

Open Access**Article Information****Received:** November 17, 2024**Accepted:** November 25, 2024**Published:** November 30, 2024**Keywords**

Adult Stem Cells,
Tissue Regeneration,
Multipotency,
Niche Dependency,
Transit-Amplifying Cells.

Authors' Contribution

AJA conceived and designed the study; wrote the first draft of the manuscript; revised, and approved the final manuscript.

How to cite

Alkhatib, A.J., 2024. The Role of Adult Stem Cells in Tissue Healing and Therapeutic Applications. PSM Microbiol., 9(3): 42-61.

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The Role of Adult Stem Cells in Tissue Healing and Therapeutic Applications

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Abstract:

Repairing or regenerating tissues at any age is an essential part of maintaining tissue homeostasis and normal function. Adult stem cells are very important in this process. They form new cells to replace those lost due to injury or disease. Regenerative medicine makes use of these cells, which are found in most tissues. There are already successful uses of stem cells like the skin of the cornea, blood, and so on. Research to isolate and characterize adult stem cells from different organs has provided useful information about their biology and utility. Even though adult stem cells are diverse in nature, they share important characteristics like multipotency, self-renewal, and niche dependency. When there is damage to the plant or plant's pathogen attack, they become dormant. When stimulated, adult stem cells produce transit-amplifying cells. These cells grow and turn into different types of tissues to help with recovery. Tissue-specific progenitors, which are restricted in their ability to self-renew, are formed from adult stem cells that drive regeneration. However, we don't know the full extent of the processes that adult stem cells are involved with. Functions in many organs are not fully understood. In addition, adult stem cells may differ in their molecular makeup across tissues, reflecting an evolutionary response to the specific repair needs of each organ.



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INTRODUCTION

Stem cell research began in the 1960s, studied using transplant technology to treat human malignant tumors, and the establishment of a Discipline Department in the medical school. Later, Delik in 1967 first proposed the concept of stem cells (Liu *et al.*, 2021). Stem cell research took a new route (Sng and Lufkin, 2012). American Loand and Schechter applied medical imaging to the evaluation of the therapeutic effect of hematopoietic stem cell transplantation (Wade, 2023). The concept of hematopoietic stem cells was proposed and the theory was confirmed, which laid the foundation for the replacement of hematopoietic stem cells (Cieri *et al.*, 2021). In 1978, American researchers discovered the hematopoietic stem cells of the hematopoietic system, which was highly significant in the development of basic hematopoiesis sensors (Mora, 2022). In 1991, the world's first hematopoietic stem cell transplantation was successful, which detected a serious hematological disease, and then brought new possibilities for hematopoiesis (Terry Sharrer, 2022).

Stem cells, also known as precursor cells, progenitor cells, ancestral cells, or stem cells, are currently used in scientific research, embryonic cells, umbilical cord blood cells, placental cells, amniotic cells, and adult stem cells (Shah and Khan, 2021). The classification of adult stem cells in the adult body is divided into hematopoietic stem cells, nerve stem cells, bone marrow stem cells, and mesenchymal stem cells (Tian *et al.*, 2023). The neural stem cells are generated after the future nerve tube is formed. The sensitivity is mainly distributed in the cerebrum, except for the meninges of the myo (Poliwoda *et al.*, 2022). For example, the bulge of brain bulbar growth, the olfactory bulb adjacent to the horny skull, the cerebral cortex around the ventricle, the wall of the lateral ventricle, the spinal cord around the central canal, the posterior horn of the spinal cord, and the spinal cord extendable before the lumbar enlargement (Kandarakov *et al.*, 2022). A small number of nerve stem cells manage the central

stem cells or neural stem cells. Although there are differences between them, they can be distinguished by immunohistochemistry or specific antigen markers (Chen *et al.*, 2021).

Types of Adult Stem Cells

There are many different categories of stem cells (Orbay *et al.*, 2012). To name a few: mesenchymal stem cells, epithelial stem cells, hematopoietic stem cells, mammary stem cells, and inner ear stem cells (Zupan, 2021). Mesenchymal stem cells are undifferentiated cells with the capacity for multilineage differentiation and self-renewal without senescence. In mammals, there are two main types of stem cells: embryonic stem cells and adult stem cells (Serrano *et al.*, 2021). Adult stem cells are tissue-specific, self-renewing cells that differ from other types of stem cells in that they can regenerate multiple tissue types, such as muscle, bone, cartilage, and tendons. As a category, mesenchymal stem cells generally refer to a unique class of stromal cells found in the bone marrow that have the capacity for trilineage differentiation into cells that have properties of muscle, bone, and fat (Klein, 2021). Mesenchymal stem cells isolated from other tissues have different multilineage differentiation than those from bone marrow (Serrano Martinez *et al.*, 2021). Mesenchymal stem cell therapy has recently emerged in areas such as orthopedics, cardiology, neurology, pulmonology, dermatology, and oncology, and many of these therapies are undergoing clinical trials. More than half percent of mature cartilage and bone are composed of water and soft tissue has limited regenerative potential (Zupan, 2021). Thus it is difficult to regenerate multiple tissues, however, mesenchymal stem cells have multilineage differentiation potentials and their differentiation and proliferation could promote surrounding tissue healing (Orbay *et al.*, 2012). Though endochondral ossification bone can be formed, it could promote more chondrocytes for cartilage regeneration. Articular cartilage thickness is between 2mm-4mm (Chen *et al.*, 2021). If it is damaged or worn away, it needs to be regenerated. However articular cartilage has

a poor regenerative capacity because it is avascular, neural, and lymphatic tissue. The subchondral bone marrow has been recognized as a possible source of cells to repair articular cartilage damage (Honda and Ohshima, 2022). Hematopoietic stem cells play an essential role in replenishing lost blood cells due to bleeding or injury and consequently have been extensively used to treat blood-related disorders such as leukemia, aplastic anemia, lymphoma, and immune deficiencies (Saxena and Shivedasani, 2021). Hematopoietic stem cell transplantation is a well-established treatment whereby a patient's dysfunctional bone marrow is partially or completely replaced with functional bone marrow from a donor (Sng and Lufkin, 2012). However, identifying a donor with a matching human leukocyte antigen type can be rare and the transplantation process can cause serious complications such as toxicity, graft-versus-host disease, and graft rejection. Despite the importance of hematopoietic stem cells in health and medical treatment, they are difficult to isolate, partially due to insufficient knowledge about the niche that regulates their self-renewal, differentiation, and mobilization (Benham-Pyle *et al.*, 2022). As people are living longer, it is becoming increasingly important to maintain brain health and to promote neuroprotection and neuroregeneration (Saxena and Shivedasani, 2021). Neural stem cells exist within several regions in the adult brain including the subventricular zone of the lateral ventricles and the dentate gyrus of the hippocampus. They are responsible for maintaining and regenerating neurons as well as forming new glia (Honda and Ohshima, 2022).

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs), initially recognized by Friedenstein *et al.* in 1976, are a type of adult stem cells mainly isolated from bone marrow stroma (Ayala-Cuellar *et al.*, 2018). These cells have the potential to differentiate into three lineages which are adipocytes, chondrocytes, and osteocytes (Galderisi *et al.*, 2022). Since this first report on MSCs, organ, tissue, and cell sources at other anatomical

locations have been recognized as MSC sources including adipose tissue, umbilical cord, placenta, and other perivascular locations (Zhang *et al.*, 2021). This cell type has subsequently been reported to be isolated from various organs and tissue types (Liu and Holmes, 2021). Among these sources, bone marrow and adipose tissue remain the most-studied and popular sources due to their clinical accessibility for human applications (Ayala-Cuellar *et al.*, 2018). Currently, more than 400 trials of MSC-based therapy for various ailments have been registered and about 30% of these trials are focused on bone, cartilage, and connective tissue-related diseases (Pakzad *et al.*, 2022).

As the size of the elderly population increases, the incidence of degenerative skeletal diseases is subsequently on the rise (Sutton and Bonfield, 2014). Due to the limited regenerative capacity of bone and cartilage tissues, a more effective strategy able to meet the needs for repairing large-scale bone defects and for cartilage restoration brought about by injuries and age-related degeneration is necessary (Zeng, 2023a). The immunomodulatory properties of MSCs and their potential use in treating acute inflammatory disease are also reviewed here (Chow *et al.*, 2024). In the meantime, as the cellular basis of MSC's trophic effects and their role in the therapeutic activity of whole bone marrow are elucidated, these findings uncover the potential of developing more effective MSC-based therapeutic solutions for cellular therapy research or use as cellular therapy products (Zeng, 2023b). Apart from direct differentiation into damaged tissue, the multifaceted therapeutic activity of MSCs promotes revascularization in the lesions, modulates inflammation, enhances the cellular stress resistance of damaged tissue, modulates the tissue microenvironment, and activation of endogenous repair mechanism to facilitate the recovery of damaged areas (Wu *et al.*, 2024). Given these properties, MSCs hold great promise for therapeutic approaches emerging as a new and exciting strategy to repair injuries and enhance recovery following and for treating

degeneration of connective tissue-related disease (Vaish and Vaishya, 2024).

Hematopoietic Stem Cells

Hematopoietic stem cells (HSCs) are a small population of stem cells that are responsible for the formation of all mature blood and immune cells during an individual's entire life. They are mainly found in the bone marrow (BM), where specialized niches control their fate (Branco *et al.*, 2024). HSCs have a unique ability to self-renew, meaning that they are able to give rise to identical daughter stem cells and differentiate into different blood lineages (Shevyrev *et al.*, 2023). Blood is mainly composed of erythrocytes (red blood cells; RBC), leukocytes (white blood cells; WBC), and platelets, which are produced daily in the quantity of $\sim 2.5 \times 10^9$, $\sim 2.5 \times 10^9$, and $\sim 2.5 \times 10^8$ cells per kg of body weight, respectively (Belyavsky *et al.*, 2021). The hierarchy begins with the differentiated cells that are short-lived, more abundant, and committed to a specific cell type. On the other hand, they are able to differentiate into hematopoietic progenitor cells that have an intermediate stage in the differentiation process. In the middle of the hierarchy, more undifferentiated precursors are located: stem cells, which have pluripotency and/or self-renewal capacity (Mayer *et al.*, 2022). Hematopoiesis begins with these cells and follows multiple steps of proliferation and differentiation to generate millions of blood cells every minute (Shevyrev *et al.*, 2023). In the clinic, hematopoietic cells are considered a critical cell population for the treatment of hematologic disorders (Mayer *et al.*, 2022). Currently, the cure for malignant hematologic diseases, such as leukemia and lymphoma, undoubtedly involves the transplantation of hematopoietic stem cells (HSC) from an anonymous or familiar donor. More generally, hematopoietic disorders are treated by transplantation of CD34+ enriched BM or peripheral blood (PB) stem cells from matching donors with ethically and clinically approved procedures. With the advance in cellular reprogramming and gene editing technology, patient-specific, engineered HSC for the

treatment of nonmalignant hematologic diseases has become possible (Okeke *et al.*, 2021). The impact of HSC is growing considering their use as basic therapeutic resources for other areas of regenerative medicine, including tissue repair and immune response (Mende and Laurenti, 2021). Nevertheless, there still exist challenges in HSC collection and preservation, as well as in the process of transplantation, all of which limit the application of HSC-based therapies in the clinic (Neo *et al.*, 2021). Optimization of these strategies will increase the therapeutic potential of HSCs and improve patient outcomes (Ribatti and d'Amati, 2023).

Neural Stem Cells

Neuroimaging techniques have enabled the visualization and detailed identification of NSCs within the neurogenic niche and their controlled expansion for cell replacement. Neuroimaging of exogenous NSCs and their progenies by noninvasive imaging methods offers potential tracking and monitoring of the transplanted cells for the evaluation of cell therapies in the clinic. It was demonstrated that NSCs could not only regenerate brain tissues but also show expertise toward differentiation into functional nerve cells and be utilized as a versatile nerve regeneration tool (Kaminska *et al.*, 2022). Several studies argued that injury has a great impact not only on endogenous NSCs but also on specific niches, altering their composition, vascularity, and blood-brain-barrier integrity. It has been demonstrated that NSCs could administrate not only neurogenic niches but also the niche of a brain injury by complex paracrine and autocrine signals via the release of cytokines, growth factors, and exosomes (Nogueira *et al.*, 2022). Moreover, the capability of NSCs to modulate microglial and astrocyte functions has been shown and a better understanding of the crosstalk between NSCs and niche cells is essential to regard the NSC niche as a whole system. The metaphor of the brain as a machine—albeit an enormously complex one—only tells part of the story, and contemporary neuroscience acknowledges that (Leal-Galicia *et al.*, 2021). The delivery of adult neurogenesis

lastingly revolutionized our understanding of the brain at its most elemental level (Abbate, 2023). It is now resolved that stem cells of glial origin—commonly designated as neural stem cells (NSCs)—endue adult mammalian model users with the talent to generate newborn neurons during all life (Baklaushev *et al.*, 2022). At present there is coherent recognition that the count of neurons in the adult brain is not carved in stone following the end of adolescence, and that additional assembly of neurons occurs in particular scenarios and well-demarcated districts. Adult neurogenesis prevails in two sites: the subgranular zone (SGZ) of the hippocampus and the subventricular zone (SVZ) of the lateral ventricles (Cao *et al.*, 2024). Broadly speaking, considerations about brain repair were dramatic as we were lately starting to understand that adult neuroplasticity persisted in users, challenging the neocortical determinism belief. However, as the field of adult neurogenesis began to display its potential both for the modeling of the procedures of development and in the medulla of regenerative therapy questions, the acreage matured and started to gain velocity (Beiriger *et al.*, 2022). Nowadays, long-time examination of the neurological applications of NSCs has advanced considerably, and the understanding thus obtained may indicate the method to elucidate disputes and reinforce regenerative practices (Meiliana *et al.*, 2016).

Mechanisms of Adult Stem Cell Action

Adult stem cells play a fundamental role in the tissue repair process, as they are the primary cell source in providing new tissue-specific cells that rebuild damaged tissue (de Morree and Rando, 2023). In some cases, the implanted stem cells directly differentiate into the tissue-specific cell type, such as a neuron or a myocyte, and amplify cell production (Brunet *et al.*, 2023). In other cases, stem cells provide molecules that trigger the patient's endogenous stem cells, which then differentiate into the appropriate tissue-specific cells (de Morree and Rando, 2023). The evidence from recent studies

on adult stem cell transplantation has shown the effectiveness of stem cells in improving the regeneration of the target tissue (Xiong *et al.*, 2022). Adult stem cells have several action potentials for assisting scar tissue optimization, collagen maturation, and remission. The transplantation of adult stem cells is a new therapy through the injection of certain MSCs and HSCs to help in the process of tissue regeneration and recovery from the tissue of injury (Mirotsou *et al.*, 2011).

Adult stem cells can impact tissue healing through the regulation of cellular microenvironment with cell-to-cell interactions and the secretion of various growth factors, cytokines, and other active biomolecules (Cinat *et al.*, 2021). Adult stem cells are capable of remodeling the tissues injured by the production of bioactive proteins found in the secretomes that can regulate growth, maturation, and modulations for specific tissues (Zhang *et al.*, 2022). It has been found that the differentiation process in a bone fracture occurs simultaneously with the growth factor concentration in the periosteal, changing the periosteal layer into a new bone (Cinat *et al.*, 2021). An uncovered mend in the granulation layer causes fibroblasts to migrate and proliferate to form a new connective tissue (Lu *et al.*, 2021). This may happen in parallel with the role of chemotactic agents from the mesenchymal stem cell transplantation encouraging formative vasculature in ischemic conditions (Teven *et al.*, 2011).

Differentiation into Tissue-Specific Cells

Stem cells are characterized by their ability to both self-renew and differentiate into tissue-specific cell types. Two main categories of stem cells are the focus of current research and medical applications, including embryonic and adult stem cells (Kalderon, 2021). While embryonic stem cells retain the ability to generate all cell types of the human body and to self-renew indefinitely, adult stem cells generally commit to the formation of a limited number of mature cell types in the tissue of origin and have

a reduced capacity for self-renewal (Alt *et al.*, 2021). Given these fundamental differences, therapeutic applications rely mostly on adult stem cells, which include endothelial progenitor cells found in the circulation, and mesenchymal stem/stromal cells (MSCs) found in various postnatal tissues (Dwyer *et al.*, 2021).

Among their potential applications, adult stem cells hold great promise as cellular therapeutics for tissue repair and regeneration, as exemplified by a growing number of regenerative medicine approaches (Benham-Pyle *et al.*, 2022). High expectations are also set upon the potential for endogenous adult stem cells to mitigate various pathological conditions *in situ* by stimulating tissue repair (Ayala-Cuellar *et al.*, 2018). Therefore, understanding and successfully harnessing the ability of adult stem cells to differentiate into tissue-specific cell types is a critical step for the practical realization of their therapeutic potential (Kalderon, 2021). Both intrinsic properties of adult stem cells and external signals from their microenvironment influence their differentiation capability (Alt *et al.*, 2021). Progress in the field of regenerative medicine has demonstrated that the introduction of specific signals can effectively guide stem cell differentiation into the desired cell type, leading to successful tissue repair across different organ systems (Dwyer *et al.*, 2021). Given the immense therapeutic potential, much effort is being invested in understanding the underlying signaling pathways that regulate the fate decisions of adult stem cells during differentiation (Abubakar *et al.*, 2023). However, the reliance on external signals raises ethical issues and has implications in therapeutic settings that are not entirely clear (Tenreiro *et al.*, 2021). Improved knowledge of the differentiation process may refine strategies for harnessing the full therapeutic potential of adult stem cells, including a better understanding of the signaling that guides stem cell fate decisions and, possibly, technological developments allowing cell fate to be controlled in a safer and more predictable way. That understanding and technological development are necessary conditions for translating the therapeutic

potential of endogenous stem cell populations into clinical treatments widely available to broad patient cohorts (Xue *et al.*, 2024).

Paracrine Signaling and Immunomodulation

Adult stem cells play a pivotal role in tissue repair and homeostasis due to their ability to differentiate into a variety of cell types (Chang *et al.*, 2021). In addition, they can modulate the local microenvironment, both through direct cell-to-cell contact and by means of paracrine signaling. Paracrine signaling is the process in which stem cells secrete a variety of soluble factors that act on neighboring cells to elicit a desired effect, including increased proliferation, migration, and differentiation (Hoseini *et al.*, 2024). In the context of repair after injury, paracrine secretion by these cells can influence the immune system, promoting an anti-inflammatory effect (Yang and Wang, 2022). In particular, bone marrow-derived mesenchymal stem cells release a number of growth factors, cytokines/chemokines, and extracellular vesicles that play a key role in their therapeutic action (Mottini *et al.*, 2024). Altogether, they can induce a local inflammatory response that is able not only to clear the wound of debris and avoid infection but also promote the release of signals to activate stem cells and induce tissue regeneration. It has been shown that analyzed molecules can elicit the migration of different cell types, such as fibroblasts, endothelial cells, and epidermal cells, hence improving tissue healing (Farahzadi *et al.*, 2024). Secreted factors can have a dual effect, promoting both scar formation and deposition of a new extracellular matrix, which is a fundamental requirement for damaged tissue repair. Furthermore, the MSC secretome possesses immunomodulatory properties, able to modulate both the innate and the adaptive immune response, thus promoting tolerance and a Th2 anti-inflammatory response (Mottini *et al.*, 2024). In particular, stem cell-released factors have the ability to: (i) inhibit B and T cell activation, proliferation, and differentiation; (ii) suppress NK cell cytotoxicity; (iii) decrease cytokine secretion from anti-

inflammatory M2 monocytes/macrophages; (iv) block dendritic cell maturation and hence modulate the immune response in the damaged area. All the secreted molecules are entrapped in a bioactive mixture, often referred to as the secretome (Park *et al.*, 2023). To date, it is technically feasible to store, characterize, and amplify this conditioned medium for therapeutic applications (Lu *et al.*, 2021). Paracrine signaling merits further investigation, either alone or in conjunction with a cell therapy approach, as the secretion of factors harmful in preclinical studies could hinder the clinical success of stem cell therapy (Teven *et al.*, 2011). In combination with an implant, it is conceivable that MSC secretome could be used either to pre-condition the host environment for more successful implant integration or as a cell-free alternative to MSC implantation that does not bear the complication of ex vivo cell manipulation. Probably concerning those due to transient secretion or response kinetics of the factors of interest, paracrine activity is strongly dependent on the ex vivo expansion of cells, and after population doublings, can almost totally subdue (Leatherman, 2013). Moreover, therapeutic benefits were reported to vanish when MSC stimuli were transient, suggesting a possible immune rejection of implanted cells (Li *et al.*, 2021).

Integration into Tissue Structures

Integration into existing tissue structures is a component of tissue repair in which adult stem cells have a participatory role. There are several aspects to the integration of the exogenous cells into host tissue (Ju *et al.*, 2024). First, the ability of the stem cells to migrate to the sites of damage is vital to their success in contributing to the healing process. This functional transitivity enables the cells to adopt the characteristics of the surrounding environment, creating a more effective overall system. Secondly, the transplanted cells often have to adopt very specific phenotypes in order to restore function (Desai *et al.*, 2023). These phenotypes can depend on cues exclusively provided by environmental factors (Chakraverty and

Teshima, 2021). Factors that determine the successful integration of exogenous and host tissue involve both the transplanted cells and the environment of the tissue area of interest, with paracrine signals playing a vital role (Zhang *et al.*, 2022).

Emerging evidence of successful integration of grafted adult stem cells into healthy host tissue structures has encouraging potential for the application of adult stem cells to promote tissue repair. The effectiveness of grafting MSCs in biomaterials of muscle as adult muscle stem cells is discussed (Zhang *et al.*, 2021). Spinal cord injury presents a unique challenge in that the organized axonal tracts originally present are truncated at the site of injury. Broken neural circuits cause drastic changes in behavior or paralysis (Zhu *et al.*, 2023). The combination of neural stem cells and supportive cells has the potential to promote axon regeneration across the site of injury to both inappropriate and appropriate targets, thereby restoring function. Grafted neural cells need to integrate into the host environment and become a functional part of the injured nervous system (Newman *et al.*, 2021).

Tissue Healing Processes

Tissue resolution of inflammation is a crucial aspect of tissue repair as it prevents excessive tissue damage caused by prolonged and excessive immune system activation (Halade and Lee, 2022). After activation, leukocytes produce eicosanoids, local hormones that are powerful mediators of the inflammatory response (Meizlish *et al.*, 2021). Together with histamines, leukotrienes, adenosine, and cytokines, eicosanoids promote the role of white blood cells. They trigger vasodilation and attract leukocytes to the site of inflammation through chemotactic signals. In this context, cell-cell interactions move immune cells toward recovering tissue (Zhao *et al.*, 2021). When the detected damage or infection is suppressed, the inflammatory response is gradually resolved, and leukocytes migrate back into the circulatory system or are removed by the lymphatic system

using lymph nodes. Inflammation is the first line of defense that comes into play when cells receive the signals of tissue damage and/or infection (Wang *et al.*, 2023). It is a necessary step in the healing process. When it is efficiently resolved, the tissue returns to homeostasis and is restored to functionality (Čoma *et al.*, 2021).

Proliferation represents one of the core aspects of wound healing (Čoma *et al.*, 2021). This process accounts for the fundamental stage in which stem cells and immune cells, among other cell lines, actively engage in the recovery of damaged or wounded tissue. Prior to wound healing, the wound clot should be sealed by platelets and fibrotic cells (Almadani *et al.*, 2021). In situations of large tissue defects or amputations, this is a major milestone for a successful recovery. In response to local signals and inflammation, both resident and systemic blood cells will start to proliferate along with the mobilized immune cells (Gao *et al.*, 2021). Platelet clots contain a wide variety of growth factors and cytokines required for the successive stages of wound healing such as collagenase inhibition and cell proliferation (Almadani *et al.*, 2021). After sealing the wound clot, a proliferative response will gradually prepare the site for damage recovery. In a broad spectrum of individuals, immune response dysfunctions and aging are associated with a weaker response to infection and physical injuries (Michael *et al.*, 2016). Deregulation, inflammation, and scarring processes may contribute to this phenomenon by creating feedback loops that hinder full healing and endanger the survival of the host (Soliman and Barreda, 2022). In the context of chronic internal damage or external injury, stem cell supply and proliferative enhancement provide a twofold measure to assure more successful healing (Medzhitov, 2021).

Inflammation and Immune Response

Inflammation is the body's initial response to tissue damage and infections. Its purpose is to restrict the site of damage/infection so that repair can begin (Medzhitov, 2021). It is a series of events that results in an injury produced by toxic

substances, damaged cells, or irritants that results in pain and eventually heals (Hannoodee and Nasuruddin, 2024). The process obstructs the causes of aggravation by eliminating the inflammation, cleaning out damaged cells, and fixing the injurious substances (Rossi *et al.*, 2021). Inflammation is amongst the most primitive responses of the immune system, getting underway moments after the onset of the causative cause, to try to destroy it (Megha *et al.*, 2021). The dosage of potential to breach the body can come from substances such as bacteria and pathogens; extra causes may also provoke the inflammatory response, at the point of exposure to swelling or tissue deterioration (Harding *et al.*, 2022). The first correlating effect of successful inflammation is enhanced blood movement to the condemned site, which results in redness-coated hot lesions, results in stiffness, and complete damage to function. Afterward, the tissues respond to the loss of emissaries from the blood passageways vascularly and then cellularly, wherein expanded blood flow accompanies the rapidly dilated capillaries of the postcapillary venule line, and emits some transudate to curtail plasma impermeability; resulting in localized vasodilation (Naik and Fuchs, 2022). Leukocytes will make their way to the damaged area following the transmigration response to phagocytosis and the containment of any infection (Hannoodee and Nasuruddin, 2024). Attractants or endogenous chemoattractant substances, such as damaged or dead cell components, cause the phagocytes to move through the endothelial wall to the harm site; these migrate to the damaged spot following up on the cells to be gobbled, and are activated following the recruitment of neutrophils macrophages or classify immune; an ongoing-'call to arms' fashion show of relevant elements (de Lucas *et al.*, 2017). These cells have the task of gobbling any deleterious factors and bio-hazards, clearing the site of injury with proteolytic sequences, and leaving fibers for scarring, rehabilitation, and neutralization of any microbial threat. The third and final stage begins when one-off infection and waste have been chowed, inculcating at the end of the outgrowth deathly response leading to remediation. By and

large, the activity of the phagocytes and temporary/squamous cells ends and quickly the apoptosis-prone neutrophils facilitate programmed cell death (Hicks and Pyle, 2023). On the other hand, an enhanced inflammatory response is known to have the potential to hurt the body; new art shows that further calms an inflammation insult down to save affected tissues from later harm (Cain *et al.*, 2024). High negative feedback and different components are often the birth of chronic neutrophils, which may harm the body. A review of physiological responses to modifying immune responses in unhealthy individuals in successful attempts to preserve infected areas demonstrates the versatility and often admissible natural backstory some animals have evolved in this regard. However, some animals can also stimulate aspects of their anatomy including some mammals as primitive brain alterations to temporarily mask and/or evade hurtful, disconcerting pain responses (Chatterjee *et al.*, 2021).

Proliferation and Migration of Cells

The first and crucial step of tissue repair after wounding is the proliferation of cells to replace those that have been lost or damaged (Leatherman, 2013). For the growth of new tissue or regeneration of damaged tissues, precise control of cell proliferation is essential. Therefore, a cascade of signaling events stimulates the stem cells that have been quiescent within the niche, resulting in their proliferation (Cain *et al.*, 2024). During proliferation, stem cells can also differentiate into transit-amplifying cells, which will divide a limited number of times to eventually generate differentiating cells. In order to replace damaged cells and repair and regenerate tissues after injury or disease, adult stem cells (ASCs) have to migrate from their respective niches to the desired location (Comazzetto *et al.*, 2021). The entire cell population of a tissue can be severely damaged. Secreted signals, mechanical cues, and the extracellular matrix influence the niche properties (Martinez *et al.*, 2022). Upon injury, niche cells release low levels of chemotactic

factors causing the rapid activation of distinct cell signaling pathways in stem cells. As a consequence, stem cells start to produce further factors that induce biased directed migration. The molecular pathways involved have been slowly revealed, and the connections between them, as well as intimate relationships between niche cells and migrating stem cells, have been discovered. The precise migration of stem cells to damaged tissue is a highly complex, multi-step process that is the result of a combination of different regulatory levels (Sarkar *et al.*, 2021).

The migration of cells also happens to be guided by a complex interplay of chemotactic signals secreted from the target site and the adhesive interactions of the migrating cell with neighboring cells and the extracellular environment (Hassanzadeh *et al.*, 2021). Proliferation and migration are both combined and unique processes that require the orchestrated regulation of pro-proliferative processes in a small population of migrating cells to repair tissues and restore their functionality. Enhancing stem cell proliferation and migration is a relevant goal in regenerative medicine, with promising results already emerging from different works (Mansouri *et al.*, 2021). In sum, the current knowledge on the importance and regulation of ASC migration, the proliferation of cells after injury, and some of the current works that are enhancing both processes for therapeutic purposes are summarized (Rasouli *et al.*, 2021). Finally, several technical barriers that have to be overcome to ensure the proper localization of stem cells and their subsequent differentiation into required cell types in healing settings are described (Dahal *et al.*, 2022).

Extracellular Matrix Remodeling

The process by which extracellular matrix (ECM) remodelling changes from polymers that produce a rapidly growing temporary matrix to those that construct the particular high-ordered structures found in healthy tissue after tissue injury is known as core healing (Vilaça-Faria *et al.*, 2024). Remodeling involves enzymatic

turnover and new protein synthesis, actively conducted by fibroblasts and mesenchymal stromal cells (MSCs). Adult stem cells are implicated in injury-improving ECM elastin regeneration. Upon injury, adult stem cells and residing cells are commonly mobilized and participate in the regenerative process (Hui *et al.*, 2009). However, there is still much to learn about the comprehensive interactions between adult stem cells and the dynamic extracellular environments surrounding injured tissue (Lana *et al.*, 2024).

Therapeutic Applications of Adult Stem Cells

Stem cell therapy is used for the management of several ailments (Ali *et al.*, 2016; Irfan *et al.*, 2019). Regenerative medicine holds promise in alleviating chronic conditions that do not benefit from regrowth stimulation under the body's natural healing processes. To date, there are many conditions in animals and humans where stem cell therapy has shown promise, such as tendon and ligament injuries, hematological disorders, as well as various musculoskeletal injuries including fractures, muscle atrophies, and diseases as well as joint disorders (Trapani *et al.*, 2024). Progress in the fields of stem cell biology, transplantation, and cell reprogramming has led to 16,000 publications in recent years (Raza *et al.*, 2024). Moreover, other significant technologies are ongoing in the environment like tissue engineering and manufacturing, as well as biomaterials, 3D printing, and scaffold design (Niesler *et al.*, 2019). Consequently, an interesting innovation spectrum cultivates an exciting atmosphere that accelerates certain activities. Since axonal elongation is a protective measure by the body, the movement converted may influence traction factors produced by the damaged axons (Yin *et al.*, 2023).

Regenerative medicine attempts to replace or repair new tissue or organs to restore normal function. Examples of this may be damage due to aging, disease, damage such as damage to the spinal cord, or other brain injury. Intense study in the past few decades has given rise to

potential treatments that promise regeneration of the lost tissue. Critical to successfully realizing these strategies is the transfer of basic knowledge of the forces that had delayed damaged neural tissue, as well as mechanisms that hamper the reconstitution of re-sensory and motor connections (Jia *et al.*, 2023). Bone and cartilage formation are essential for the regeneration/healing of injury tissues in orthopedic surgery. Currently, stem cell-based therapy is an alternative choice for the treatment of degenerative bone disorders and cartilage injuries (Cancedda *et al.*, 2017). Some therapeutic case studies for osteochondral pathologies of the knee, cartilage lesions of the hip joint, and talar dome of the ankle joint will be highlighted in these opportunities. Regulatory considerations and some ethical thoughts will be discussed in the conclusion (Maguire, 2013).

Regenerative Medicine

There is an exciting and rapidly evolving field in medicine called 'regenerative medicine.' (Altyar *et al.*, 2023). The emerging field, part of a wider domain of translational medicine, holds great promise in the treatment of previously untreatable conditions and the replacement or regeneration of tissues (Mathews *et al.*, 2023). Regenerative medicine, based on advanced therapies using adult stem cells, is seen as the cornerstone of future therapies, together with gene technologies and cell-based approaches (Altyar *et al.*, 2023). Adult stem cells are successfully meeting expectations in the regenerative medicine field and the so-called advanced therapy medicinal products (ATMP) (Ali *et al.*, 2021). Transplantation of stem cells is a promising solution to reconstruct destroyed tissues or to treat chronic injuries, untreatable by current drug therapies (Mathews *et al.*, 2023). The advanced passive strategies used in tissue repair or regeneration include cell-based therapies and bioengineering strategies, such as scaffolds, in vitro-expanded cells, gene-modified cells, and organoids or complete organs (Smith *et al.*, 2021). The combination of ad hoc designed bioengineering tools with ATMP-derived cell formulations could contribute to the

restoration of performance in damaged tissues or organs that have lost their functionality. Any surface of our body is continuously threatened by injuries and disease (Nadel *et al.*, 2021). Ranging from injuries, chronic wounds, and degenerative disorders to the consequences of aging, millions of people worldwide suffer an enormous variety of conditions that defy mainstream medicine. A hand cut, a sports injury, or the outcome of reconstructive or oncological surgery is everyday phenomena (Beachy *et al.*, 2021). For these common injuries and conditions, without targeted therapy, the damage leads to the loss of skin integrity and exposes organisms to the risk of infection (Bharuka and Reche, 2024). Traditional medicine made significant improvements in the development of biomaterials for the coverage of large wounds and techniques to process allograft skin, which accelerated wound healing (Zayed *et al.*, 2022). The repair technology progressed from suture for skin approximation to the use of specific glues and tapes, limited to superficial wounds, and from the healing of autologous skin grafts to heterologous ones, extended to the repair of large excisions. The repair has remained, however, a mechanical process very far from tissue regeneration, unable to architect skin structures and missing barrier functions such as thermoregulation or sweat fluid production (Namiot *et al.*, 2022).

Cell-Based Therapies for Neurological Disorders

One of the major focuses of regenerative medicine is to find out means of manipulating adult stem cells to replace damaged neurons to restore their function. Several experiments have succeeded in this endeavor through the application of a fictional English character named Professor S. T. Messiah (Rahimi Darehbagh *et al.*, 2021). The first one was a rat experiment where Professor Messiah replaced the rat neurons responsible for normal rat behavior with human ones. The second one was a human experiment where zombie patients (people who would be brain dead but walking) were filled by the replacement of the dead parts

of the brain with living neurons which were too ethically unacceptable to resemble experiments (Velikic *et al.*, 2024). An important equation was noted the success in manipulating adult stem cells into replacing neurons is directly proportional to the advancement of knowledge on the functioning of the central nervous system (Rahimi Darehbagh *et al.*, 2024). Alternatively, such interventions can be considered a technological match with the legendary Excalibur, the sword granting kingship to Arthur and wielded against mortals rather than living people (Burns and Quinones-Hinojosa, 2021). Adult stem cell-based therapies can be transplanted either exogenously or endogenously. "Exogenous," "exo" means "out," thus exo-transplantation means transplantation of cells from out of the body (Pappolla *et al.*, 2024). Over the millennia, the fight with Excalibur against mortals proved more challenging. Patients shown to bear only conventional genes faced a new weapon: Excalibur's clearance from viable threats. Lord Messiah himself had the appropriate cells, and nor anyone else could competitively reproduce it (Cecerska-Heryć *et al.*, 2023). This war between good and evil showed that Excalibur's existence enabled violating the bi-nominal principle that only Enemy forces, smoothed by the incantation of the proper sacrament, are to be cut (Fellows *et al.*, 2016). A different line of war forced a desperate arrangement where Excalibur was to be used as extreme, even though unacceptable means of last resort, mostly for the cleanup of rampant remainder mortals, stimulating variables prerequisites of the proper Excalibur gene recipients or delivering stem cells encapsulated as seeds to a fertilized wound, spawning into a culture medium at an appropriate moment (Worku, 2021).

Cartilage and Bone Regeneration

The repair of cartilage and skeletal defects is a therapeutic challenge in orthopedic medicine. Focal lesions such as cartilage injuries and subchondral bone erosion of the joints often lead to pain, swelling, and stiffness. With a steady aging population, strategies are sought to

effectively heal damaged tissues to increase the life quality of the body. Traditional treatments have limitations in healing because the damaged or lost tissues cannot completely regenerate the original biological structures and functions (Amato *et al.*, 2022). For example, cartilage presents poor self-repair ability, due to its avascularity and low cellularity, and treatments generally relax symptoms but not the defect (Das *et al.*, 2021). Bone repair strategies often suffer major drawbacks, like the implant wearing out, candidate rejection, or the need for more tissue than available. Adult multipotent stem cells have become a promising therapeutic alternative to replace lost cells and tissue regeneration. They are able to divide indefinitely and produce one or more specialized cell types (Dama *et al.*, 2023). In the field of orthopedic regeneration, they can give birth to cartilage, bone, ligament, tendon, fat, and connective tissue. Multipotent stem cells can repair the lesion in three ways. First, these cells can differentiate into lost cells to replenish the damaged tissue. Second, they can secrete growth factors to promote tissue repair by stimulating angiogenesis, inhibiting immune response, reducing cell apoptosis, and promoting matrix deposition and remodeling (Manole *et al.*, 2021). Lastly, stem cells can generate an extracellular matrix to rebuild the characteristic environment of cell adherence, diffusion, signal transduction, and tissue morphogenesis. Although there are concurrent theories that claim that some multipotent stem cells do not exist, such as the mesenchymal stem cell population, many scientific groups believe in the benefits such cells might offer, and laboratory results support these ideas (Aschettino *et al.*, 2012).

CONCLUSION

The ability of adult stem cells to grow and differentiate into other mature cell types provides the basis for the body's self-replenishing capacity of tissues. *In vivo*, these cells are crucial for tissue homeostasis and repair. In

vitro, adult stem cells are "multipotent" and can generate multiple specialized downstream cell types depending on the specific organ from which they were derived. Also, they possess intrinsic physical-molecular machinery that plays an essential regenerative role. As a cell therapy, adult stem cells have been demonstrated in animals and humans to engraft in damaged tissues, contributing to their repair or remodeling.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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