Review Article

Stem Cells Types, Their Sources And Role In Cardiac Regeneration

Sadia Nazir[1], Shamaila Doggar[2], Hafiza Swaiba Afzal[3], Tahir Maqbool[4*]

[1.] Lahore Medical and Dental College, Lahore.
[2.] Fatima Memorial College of Medicine and Dentistry, Lahore.
[3.] Sahiwal Medical College, Sahiwal.
[4.] Institute of Molecular Biology and Biotechnology/center for research in molecular medicines, Lahore.
Corresponding author:
Tahir Maqbool
Institute of Molecular Biology and Biotechnology/ Center for Research in Molecular Medicines, Lahore.
Email: tahir.maqbool@imbb.uol.edu.pk
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Abstract

Stem cells are unique cells that can differentiate into various cell types, making them a valuable tool in regenerative medicine. Stem cells can be obtained from various sources, including embryonic tissue, fetal tissue, adult tissue, and induced pluripotent stem cells (iPSCs). Stem cells can be obtained from different sources, like bone marrow, peripheral blood, umbilical cord blood, adipose tissue and dental pulp. Each with its advantages and disadvantages. The choice of source for stem cell extraction depends on the type of cells required, the quantity needed, and the patient's medical condition. Further research is needed to optimize the extraction and isolation of stem cells from different sources and to determine their efficacy in treating various diseases and conditions. Regenerative medicine researchers are exploring ways to use stem cells to replace damaged cells or tissues that cannot be regenerated naturally by the body. This approach holds great promise for treating a range of diseases and injuries, including heart disease, spinal cord injuries, and diabetes.

Introduction:

Stem cells:

Stem cells are undifferentiated cells that possesses the properties of self-renewal, proliferation and differentiation. These are one of the principal cells of the body that have capability to grow into approximately 200 different types of body cells. Stem cells are classified in several different ways; one way to classify them according to their differentiation potential and other way is to on the basis of evolutionary stages [(1)].

Classification of stem cells on the basis of differentiation potential:

The stem cells are classified into following cells; totipotent, pluripotent, multipotent, unipotent and nullipotent.

Classification of stem cells on the basis of evolutionary stage:

Stem cells are classified on the basis of their evolutionary stages such as; embryonic stem cells, fetal stem cells, adult stem cells and iPSCS fetal stem cells, adult stem cells and iPSCS as shown in the figure 1 below.

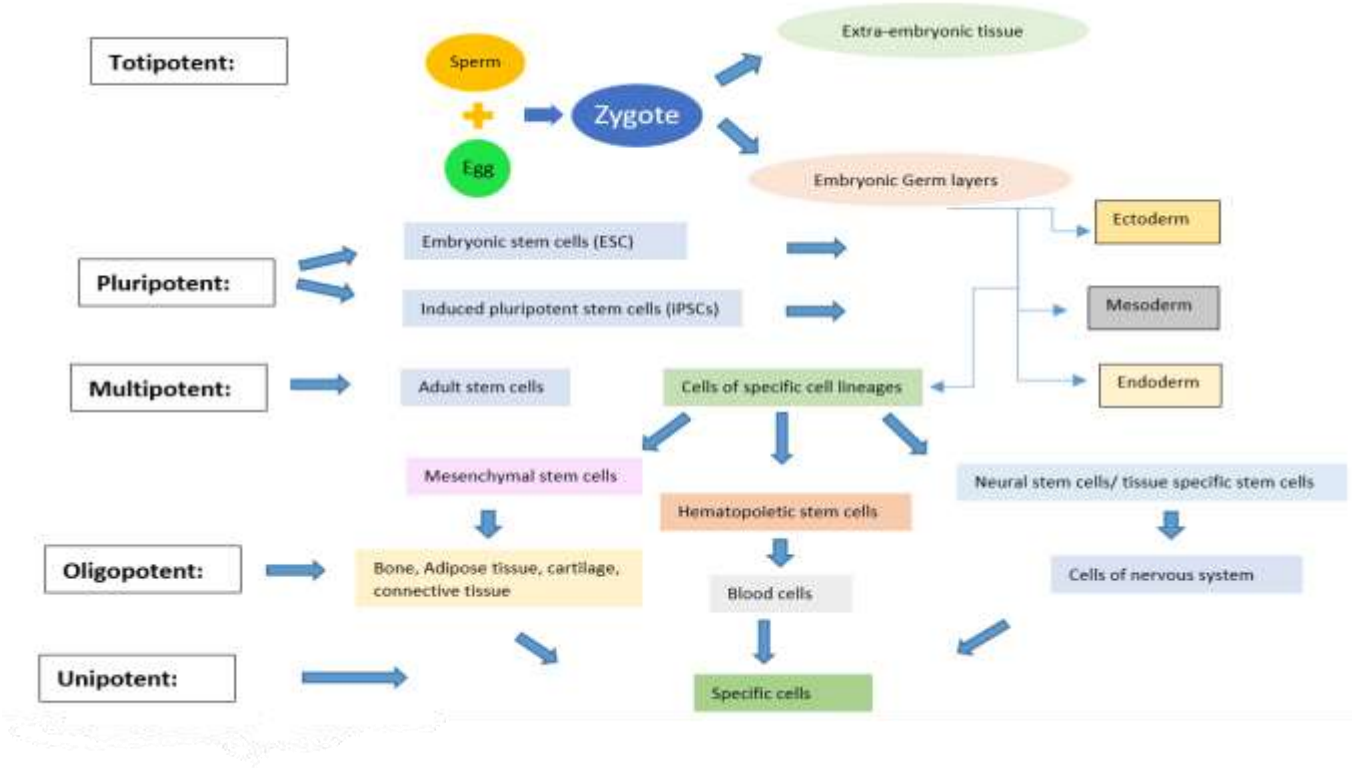

Figure 1: Classification of Stem cells.

Stem cells can be obtained from various sources, including embryonic tissue, fetal tissue, adult tissue, and induced pluripotent stem cells (iPSCs) [(2)].

1. **Embryonic Stem Cells (ESCs)** Embryonic stem cells (ESCs) are derived from the inner cell mass of the blastocyst, a structure formed after the fertilization of an egg by a sperm [(3)]. ESCs are pluripotent, meaning they can differentiate into any cell type in the body. ESCs are considered the gold standard for stem cell research due to their ability to differentiate into any cell type, but their use has been limited due to ethical concerns surrounding their extraction from human embryos [(4)]. Additionally, there is a risk of teratoma formation, which is the development of a tumor consisting of different types of cells that arise from the ESCs (5).
2. **Fetal Stem Cells (FSCs)** Fetal stem cells (FSCs) are obtained from aborted fetal tissue or miscarried embryos [(6)]. FSCs are also pluripotent and can differentiate into various cell types. FSCs are considered a controversial source of stem cells due to ethical concerns, but they are still used in research and clinical trials [(7)].
3. **Adult Stem Cells (ASCs)** Adult stem cells (ASCs) are found in various tissues in the body, including bone marrow, adipose tissue, and blood. ASCs are multipotent, meaning they can differentiate into a limited number of cell types [(8)]. ASCs are relatively easy to obtain and can be collected through minimally invasive procedures, such as bone marrow aspiration. ASCs are also less likely to cause an immune response since they are derived from the patient's own body [(9)].
4. **Induced Pluripotent Stem Cells (iPSCs)** Induced pluripotent stem cells (iPSCs) are generated by reprogramming adult cells, such as skin cells, into an embryonic-like state. iPSCs are pluripotent and have the potential to differentiate into any cell type. iPSCs have become an essential tool in regenerative medicine research as they offer a non-controversial and readily available source of pluripotent stem cells [(10)].

Each source of stem cells has its advantages and limitations, and the choice of source will depend on the research or clinical application. ESCs offer the most versatility but are limited by ethical concerns [(11)]. FSCs are also pluripotent, but their use is controversial. ASCs offer a readily available and relatively safe source of stem cells but are limited in

their differentiation potential [12]. Finally, iPSCs offer a non-controversial source of pluripotent stem cells, but there are concerns about their safety and efficacy for clinical applications [13]. The source of stem cells is an essential consideration for stem cell research and clinical applications. Researchers and clinicians must carefully consider the advantages and limitations of each source and choose the most appropriate source for their application [14]. With ongoing research and advancements in technology, it is likely that new sources of stem cells will be discovered in the future, further expanding the possibilities for regenerative medicine [15].

Stem cells are undifferentiated cells that can give rise to various types of cells in the body. They have the potential to treat a wide range of diseases and conditions by replacing damaged or diseased tissues [16]. However, the success of stem cell therapy depends on the quality and quantity of stem cells obtained for transplantation. These are the few sources of stem cell extraction with their advantages and disadvantages.

1. **Bone Marrow**: Bone marrow is one of the most commonly used sources of stem cells. It is a spongy tissue found in the bones and contains hematopoietic stem cells, which can give rise to different blood cells [17]. Bone marrow aspiration is a relatively simple procedure that involves extracting stem cells from the bone marrow using a needle. This method has been used for decades and has a well-established safety record. However, bone marrow aspiration can be a painful and invasive procedure and may require anesthesia.
2. **Peripheral Blood**: Peripheral blood contains hematopoietic stem cells that can be collected through a process called apheresis [18]. Apheresis involves extracting blood from the donor, separating the stem cells from the other components of blood, and returning the remaining blood components back to the donor. This method is less invasive than bone marrow aspiration and does not require anesthesia. However, the number of stem cells obtained through apheresis may be lower than that obtained through bone marrow aspiration.
3. **Umbilical Cord Blood**: Umbilical cord blood is collected from the umbilical cord and placenta after childbirth. It contains hematopoietic stem cells that can give rise to different blood cells. Cord blood is a readily available source of stem cells, and its collection is a non-invasive and painless procedure [19]. Moreover, cord blood has a lower risk of transmitting infectious diseases compared to other sources of stem cells. However, the number of stem cells obtained from cord blood is limited, and the stem cells may not be suitable for all patients [20].
4. **Adipose Tissue**: Adipose tissue, commonly known as fat, contains mesenchymal stem cells that can give rise to different types of cells such as bone, cartilage, and muscle cells. Adipose tissue can be obtained through liposuction, a minimally invasive procedure that involves extracting fat cells from the body using a cannula [21]. Adipose tissue is an abundant source of stem cells, and the extraction procedure is relatively simple and safe. However, the quality of stem cells obtained from adipose tissue may be lower than that obtained from other sources.
5. **Dental Pulp**: Dental pulp is a soft tissue found in the center of the tooth that contains mesenchymal stem cells. Dental pulp can be obtained from extracted teeth or wisdom teeth. The extraction of dental pulp is a non-invasive procedure and does not require anesthesia. Dental pulp stem cells have the potential to differentiate into various cell types, including bone, cartilage, and neural cells. However, the number of stem cells obtained from dental pulp is limited, and the extraction procedure may not be feasible for all patients [22].

Stem cells and regenerative medicine:

Stem cell regeneration refers to the process of using stem cells to repair or replace damaged tissues or organs in the body. Stem cells are unique cells that have the ability to develop into different types of cells and tissues in the body, such as muscle, bone, nerve, or blood cells.

Although stem cell regeneration is a promising field of research, there are still many challenges to overcome, including the need to identify the best sources of stem cells, develop safe and effective methods for delivering stem cells to damaged tissues, and ensure that stem cells differentiate into the correct cell types needed for regeneration. The major contribution of stem cells to modern medicine lies in their broad use in basic research as well as in their clinical applications that allow us to develop new therapeutic strategies [23] . A number of studies have demonstrated that stem

cells are capable of replacing damaged tissue or even regenerating organs. Besides making a significant contribution to the development of restorative medicine, their study also helps us to understand complex events that occur during human development. For practical point of view, in cell therapy procedures 13% ESCs, 2% fetal stem cells, 10% umbilical cord and 75% adult stem cells are used. Cell therapy has been most frequently used to treat cardiovascular and ischemic conditions, diabetes, hematopoietic conditions, liver diseases, and, more recently, orthopedic conditions [24, 25].

Stem cells and cardiac regeneration:

Heart diseases are one of the leading cause of morbidity and mortality worldwide, with limited therapeutic options available. The heart has limited regenerative capacity, and after a heart attack, the loss of cardiac muscle cells (cardiomyocytes) can lead to heart failure. Due to increasing prevalence of heart diseases and limited regenerative potential of cardiac cells, stem cells therapy shows promising results [26]. Stem cells have the potential to differentiate into cardiomyocytes, and studies have shown that transplantation of stem cells can improve cardiac function in animal models of heart failure and clinical trials. Many studies conducted so far on use of different stem cells as therapeutic agent in different heart diseases [23, 27, 28]. Each type of stem cell has advantages and disadvantages based on its characteristics and the requirements of each therapeutic protocol.

There are different types of stem cells that have been explored for cardiac regeneration, including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), cardiac progenitor cells (CPCs), mesenchymal stem cells (MSCs), and hematopoietic stem cells (HSCs) [28].

iPSCs have been shown to differentiate into cardiomyocytes and have been used for cardiac regeneration in animal models of heart failure. However, the use of iPSCs is still limited by safety concerns, including the risk of genomic instability and tumorigenicity [29]. Cardiac progenitor cells (CPCs) are a type of stem cell that specifically gives rise to cardiomyocytes. CPCs have been isolated from the heart tissue of adult humans and animals and have shown promising results in preclinical studies for cardiac regeneration. However, the number of CPCs that can be isolated from the heart tissue is limited, and their differentiation potential is often compromised by the age and disease state of the donor [30].

Mesenchymal stem cells (MSCs) are multipotent stem cells that can differentiate into a variety of cell types, including cardiomyocytes. MSCs have been isolated from various tissues, including bone marrow, adipose tissue, and umbilical cord tissue. MSCs have been shown to improve cardiac function in animal models of heart failure and in clinical trials. MSCs have immunomodulatory properties and can secrete trophic factors that promote angiogenesis and tissue repair. However, the differentiation potential of MSCs into cardiomyocytes is limited, and the mechanisms by which MSCs improve cardiac function are still not fully understood [31].

Hematopoietic stem cells (HSCs) are stem cells that give rise to blood cells, including red blood cells, white blood cells, and platelets. HSCs have been shown to differentiate into cardiomyocytes in animal models of heart failure and in vitro. HSCs have also been used in clinical trials for the treatment of heart failure. However, the differentiation potential of HSCs into cardiomyocytes is limited, and their use is often associated with low engraftment rates [32].

Embryonic stem cells and cardiac regeneration: Embryonic stem cells are pluripotent cells that have the ability to differentiate into all cell types in the body, including cardiac cells. This unique property of embryonic stem cells has led to a great deal of research focused on their potential use in cardiac regeneration.

Under specific conditions, ESCs can differentiate into somatic cells of all three embryonic germ layers, including fibroblasts, endothelial cells, smooth muscle cells, and cardiomyocytes. They are pluripotent and can proliferate indefinitely [33]. These properties enable large quantities of cardiac cells to be generated in vitro, which are essential for regeneration. There are several ways in which embryonic stem cells can be used for cardiac regeneration. One approach is to differentiate the stem cells into cardiac cells in the laboratory and then transplant them into the damaged heart tissue. This approach has shown promise in animal studies and early clinical trials [34]. Studies show that cardiomyocytes derived from embryonic stem cells (ESC-CMs) can integrate into a recipient's heart. There is a limited number of transplanted ESC-CMs that survive, proliferate, and mature in the body [35, 36, 37].

Despite the promising results from preclinical studies and early clinical trials, there are still many challenges to overcome before embryonic stem cell-based therapies can be widely used for cardiac regeneration. One major challenge is the risk of tumor formation. Embryonic stem cells have the ability to divide and differentiate into multiple cell types, which can lead to the formation of teratomas, tumors that contain a mix of different cell types. To address this challenge, researchers are exploring ways to control the differentiation of embryonic stem cells and prevent the formation of teratomas. Another challenge is the potential for rejection by the immune system. Embryonic stem cells are derived from donated embryos or created using cloning techniques, and thus have the potential to be recognized as foreign by the immune system [38, 39]. To overcome this challenge, researchers are exploring ways to use immune-matching techniques or genetically modify the cells to reduce the risk of rejection.

Despite these challenges, there have been some promising results from early clinical trials of embryonic stem cell-based therapies for cardiac regeneration. For example, clinical trial conducted by the Tang et al. 2010 showed that embryonic stem cell-derived cardiac cells could be safely transplanted into patients with ischemic heart injury [40]. The study also showed some improvements in heart function in some patients. Another early clinical trial conducted by Menasché et al. 2018, showed that injecting a patient's own stem cells into their damaged heart tissue could improve heart function and reduce symptoms of heart failure. This approach, known as autologous stem cell therapy, has the potential to overcome some of the challenges associated with using embryonic stem cells, such as immune rejection and tumor formation [41].

In conclusion, embryonic stem cells offer a promising avenue for cardiac regeneration, but there are still many challenges that need to be addressed before these therapies can be widely used in clinical practice. Despite these challenges, there have been some promising results from preclinical studies and early clinical trials, and researchers are continuing to explore ways to improve the safety and efficacy of these therapies. Ultimately, the goal is to develop safe and effective treatments that can improve the lives of patients with heart disease and other debilitating conditions.

Induced pluripotent stem cells (iPSCs) and cardiac regeneration:

Induced pluripotent stem cells (iPSCs) have the potential to revolutionize the field of regenerative medicine, including cardiac regeneration [42]. iPSCs are adult cells that have been reprogrammed to a pluripotent state, meaning they have the ability to differentiate into any cell type in the body, including heart cells. iPSCs is a promising tools for cardiac regeneration research and may provide a safer and more ethical approach to this important area of regenerative medicine [43].

In 2007, Takahashi et al. demonstrated that it is possible to reprogram adult cells, specifically fibroblasts, back into a pluripotent state using a combination of retroviral vectors containing the transcription factors Oct 3/4, Sox2, Klf4, and c-Myc. These reprogrammed cells were named induced pluripotent stem cells (iPSCs) [44]. iPSCs share many characteristics with embryonic stem cells (ESCs), including the ability to differentiate into all three germ layers and self-renew indefinitely. This discovery was a significant breakthrough in stem cell research, as it provided a new source of pluripotent cells that did not require the destruction of embryos, which had been a controversial issue [45].

Cardiac regeneration using iPSCs involves generating new heart tissue to replace damaged or diseased heart tissue. This can be achieved by differentiating iPSCs into cardiac cells, which can then be implanted into the damaged area of the heart. Once implanted, these cells can integrate with the existing heart tissue and form new muscle, improving heart function. Several researches in animals have shown promising results for using iPSCs for cardiac regeneration [46-48]. In one study in 2021, conducted by Zhao et al. in which iPSCs were used to create cardiac patches that were implanted onto the damaged heart tissue of pigs. The patches integrated with the heart tissue and improved cardiac function [49].

However, there are still challenges that need to be addressed before iPSCs can be used for cardiac regeneration in humans. One challenge is ensuring that the implanted cells do not form tumors or cause other adverse effects. Another challenge is controlling the differentiation of the iPSCs into cardiac cells and ensuring that they integrate properly with the existing heart tissue. Despite these challenges, iPSCs hold great potential for cardiac regeneration and could one day provide a new treatment option for heart disease [11]. Furthermore, iPSCs can also be used to model heart diseases and develop personalized medicine. By taking cells from a patient, reprogramming them into iPSCs and

differentiating them into heart cells, researchers can study the mechanisms behind various heart diseases and test potential therapies in vitro [50,51].

The preclinical study in 2009 provides important insights into the potential use of induced pluripotent stem cell (iPSC) derived cardiomyocytes for improving cardiac function [52,53]. However, there are also several challenges and concerns that need to be addressed before this approach can be translated into clinical practice. One major concern is the use of viral vectors for the generation of iPS cells. Viral vectors can introduce new potential side effects, including inflammation, rejection, and even a fatal immune response in rare cases. Additionally, viral genome insertion can disrupt cellular function and potentially cause oncogenic changes. However, newer iPSC generation methods that use non-integrating viruses or do not require viral vectors altogether are showing promise and may help address these concerns [54].

Another challenge is the maturation, integration, and coupling of iPS-derived cardiomyocytes within the heart. Like embryonic stem cell-derived cardiomyocytes, iPS-derived cardiomyocytes may require additional cues to properly mature and function within the complex environment of the heart. Additionally, proper integration and coupling with existing cardiac tissue will be critical for long-term functional improvement. Finally, the risk of teratoma formation is another important consideration. While iPS cells are not as likely to form teratomas as embryonic stem cells, the potential risk still exists and must be carefully monitored and minimized through rigorous safety protocols [55].

Recent studies have shown that it is possible to reprogram somatic cells into different cell types. One approach to achieve this is by inducing pluripotency in fibroblasts, which involves the introduction of specific transcription factors (Oct4, Sox2, Klf4, and c-Myc) to reset the cell's gene expression profile back to a pluripotent state. This technique has been successfully used to reprogram somatic cells into a variety of cell types, including cardiomyocytes, neurons, and insulin-producing beta cells. The use of direct reprogramming techniques has the advantage of avoiding the formation of teratomas that can arise from the use of iPSCs [56-58].

Researchers have been investigating the use of genetic factors, chemical inhibitors, and signaling molecules to improve the efficiency of reprogramming cells into induced pluripotent stem cells (iPSCs) [59]. A recent studies in 2014 by Lu et al. and Santos et al. found that depleting the Mbd3 gene, which is part of the Mbd3/NuRD repressor complex, can overcome a major obstacle to achieving pluripotency in cells. However, these iPSCs were found to be tumorigenic [60,61]. To address this issue, Tohyama et al. (2017), differentiated iPSCs into cardiomyocytes before transplanting them into the heart, resulting in improved cardiac function and integration with the host tissue. Additionally, bioengineering strategies are being explored to enhance the efficacy of iPSC-derived transplants. However, before these cells can be considered for clinical use, their safety and functionality must be thoroughly evaluated in vivo [51].

Overall, recent advances in cellular reprogramming have expanded our understanding of cellular plasticity and provided new tools for regenerative medicine. While the use of iPS-derived cardiomyocytes for improving cardiac function holds promise, there are still several challenges and concerns that must be addressed before this approach can be safely and effectively translated into clinical practice.

Mesenchymal stem cells (MSCs) and cardiac regeneration:

Mesenchymal stem cells (MSCs) have the potential to differentiate into various cell types, including cardiomyocytes, which are the cells that make up the heart muscle. The differentiation of MSCs into cardiomyocytes is a promising approach for regenerating damaged heart tissue and treating heart disease. The differentiation of MSCs into cardiomyocytes involves several steps, including the induction of the MSCs towards a cardiac lineage, the activation of cardiac-specific genes, and the maturation of the resulting cardiomyocytes [62,63].

One of the approaches to induce MSCs towards a cardiac lineage is by exposing them to a combination of growth factors and chemicals that promote cardiac differentiation. These factors include BMP-2 (bone morphogenetic protein-2), TGF-β (transforming growth factor-β), and Wnt signaling inhibitors [64,65]. Once the MSCs are induced towards a cardiac lineage, they can be further differentiated into cardiomyocytes by exposing them to specific growth factors such as Activin A, BMP-4, and FGF-2 [66]. This process can be further enhanced by culturing the cells on a substrate that mimics the cardiac microenvironment, such as a hydrogel or a matrix made of cardiac extracellular matrix proteins. Finally, the resulting cardiomyocytes can be further matured by subjecting them to electrical and mechanical

stimulation, which mimics the mechanical forces and electrical signals experienced by cardiomyocytes in the heart. This maturation process results in cardiomyocytes that exhibit more mature features, such as improved contractility and more organized sarcomeres [67,68].

Bone marrow-derived cells (BMCs) are a type of stem cell that can be extracted from a patient's bone marrow and include hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and endothelial stem/progenitor cells (EPCs). Unlike other stem cells that are differentiated into cardiomyocytes in vitro before transplantation, BMCs are directly transplanted into the body. Some researchers believe that BMCs have the potential to differentiate into non-hematopoietic cells such as cardiac cells, while others argue that these cells have limited differentiation potential and cannot generate cardiomyocytes [69-71]. Therefore, BMCs are not considered as candidates for "true" regeneration, but rather for their paracrine effects. Nonetheless, BMCs are currently the most frequently used cell source for cardiac repair in clinical trials, and studies in both animals and humans have shown that transplantation of BMCs is safe [72].

A recent studies found that transplanting bone marrow cells (BMCs) typically improves left ventricular (LV) function, reduces infarct size, and mitigates remodeling, with potential effects on clinical outcomes like mortality and morbidity [32,73].

In 2001, Orlic et al. demonstrated that bone marrow-derived cells (BMCs) could regenerate the damaged myocardium by transplanting hematopoietic stem cells (HSCs) marked by the c-kit protein in a mouse model of myocardial infarction (MI) [74]. However, subsequent studies have challenged the claim that HSCs can differentiate into cardiovascular cells. Nevertheless, the study found that transplantation of BMCs, including c-kit+ cells, resulted in improved cardiac function. Other cell surface markers, such as CD133+ and CD34+, have also been identified to enrich populations of human HSCs. CD34+ cells have been considered for clinical use in cardiac regeneration and are currently used to treat hematopoietic deficiencies after radiation or chemotherapy. However, clinical trials testing c-kit+ cells have not been conducted, making it difficult to compare their efficacy with other cell types [75].

Hristov M et al. in 2003, studied that a type of cells found in bone marrow, called endothelial progenitor cells (EPCs), can also be found in peripheral blood and express CD34. This led to studies investigating the potential of CD34+ cells for angiogenesis and cardiac regeneration [76]. A study reported successful differentiation of these cells into endothelial cells, cardiomyocytes, and smooth muscle cells after transplantation into an infarcted heart [77]. However, a study by Norol and colleagues did not find any evidence of cardiac regeneration following transplantation of CD34+ cells in non-human primates [78]. Clinical trials using bone marrow mononuclear cells (BMCs), which include hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and monocytes, have shown promising results in improving left ventricular ejection fraction (LVEF) in patients with acute myocardial infarction (MI) and chronic ischemic heart disease (IHD) with congestive heart failure. However, the mechanisms underlying this improvement are still debated, and the results of clinical trials have shown significant heterogeneity, with some studies reporting conflicting findings [79]. A recent analysis by Sheng et al. in 2019, reported significant and sustained improvement in LVEF and morbidity and mortality in patients with chronic IHD and congestive heart failure following BMC therapy. However, the analysis also noted the high degree of heterogeneity in the results [80].

Adipocyte stem cells, also known as adipose-derived stem cells (ASCs), are a type of mesenchymal stem cell that can be isolated from adipose tissue (fat). ASCs have similar properties to other MSCs, such as the ability to differentiate into multiple cell types and their anti-inflammatory and immunomodulatory effects [81]. In recent years, there has been growing interest in the potential of ASCs for cardiac regeneration. Studies have shown that ASCs can improve heart function and reduce scar tissue formation in animal models of heart injury. ASCs can differentiate into cardiomyocytes and other cell types that are important for heart function [82,83]. They also secrete growth factors and other signaling molecules that promote the growth of new blood vessels and support the survival of existing heart tissue [67,84]. Several preclinical and clinical studies have investigated the safety and efficacy of ASC therapy for heart disease. Results from these studies have shown that ASC therapy can improve heart function and reduce scar tissue formation in patients with ischemic heart disease or heart failure. However, more research is needed to fully understand the therapeutic potential of ASCs for cardiac regeneration, including the optimal dose and timing of the injections, the potential for immune rejection of the transplanted cells, and the long-term safety and efficacy of the therapy [82,85]. In summary, the differentiation of MSCs into cardiomyocytes involves a complex series of steps, including induction

towards a cardiac lineage, activation of cardiac-specific genes, and maturation. This process holds promise for the development of novel therapies for heart disease and the regeneration of damaged heart tissue.

Cardiac stem cells (CSCs):

For many years, it was believed that cardiac tissue was incapable of generating new parenchymal cells as it was thought to be terminally differentiated. Nevertheless, resident cardiac stem cells (CSCs), which are progenitor cells in the cardiac lineage, have been discovered in cardiac tissue [87]. These CSCs express stem cell marker proteins like lsl-1, c-kit, and Sca-1, [88] and can be isolated from both fetal and adult cardiac biopsies. When expanded in culture, they retain their progenitor state and can differentiate into various cardiovascular cell types, such as cardiomyocytes, endothelial cells, and smooth muscle cells [89,90]. Following a myocardial infarction (MI), newly formed myocytes and cardiac stem cells are detected in the border area of the infarct, suggesting that the heart possesses some regeneration capacity, albeit insufficient. The transplantation of CSCs aims to enhance and exploit the heart's natural regenerative capacity. CSCs have the added advantage of being able to differentiate into cardiovascular cell types in vivo, eliminating the need for pre-implantation in vitro differentiation [91]. Recently, the outcomes of the first phase 1 clinical trials using CSC infusion were released. Intracoronary autologous CSC injection seems to be safe, and preliminary findings have demonstrated an increase in viable myocardium, left ventricular ejection fraction, and other clinical indicators, albeit with varying results between trials. Larger randomized, blinded trials with appropriate controls will be necessary to thoroughly assess the clinical impact of CSC injection [92]. Until a decade ago, the dogma that the heart was a terminally differentiated organ and could not generate new parenchymal cells heavily influenced cardiology research. Consequently, it was thought that the only response of cardiomyocytes to stress was either hypertrophy or death. However, there is now evidence indicating that myocytes undergo replication, mitotic division, and spontaneous regeneration in the heart [93,94].

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