associated illnesses may greatly benefit from cell-replacement therapy. Animal models of Alzheimer's disease have shown some progress in stem cell treatment since the development of stem cell technology and the capacity to differentiate stem cells into various kinds of CNS neurons and glial cells. While these preclinical investigations are encouraging, a great deal more work has to be done before stem cell treatments can effectively treat Alzheimer's disease and associated conditions [68].

5 | Conclusion

Numerous therapeutic uses of stem cell treatment are being researched. It is known that these cells can settle in some tissues, especially in diseased or damaged states. It is yet unclear how MSCs and ESCs migrate; however, evidence points to the involvement of chemokines, as well as their receptors and adhesion molecules. The involvement of adhesion molecules and chemokine receptors on stem cells, as described in

some research, may facilitate the development of therapeutic approaches to improve the recruitment of ex vivo-cultured MSCs to injured or diseased tissues.

This might result in some therapeutic opportunities, including promoting tissue regeneration, treating hereditary illnesses (such as those affecting the bone), reducing persistent inflammation, and using these cells as delivery systems for biological medicines. However, further clinical research is required to ascertain the distribution and therapeutic processes of MSCs and ESCs in vivo to maximize their application within a customized regenerative medicine approach. To include nature's fundamental regenerative aspect within the range of clinical treatment, a joint effort including physicians, veterinarians, scientists, biotechnologists, industry, and regulatory bodies will be necessary. Research on stem cells has great promise for innovative regenerative engineering and cell treatment applied at the cellular level.

Author Contributions

Segun Stephen Folorunso conceptualized the study and led the research on recent developments in stem cell technology. David Oluwasegun Ogbe contributed to the analysis of biochemical processes and metabolic feedback in stem cell differentiation. Godwin Iheanacho Udeh focused on the challenges related to cell survival and immune-mediated rejection, while Saheed Omobowale Shitta provided insights on stem cell therapy applications for degenerative diseases. Adetayo Olaniyi Adeniran assisted with the overall coordination and writing of the manuscript. All authors contributed to the literature review and approved the final manuscript.

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Data Availability

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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