Article published online: 2024-07-01



# Simplifying Stem Cell Therapy for IRs: Exploring New Horizons in Interventional Radiology and Cell Therapy

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Arab J Intervent Radiol 2024;8:54–62.

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## Abstract

The effective treatment of various diseases requires not only medications but also precise delivery methods to the body and specific organs. In this regard, radiology plays a crucial role, acting as the eyes of physicians. In contrast, interventional radiology serves as its hands, acting as one of the most effective drug delivery systems. Among interventional radiology disciplines, arterial drug delivery through arteries holds paramount importance as organs primarily receive nourishment directly from them. Furthermore, regenerative medicine is a burgeoning field dedicated to repairing diverse body tissues without relying on pharmaceutical drugs. Stem cells, inherent in various parts of our bodies, are vital for tissue regeneration and reconstruction. Depending on the treatment approach, stem cells can be sourced from the patient's body (autologous) or another individual (allogeneic). There exist various types of stem cells across species, with regenerative properties observed in animals and even plants. However, targeted cell therapy is preferred over systematic injections throughout the body for better efficacy. This article aims to familiarize interventionalists with stem cells and provide them with a clear and helpful explanation of their functions, mechanisms of action, different sources, and other relevant aspects. This will help them select the most appropriate cells for their therapeutic purposes. By comprehensively understanding the significance of stem cells in interventional radiology, we can implement optimal methodologies to address diverse medical conditions efficiently.

**Keywords**
- drug-delivery
- interventional radiology
- regenerative medicine
- stem cell

## History of Stem Cells

In the early 1960s, a notable scientific advancement emerged from studies on mice bone marrow transplantation. This research opened the door for modern stem cell biology and is primarily attributed to James Till and Ernest McCulloch. However, the groundwork for the adult stem cell field was established earlier, in 1953, by two prominent Canadian scientists, Yves Clermont and Charles Philippe Leblond.[1]

Stem cells have been around since before humans existed. They can be found in both animals and plants. Stem cells in plants are unique cells that are located in the meristematic

DOI https://doi.org/10.1055/s-0044-1787158.
ISSN 2542-7075.



Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

tissues. They supply the plant with a constant stream of precursor cells capable of differentiating into various tissues, ensuring the plant's health and vigour.[2]

Regenerative medicine is an emerging scientific field dedicated to repairing damaged body parts using biological processes. This ability to regenerate extends beyond humans and is observed in various animals, such as hydras and planarian flatworms.[3,4]

Advanced mammals, higher in the vertebrate hierarchy, often lose regeneration abilities, limited mainly to wound healing. Yet, complete organ replacement remains possible. For example, in humans, a portion of the liver can regenerate fully, and elk antlers can completely regrow after shedding.[4]

During the initial stages of stem cell discovery, researchers noticed that in cases of leukemia, the bone marrow produced both diseased and healthy cells. Since it was not practical to selectively remove only the diseased cells, they resorted to eliminating all cells through chemotherapy. Afterwards, stem cells were introduced to facilitate the production of healthy cells.[5]

To understand this better, imagine a scenario where a city has both sick and healthy individuals. To address this issue, the entire population is cleared out. Eventually, fertile families are resettled to start the production of a new, healthy generation.

## What is Stem Cell? The Trajectory of Stem Cells in the Human Body: From Birth to Maturity and Laboratory

A stem cell is a type of cell that remains undifferentiated. To be classified as a stem cell, it must exhibit two essential characteristics. First, it must have the capability of self-renewal, allowing it to replicate into additional cells with a similar unspecialized nature. Second, it must possess the capacity to differentiate into various specialized cell types and form organs.[6]

Totipotent cells possess the extraordinary ability to mature into any cell type within the body, which is crucial for both fetal and placental development. On the other hand, pluripotent cells, though versatile, cannot give rise to a fully formed organism. They, however, hold the potential to develop into approximately 200 different cell types in the body.[7]

Cell differentiation is the intricate process where stem cells develop into specialized cells. This process occurs naturally during embryonic development. Initially, stem cells are totipotent, which can differentiate into all cell types of the body. As differentiation progresses, their potency decreases, and they become more specialized. The fate of pluripotent cells, which are directed toward one of the endoderm, mesoderm, or ectoderm as three germ layers, is determined by factors such as their location within the embryo and chemical signals. Once a stem cell commits to a specific germ layer, it becomes multipotent, meaning that it can generate various cell types within that layer. During differentiation, cells undergo genetic and physical transformations, gradually losing potency until they become unipotent and can only produce one cell type. Within each germ layer, pluripotent cells possess unique differentiation potential. Ectoderm cells, derived from the outermost layer, can differentiate between skin cells and neurons. Mesoderm cells, originating from the middle layer, possess the capacity to transform into muscle cells, like those found in the heart or skeletal system, as well as red blood cells, among others. Endoderm cells, originating from the innermost layer, can develop into various organ cells, such as those found in the lungs, thyroid, or pancreas.[8,9]

Cell differentiation, a crucial process during embryonic development, sees stem cells transform into specialized cells. Stem cells, initially totipotent, can become any cell type. As differentiation progresses, they become more specialized. Pluripotent cells commit to one of the endoderm, mesoderm, or ectoderm—guided by location and chemical signals. Once committed, they become multipotent, capable of generating various cell types within that layer. Throughout differentiation, cells undergo genetic and physical changes until becoming unipotent, producing only one cell type. Endoderm cells are used to connect various organ cells like those in the lungs or pancreas, and ectoderm cells give rise to skin cells and neurons, mesoderm cells to muscle cells, and red blood cells.[10,11]

In addition to induced pluripotent stem (iPS), totipotent, multipotent, and pluripotent adult stem cells reside in body tissues and are differentiated exclusively into the tissue they inhabit. For instance, muscle tissue stem cells specialize solely in muscle differentiation[12] (►**Fig. 1**).

## What are Autologous and Allogenic? Which One is the Choice?

Autologous mesenchymal stem cells (MSCs) are easily obtainable and typically evade immune rejection postinfusion; however, their isolation, in vitro expansion, and release processes are time-consuming, and there is a risk of systemic diseases in patient-derived autologous MSCs. Allogenic MSCs present benefits such as donor variability, multiple origins, minimal immune reactivity, and easy accessibility. However, they could trigger an immune reaction and potentially evoke immune memory in specific situations.[13–15]

Despite the challenges, allogeneic MSC therapy is on the rise in clinical translation, deemed clinically safe and effective, with strategies suggested to mitigate potential antidonor immune responses, including the use of immunosuppressive drugs as proposed by Lohan et al. However, the ongoing debate surrounding the risks and limitations of autologous versus allogeneic MSCs, including donor-donor heterogeneity, underscores the need for further research and discussion in all clinical settings.[16]

The versatility and diverse functions of MSCs present potential challenges for ensuring the effectiveness and safety of different cell therapies in clinical settings. Understanding how MSC biological properties interact with their microenvironment is crucial for grasping their role in medical practice. However, clinical data do not definitively determine whether autologous or allogeneic MSCs offer superior

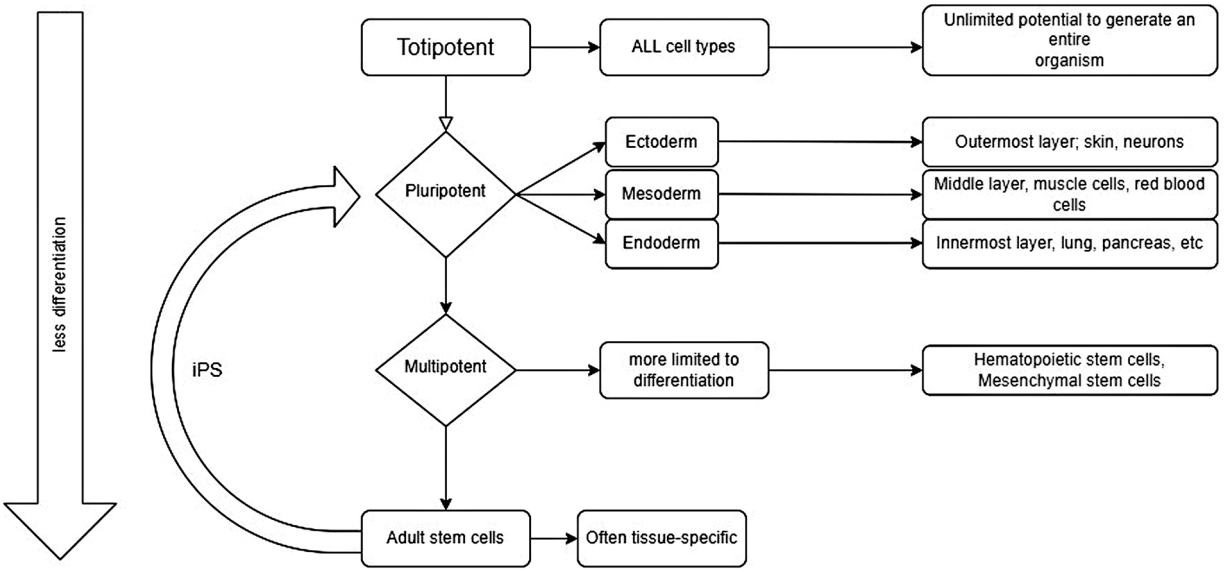


**Fig. 1** The journey of stem cells in the human body: from birth to maturity.

therapeutic benefits. To ensure safe and effective MSC transplant therapies, personalized approaches, including donor-controlled practices and analysis of disease-associated genetic variations in MSCs, are recommended.[17]

## Mechanism of Action

*Multifaceted interaction*: The therapeutic effect of MSCs is based on their regenerative capabilities and capacity to regulate the immune system. These effects are from multiple mechanisms, as MSCs impact various tissue and immune cells through diverse factors and processes.[18]

Human MSCs (hMSCs) demonstrate strong immune regulatory capabilities, rendering them appealing for treating human diseases characterized by inflammation and tissue injury. All the specific mechanisms of MSCs vary depending on the environmental context and the type of repair process needed. Significantly, observations have demonstrated that hMSCs can ameliorate graft-versus-host disease (GVHD) without causing adverse effects, enhancing their appeal as treatment options for a spectrum of diseases. The proposition that a primary mechanism of hMSC involves the stimulation of human regulatory T cells appears credible.[19]

The immunoregulating characteristics of MSCs are impacted by environmental factors, resulting in a complex interplay that determines their therapeutic effects. MSCs can adopt both anti-inflammatory and proinflammatory phenotypes depending on local cues within tissues. Their reaction to interferon-γ and other inflammatory factors and stimulation of Toll-like receptor (TLR) signaling can influence their secretome composition and function. Notably, MSCs can promote the differentiation of T cells into regulatory or proinflammatory subsets based on cytokine levels like transforming growth factor (TGF)-β and interleukin-6.[20]

Moreover, MSCs can adopt immunosuppressive phenotypes when exposed to various TLR ligands, thereby influencing their interactions with immune cells and therapeutic effectiveness. The divergent outcomes seen in MSC-based therapies in autoimmune or GVHD models may stem from the polarization of MSCs in response to changes in the microenvironment. These discoveries emphasize the significance of comprehending the dynamic interplay between MSCs and their surroundings to enhance their therapeutic efficacy.[20,21]

## Sources of Stem Cells: Where and How Can We Find Them in the Body?

Depending on the intended purpose for using stem cells, factors such as cell availability, the targeted organ, etc., researchers, especially interventional radiologists, should select the most appropriate source of cells. When categorizing stem cell reservoirs in humans, various sources are considered, including embryonic, fetal, infant, and adult origins (►**Fig. 2**).[22]

In the following sections of the article, we will examine the mentioned cellular sources.

### Umbilical Cord

In the past, during childbirth, the umbilical cord and its pair were discarded. Still, gradually, with advances in medical knowledge, it was discovered that the umbilical cord and its pair are rich in pluripotent and hematopoietic stem cells.[23]

Recent research has underscored the potential therapeutic applications of umbilical cord blood in treating disorders related to bone marrow and congenital metabolic issues. Unlike bone marrow, umbilical cord blood does not necessitate precise human leukocyte antigen tissue matching, exhibits lower rates of GVHD, and can be utilized allogenically.[24,25]

In the application of stem cells, a crucial consideration is the accessibility of stem cell sources. Regarding umbilical cord stem cells, due to the low risk of GVHD, there is no necessity to procure cells from the patient in an autologous

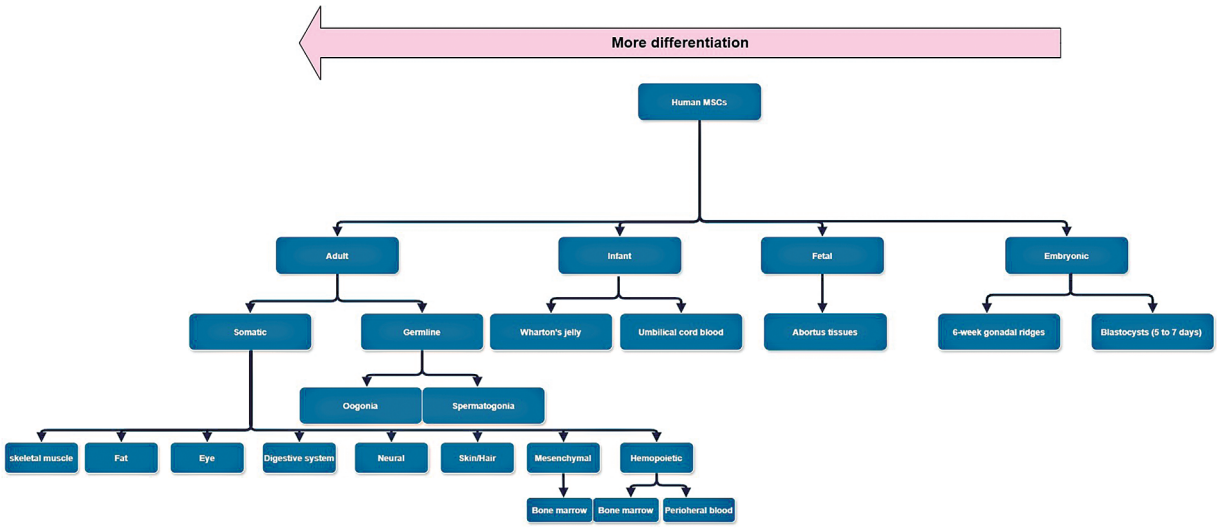


**Fig. 2** Adult stem cells in the human body.

manner. This aspect simplifies the utilization of this source significantly compared with others. Furthermore, because of the potential for off-the-shelf availability, establishing a bank of MSCs is feasible. All these factors simplify stem cell utilization. Umbilical cord-derived MSCs, in particular, are easier to collect and pose no health risks to mothers or newborns. They offer advantages over bone marrow stem cells in terms of accessibility and ease of collection. Additionally, umbilical cord stem cells can be cryogenically stored for future therapeutic use, with Wharton's jelly extraction holding promise for efficient banking.[26]

Research suggests that these MSCs show immune tolerance and can traverse MHC barriers while avoiding triggering immune reactions. They also suppress lymphocyte proliferation and cytotoxic T cell formation, possibly through prostaglandin E2 and TGF-β1 mechanisms. Similar immunosuppressive effects are seen in umbilical cord-derived MSC-like cells, hinting at therapeutic potential.[26–29]

## Homing of Umbilical MSC

Significant evidence suggests that MSCs possess a unique ability to migrate to pathological areas, guided by chemokines and other signals originating from those sites.[26]

However, when umbilical cord MSCs are administered intravenously, they have been observed to relocate to the lung, liver, and spleen after several days.[30] Consequently, direct injection via interventional radiology (IR) delivery facilitates localized therapy and enhances concentration within the targeted region.

Aside from their immunosuppressive characteristics, MSCs exhibit an affinity for injured or actively growing tissues. For instance, when injected into the brain, MSCs transfer along established routes, such as the corpus striatum. Following injection into the lateral ventricle of neonatal mice, they disperse across the forebrain and cerebellum, integrating into the central nervous system's framework and displaying markers typical of mature astrocytes and neurons.[31,32] In injured spinal cords, MSCs were observed to form guiding structures, facilitating the regeneration of fibers.[33]

MSCs have been implicated in aiding regeneration in conditions like stroke[34,35] or myocardial ischemia.[36,37] The cells disperse across the forebrain and cerebellum, integrating into the structure of the central nervous system. Upon injection into the lateral ventricles of neonatal mice, they demonstrate the expression of mature astrocyte and neuron markers.[38,39]

## iPS Stem Cells

The creation of iPS cells from somatic cells through defined transcription factors offers significant promise for regenerative medicine. These cells present advantages like the ability to derive patient-specific cells and avoid ethical concerns associated with embryonic tissue. However, challenges such as reprogramming factor delivery, genomic instability, and epigenetic memory remain to be addressed before widespread clinical translation. Despite these hurdles, iPS cells hold great potential for various applications, like cell replacement therapies, pharmacological screening, and disease modeling. The minimally invasive nature of iPS cell generation and their potential for personalized interventions further underscore their importance. While more research is needed, promising preclinical studies suggest a rapid move toward clinical application within just 8 years since their discovery.[40–43]

## Fetal Stem Cell

Fetal blood, particularly in the first 3 months, is abundant in hematopoietic stem cells that differentiate more rapidly. Another notable aspect of fetal blood is that, alongside hematopoietic stem cells, it also generates nonhematopoietic stem cells. Both types of these cells possess the capability to transform into various types of bodily tissues. Using fetal cells not only offers a higher potency relative to other categories of adult stem cells but also presents fewer ethical challenges compared with embryos. These cells also

exhibit high capability in laboratory studies and gene therapy research.[44]

Despite all the advantages of fetal stem cells, their use poses several challenges: obtaining consent from the parents of aborted fetuses, managing host immune responses, selecting the best method of cell delivery into the body, purifying the desired tissue from the stem cell source, and culturing it in the laboratory, among other factors. Current research focuses on elucidating the mechanisms underlying fetal stem cell engraftment, homing, and differentiation.[44]

Successful cases, like the management of X-linked severe combined immunodeficiency using fetal liver cells in utero, highlight the therapeutic promise of fetal stem cells in addressing severe genetic disorders.[45]

### Embryonic Stem Cells

Embryonic stem cells (ESCs) show significant potential for tissue engineering and regenerative medicine. These pluripotent cells offer invaluable insights into early differentiation processes and have been studied across various species, including rodents, primates, and humans. However, the clinical application of ESCs faces obstacles, such as the challenge of generating a pure population of mature progeny, avoiding teratoma formation, and ensuring efficient purification methods. Additionally, the risk of host rejection of allogeneic ESC-derived implants necessitates lifelong immunosuppressive drug use, which comes with associated side effects. These hurdles underscore the need for ongoing research to address technical and ethical challenges before ESC-based therapies can progress to clinical trials.[46–50]

### A Glance at Adult Stem Cells

Adult stem cells are specific to certain organs within mature organisms, committed to their predetermined paths of differentiation.[51]

Adult stem cells originate from various locations within the body (►**Fig. 2**).

Here is a glance at adult stem cells.

### Bone Marrow Stem Cells

In preliminary in vivo investigations, it was discovered that cells derived from bone marrow demonstrated the ability to transform into diverse tissue categories, such as muscle fibers, hepatocytes, microglia, astroglia, and neuronal tissue.[52–55]

Subsequent experiments focused on refined stem cells, particularly hematopoietic stem cells, which were demonstrated to produce functional tissue cells. For instance, transplantation of purified hematopoietic stem cells successfully restored liver functions of tyrosinemia type I in an animal model.[56]

Moreover, studies highlighted the versatility of hematopoietic stem cells in generating cardiomyocytes, vascular structures, and other cell types involved in arterial remodeling.[57,58]

Yet, the physiological significance of these findings warrants further investigation due to uncertainties surrounding the functional relevance of the transdifferentiated progeny.[59]

These results emphasize the potential therapeutic uses of hematopoietic stem cells in the realm of regenerative biology. Further elucidating the mechanisms underlying the differentiation and functionality of these cells could pave the way for innovative treatments targeting a large number of diseases.[51]

### Peripheral Blood Stem Cell

Given that bone marrow stem cells can travel to organs via the peripheral blood, the logical progression was to investigate whether stem cells from peripheral blood undergo a differentiation process tailored to solid organs, akin to bone marrow stem cells.[60]

Several research investigations indicate that human stem cells present in the bloodstream, triggered by cytokine administration, contribute to the formation of non-lymphohematopoietic tissues. For instance, endothelial progenitor cells have been observed to support ocular neovascularization in mice and neovascularization in ischemic myocardium in rats.[61]

### Digestive Tract Stem Cell

The digestive tract varies in epithelial coverings from squamous in the oral cavity and esophagus to glandular structures in the stomach and intestine, and crypts in the colorectum. In the esophagus, cell proliferation mainly occurs in basal layers, showing diverse differentiation patterns, indicating the presence of stem cells.[62,63]

Stem cells are thought to be situated close to the gastric pit, with bidirectional cell flux facilitating tissue turnover.[64,65]

In the liver, the intrahepatic biliary tree harbors a facultative stem cell compartment activated during regeneration, contributing to hepatocyte and biliary epithelial cell replenishment. Unique markers, pluripotency-associated factors, have been identified in putative liver stem cells, suggesting their localization near portal tracts.[66,67]

The pancreas comprises exocrine and endocrine tissues, with β cell renewal being crucial for diabetes treatment. While pancreatic stem cells remain elusive, evidence suggests potential β cell derivation from ductal cells, particularly in response to injury.[68,69]

### Adipose Tissue Stem Cells

Adipose-derived stem cells (ASCs) were initially recognized as MSCs in adipose tissue back in 2001.[70] Multiple terms have been applied to describe these cells. Finally, in 2004, they were formally termed ASCs.[71]

ASCs are retrievable from various adipose tissue types, notably subcutaneous fat, which holds clinical importance. Extraction sites include the abdomen, thigh, and arm. The ample presence of adipose tissue in humans suggests a potential for obtaining ASCs in abundance. Their capability to change into diverse cell types, release cytokines, and modulate the immune system highlights their crucial role in tissue regeneration.[71–73]

### Female Reproductive Tract

The female reproductive tract features specialized epithelial linings in the uterus, cervix, and mammary glands, each harboring distinct stem cell populations. In the uterus, endometrial glands house stem-like cells similar to those found in intestinal crypts; in mammary glands, stem cells are located within terminal ductal lobulo-alveolar units, capable of differentiating into luminal and myoepithelial cells.[74,75]

Studies suggest that the side population (SP) fraction in mammary glands contains enriched stem cell populations, facilitating tissue regeneration. Human mammary gland phenotypes reveal specific markers for myoepithelial, luminal, and stem cells, providing insights into tissue organization and regeneration. Isolation of mammary ductal cells proficient in mammosphere production further elucidates the stem cells. These findings contribute to our understanding of tissue dynamics and potential therapeutic strategies within the female reproductive tract.[75,76]

### Male Gonadal and Sex Tissue

Spermatogonial segmentation leads to spermatozoa differentiation, with mouse testicular stem cells expressing specific markers and demonstrating high regenerative potential. Similarly, in humans, two types of A spermatogonia exist: Apale, which are progenitor cells and Adark, likely stem cells.[77,78]

The prostate gland, enveloping the urethra, houses stem cells primarily located within ducts in mice, expressing markers like p63. Notably, individual murine prostatic cells exhibit the capability to form functional acini and demonstrate the presence of different stem cell markers. Human prostatic stem cells coexist with basal cells and exhibit cytokeratin-based differentiation pathways, with CD133-expressing basal cells demonstrating high proliferative potential and regenerative capacity.[79–81]

### Central Nervous System

In the central nervous system, astrocytes are the primary kind of stem cells in the brain, supplemented by additional neural stem cells in specific regions. Transcriptional regulation is involved in maintaining stem cell function, with Hmga2 identified as a factor in suppressing age-related changes. Similarly, within the human brain, astrocytes located in the subventricular zone exhibit proliferative capabilities and can generate neurospheres with differentiation potential across three lineages.[82–84]

### Eye

In the eye, the corneal epithelium renewal process involves cells from across the cornea rather than solely from the limbus, contrary to previous beliefs. However, the limbus may still harbor enriched stem cell populations, as suggested by the discovery of a SP exhibiting high clonogenicity. In mice, the ciliary margin of the retina contains cells with stem cell features, expressing various transcription factors, and capable of multipotential differentiation.[85,86]

### Stratified Squamous Epithelia

The skin's stratified keratinizing squamous epithelium, the interfollicular epidermis, and the outer root sheath of hair follicles are composed of a basal layer where cell division primarily occurs. Recognition of epidermal stem cells has depended on label-retaining cells or β1 integrin expression enrichment.[87]

In mice, bulge stem cells expressing K15 regenerate the entire hair follicle and sebaceous gland. CD200 expression selection boosts colony-forming efficiency in human hair bulge cells.[88–90]

### Heart and Skeletal Muscle

Both heart and skeletal muscle possess regenerative potential through various stem/progenitor cell populations.[91–94]

Cardiomyocytes and cardiac stem cells demonstrate the ability to differentiate into diverse cardiac cell types, contributing to cardiac repair postmyocardial infarction. Similarly, satellite cells have historically been considered the primary contributors to muscle regeneration, but recent evidence suggests a more complex interplay involving multiple cell sources or previously unrecognized lineages. Muscle SP cells and nonmyogenic cells like mesoangioblasts and bone marrow-derived cells also participate in muscle repair, highlighting the need to understand their roles and relationships with classical satellite cell markers for comprehensive comprehension of muscle regeneration mechanisms.[95]

## Conclusion

Given the remarkable effectiveness of regenerative medicine in treating diseases, the convergence of IR and regenerative medicine could revolutionize medical science.

An interventionalist must understand various sources of stem cells and their function. Stem cells are attracted to highly inflammatory sites, where they mitigate inflammation and differentiate into target tissue cells. While allogeneic sources of stem cells are more readily available, they come with the risk of recipient immune responses.

Among all sources, umbilical cord blood stands out due to its off-the-shelf availability and abundance. Additionally, bone marrow serves as a valuable source due to the high potency of its cells. However, embryonic and fetal stem cells, despite their high potency, pose ethical challenges and are less accessible. The most crucial aspect of utilizing adult stem cells is that they often differentiate into cells of their heritage rather than multiple lineages as they are mature and gradually lose their differentiation ability from the embryonic to the mature cell stage. ASCs, initially recognized as MSCs in 2001, have emerged as pivotal players in regenerative science due to their abundant availability in various adipose tissue types, versatile differentiation potential, and immunomodulatory properties, promising significant advancements in therapeutic applications for tissue regeneration. iPS cells offer personalized regenerative solutions, overcoming ethical hurdles, yet face challenges like reprogramming and genomic instability, potentially hindering their clinical

translation despite their diverse applications and rapid progress in regenerative medicine.

Consideration of the diameter of stem cells in arterial delivery poses a challenging aspect for vascular interventionalists, particularly in cases like brain capillaries where artery diameter is minimal.

The combination of IR and regenerative medicine is a very new subject, and research in this area is rapidly expanding. It could potentially lead to revolutionary advancements in medical science.

### Note

The part of the article is presented in PAIRS congress 2024, 2/10/2024, HALL B, Stem cell therapy in IR, What IRs should know?, Presented by**:** Dr. Maedeh Rouzbahani.

### Ethical Approval Statement

This review article adheres to the principles outlined in the Declaration of Helsinki.

### Conflict of Interest

None declared.

### Acknowledgment

We extend our heartfelt gratitude to Professor Jafar Golzarian for his invaluable support, unwavering guidance, and insightful feedback throughout our project. His presence alongside us and his thoughtful contributions have significantly enriched the depth and quality of our work.

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