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Stem Cells: From Fundamental Biology to Regenerative Medicine

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Abstract

This article provides a comprehensive overview of stem cells, tracing their journey from fundamental biology to applications in regenerative medicine. Defined by their abilities for self-renewal and differentiation, stem cells play critical roles in embryonic development, tissue maintenance, and repair. The article categorizes stem cells based on their potency—totipotent, pluripotent, multipotent, oligopotent, and unipotent—and explores their distinct biological functions. A major breakthrough in the field was the development of induced pluripotent stem cells (iPSCs), which enable personalized medicine by reprogramming adult somatic cells into pluripotent ones. The article further discusses clinical applications of stem cell therapy, including the use of mesenchymal stem cells (MSCs) in treating osteoarthritis, myocardial infarction, and Crohn's disease, and hematopoietic stem cell transplantation for hematological disorders. Tissue engineering, which combines stem cells with biomaterials, expands the potential of regenerative therapies. In parallel, stem cell-derived organoids provide physiologically relevant *in vitro* models for disease modeling, drug screening, and developmental studies. Despite challenges such as tumorigenicity, immune rejection, and ethical concerns, stem cells remain a cornerstone in advancing precision medicine and therapeutic innovation.

Keywords

Stem Cells, Self-Renewal, Differentiation, Induced Pluripotent Stem Cells (iPSCS), Tissue Engineering, Organoids, Regenerative Medicine, Precision Medicine, Crohn's Disease, Hematopoietic Stem Cell Transplantation

1. Introduction

Stem cells are the "building blocks" of all cells, tissues, and organs in an animal's body. They possess two defining characteristics: the ability to self-renew through

mitotic division and the ability to differentiate into specialized cell types. From an embryo to an adult, stem cells are present and essential for growth, maintenance, and repair of tissues. Based on their stemness, stem cells could be classified into five main categories:

Totipotent stem cells have the highest differentiation potential, capable to differentiate into an entire organism, including both embryonic and extra-embryonic tissues. These cells are found only during the earliest stages of embryonic development, particularly in the initial few divisions of the zygote.

Pluripotent stem cells can differentiate into any cell type of the three germ layers—ectoderm, mesoderm, and endoderm—but not extra-embryonic tissues. They represent an intermediate state between totipotent and multipotent cells. Two examples of pluripotent stem cells are embryonic stem cells (ESCs) and induced pluripotent stem cells [1] [2] (iPSCs), both of which play critical roles in developmental biology and regenerative medicine.

Multipotent stem cellshave the ability to differentiate into multiple, but limited, cell types within a specific lineage or tissue. Unlike pluripotent stem cells, which can become almost any cell type in the body, or totipotent stem cells, which can form an entire organism, multipotent stem cells are more restricted in their differentiation potential. For example, hematopoietic stem cells (HSCs) give rise to various blood cells, including red and white blood cells and platelets, but cannot generate cells outside the hematopoietic lineage. Similarly, mesenchymal stem cells (MSCs) can form bone, cartilage, and adipose tissue, but not neural or hepatic cells. Unlike pluripotent and totipotent cells, multipotent stem cells are often found in adult tissues and primarily function in tissue maintenance and repair.

Oligopotent stem cells exhibit a more restricted differentiation capacity, producing only a few closely related cell types within a specific tissue or lineage. For instance, myeloid progenitor cells can differentiate into red blood cells, platelets, and certain white blood cells; while lymphoid progenitor cells give rise to B cells, T cells, and natural killer (NK) cells. These cells play a vital role in maintaining and replenishing specialized cell populations, and contribute to the maintenance of immune and circulatory systems.

Unipotent stem cells are the most specialized stem cells, which are capable of generating only one cell type. Despite their limited plasticity, they play a critical role in tissue regeneration. A key example is muscle satellite cells, which exclusively generate skeletal muscle fibres to aid in muscle growth and regeneration. Another example is spermatogonial stem cells, which generate sperm in the testes. Other examples are epidermal stem cells that replenish the skin. Though less versatile than pluripotent stem cells, unipotent stem cells are indispensable for maintaining the structure and function of mature tissues.

2. Key Functions of Stem Cells: Self-Renewal and Differentiation

Stem cells are defined by two essential functions: self-renewal and differentiation.

Self-renewal refers to the capacity of stem cells to undergo numerous cycles of cell division while maintaining an undifferentiated state. This process is strictly regulated to prevent uncontrolled growth, which could result in tumours, or depletion, which might impair tissue repair. Self-renewal often occurs through asymmetric division, whereby one daughter cell retains stem cell properties, and the other progresses toward differentiation. This balance allows tissues to maintain a steady supply of stem cells for future regeneration while also producing specialized cells for immediate function. For example, hematopoietic stem cells in the bone marrow continuously self-renew while generating a steady supply of blood cells throughout life.

Differentiation is the process by which stem cells acquire specialized functions and morphologies. The extent of differentiation potential depends on the cell's potency. Pluripotent stem cells like ESCs can generate neurons, cardiomyocytes, or hepatocytes, while multipotent stem cells like MSCs are limited to generate musculoskeletal lineages. Differentiation is orchestrated by complex signalling pathways involving genetic, biochemical, and mechanical cues. These cues regulate transcriptional networks and activate lineage-specific pathways such as Wnt, Notch, Hedgehog and TGF-β, which drive cells through different stages. On the other hand, the microenvironment, or stem cell niche [3], also plays a critical role by supplying chemical or biological signals that ensure proper timing and direction of differentiation. Through these mechanisms, stem cells contribute to tissue development, wound healing, and physiological homeostasis.

3. The Importance of Stem Cells in Biology and Medicine

Stem cells are indispensable to both biological research and medical innovation due to their dual capacities for self-renewal and differentiation. Biologically, they play a central role in embryonic development, giving rise to all tissues and organ systems; in adult organisms, they maintain tissue homeostasis by replenishing injured or dead cells. For instance, intestinal epithelial stem cells regenerate the gut lining every few days, and hematopoietic stem cells continuously produce blood cells throughout life. Medically, stem cells are essential for developing regenerative therapies to repair or replace damaged tissues. Clinical trials using mesenchymal stem cells [4] are ongoing for conditions such as osteoarthritis, spinal cord injury, and myocardial infarction. MSC therapy has been tested in Phase II clinical trials showing improvements in pain and cartilage quality; for myocardial infarction, multiple Phase I/II trials have demonstrated feasibility and modest functional recovery following MSC administration. Moreover, induced pluripotent stem cells (iPSCs) offer personalized models for studying genetic diseases and screening new drugs, enabling advances in precision medicine. Furthermore, stem cells are used to generate organoids—miniaturized, 3D tissue models that replicate key features of human organs—facilitating research on development, pathology, and drug response *in vitro*.

Despite their promise, the clinical translation of stem cell technologies faces challenges, including the risks of tumor formation, immune rejection, and incom-

plete or unintended differentiation. Ethical considerations, particularly surrounding embryonic stem cell use, also demand careful oversight. Nonetheless, advances in gene editing, biomaterials, and *in vitro* culture systems continue to expand the therapeutic and investigative potential of stem cells. As such, they represent a powerful tool for addressing unmet needs in regenerative medicine, disease modelling, and drug discovery.

4. Induced Pluripotent Stem Cells (iPSCs): A Breakthrough in Stem Cell Research

Induced pluripotent stem cells (iPSCs) represent a milestone in stem cell research. They were discovered in 2006 by Shinya Yamanaka [2] and colleagues in Japan. They demonstrated that differentiated adult somatic cells could be reprogrammed into a "pluripotent state" by introducing a set of transcription factors—Oct4, Sox2, Klf4, and c-Myc—commonly known as the Yamanaka factors. This reprogramming process effectively resets the epigenetic and transcriptional profile of the cell, granting it the capacity to self-renew and differentiate into nearly any cell type, akin to embryonic stem cells (ESCs).

The creation of iPSCs offered a ground-breaking alternative to ESCs, which overcomes the ethical concerns associated with embryo-derived cells. iPSCs can be generated from a patient's own cells—such as skin fibroblasts or peripheral blood mononuclear cells—enabling autologous transplantation with minimal risk of immune rejection. Their accessibility and versatility have revolutionized disease modelling, particularly for genetic and neurodegenerative disorders, allowing researchers to study patient-specific cellular phenotypes *in vitro*. For example, iPSC-derived neurons from patients with Parkinson's disease or Alzheimer's disease provide valuable platforms for exploring disease mechanisms and testing therapeutic candidates.

In the field of regenerative medicine, iPSCs offer promise for cell replacement therapies targeting a wide range of conditions, including diabetes, spinal cord injuries, retinal degeneration, and cardiac disease. Their use has also accelerated the development of organoids [5]-[7] and tissue engineering approaches, further expanding their utility.

5. Stem Cell Therapy and Tissue Engineering: Applications in Regenerative Medicine

Stem cell therapy and tissue engineering represent approaches at the forefront of regenerative medicine. Stem cell therapy involves the direct transplantation of stem cells or their derivatives into damaged tissues to restore structure and function. For example, mesenchymal stem cells (MSCs) have been investigated in clinical trials for treating osteoarthritis [8], myocardial infarction, and graft-versus-host disease due to their regenerative and immunomodulatory properties. Similarly, hematopoietic stem cell transplantation remains a well-established treatment for haematological malignancies and immune disorders.

For example, allogeneic hematopoietic stem cell transplantation (HSCT) remains

the only definitive curative therapy for severe aplastic anemia [9] (SAA), particularly in younger patients with matched sibling donors. Transplanted HSCs reconstitute the patient's hematopoietic system, restoring the production of red cells, white cells, and platelets. In patients without a suitable donor, immunosuppressive therapy is often used as an alternative to target the autoimmune component implicated in the pathogenesis. Advances in HLA-matching, graft manipulation, and conditioning regimens have significantly improved the outcomes and reduced the incidence of graft-versus-host disease (GVHD). Autologous or gene-corrected HSCs are also under investigation for patients with inherited bone marrow failure syndromes or acquired forms refractory to conventional therapy.

Another application of stem cell therapy is the treatment of Crohn's disease. It is a chronic, relapsing inflammatory bowel disease marked by transmural inflammation of the gastrointestinal tract; it is driven by immune dysregulation and epithelial barrier dysfunction. Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic option due to their immunomodulatory, anti-inflammatory, and tissue-regenerative properties. MSCs can suppress pro-inflammatory cytokines, promote regulatory T cell activity, and enhance mucosal healing. Clinical trials have shown that both systemic and local administration of MSCs—particularly for treatment-refractory perianal fistulas—can induce remission and reduce fistula drainage. In 2018, the European Medicines Agency approved the first stem cell-based therapy (darvadstrocel [10]) for complex perianal fistulas in Crohn's disease. Ongoing studies are evaluating optimization of dosing, delivery methods, and the use of autologous versus allogeneic MSCs. While not yet a frontline therapy, stem cell therapy offers a valuable adjunct for patients with refractory or complicated disease such as Crohn's disease.

Tissue engineering combines stem cells with biomaterials and bioactive molecules to construct functional tissue substitutes. This approach has been applied to regenerate cartilage, skin, corneal epithelium, and even components of complex organs such as the trachea or bladder. Scaffolds made of natural or synthetic materials provide a structural framework for stem cells to proliferate, differentiate, and organize into tissue-like architectures. Advances in 3D bioprinting and organoid technology have further enhanced the ability to fabricate patient-specific constructs, offering new solutions for tissue loss due to trauma, congenital defects, or chronic disease.

For instance, tissue engineering has shown considerable promise in the development of vascular grafts for the repair or replacement of damaged blood vessels, particularly in patients with cardiovascular disease who lack suitable autologous grafts. Engineered blood vessels typically consist of a scaffold—either synthetic (e.g., polyglycolic acid, polycaprolactone) or natural (e.g., collagen, fibrin)—seeded with endothelial cells or stem cell-derived vascular progenitors. These constructs aim to mimic the structural, mechanical, and functional properties of native vessels, including compliance, patency, and anti-thrombogenicity. Mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs) [11] are frequently used due to

their capacity to differentiate into vascular cell types and secrete pro-angiogenic factors. Preclinical and early clinical studies have demonstrated the feasibility of using tissue-engineered vascular grafts in arterial bypass procedures and hemodialysis access.

Moreover, to treat patients suffering from myocardial infarction, tissue engineering approaches aim to restore myocardial structure and function by delivering viable cells, bioactive factors, or engineered cardiac patches to the infarcted region. One strategy involves seeding cardiomyocytes—derived from induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs)—onto biodegradable scaffolds [11] that provide mechanical support and promote cell survival and integration. These engineered cardiac patches can be applied epicardially to enhance tissue repair, reduce fibrosis, and improve left ventricular function. Alternatively, injectable hydrogels loaded with stem cells or growth factors have been developed to promote in situ regeneration and neovascularization.

Despite progress, clinical translation remains limited by challenges such as vascularization of engineered tissues, integration with host tissue, and long-term safety. Nonetheless, the combination of stem cell biology and tissue engineering continues to open new avenues for personalized medicine, offering the potential to restore damaged tissues, reduce the need for organ transplantation, and improve outcomes for patients with otherwise untreatable conditions.

A critical issue for clinical translation is safety, particularly the risks of tumorigenicity, genomic instability, and unintended genetic alterations. Recent clinical trials provide quantitative insights [12]: in a pooled analysis of iPSC-derived therapies, the incidence of tumorigenic events was reported as <1% across early-phase studies. Similarly, large-scale hematopoietic stem cell transplantation registries estimate secondary malignancies in approximately 2% - 5% of recipients after long-term follow-up. Off-target edits in CRISPR/Cas9-modified stem cells remain a concern, though next-generation sequencing–based monitoring shows off-target rates below 0.1% in well-designed guides. Such data highlight both the rarity and importance of vigilant monitoring of adverse genomic events.

6. Organoids: Bridging the Gap between *In Vitro* Models and *In Vivo* Physiology

While tissue engineering focuses on constructing transplantable tissues for therapeutic purposes, recent advances have also led to the development of organoids [5]-[7]—miniaturized, three-dimensional cell cultures that mimic the architecture and function of real organs. Organoids offer a powerful platform to tissue engineering, serving as physiologically relevant models for studying human development, disease mechanisms, and drug responses *in vitro*. Unlike conventional two-dimensional cell cultures, organoids self-organize into complex structures that recapitulate key features of their *in vivo* counterparts, including cellular diversity, spatial organization, and partial functionality. Organoids have been generated for a wide array of human organs, including the intestine, brain, liver, kidney, pancreas, and

lung. Their utility spans a broad range of applications—from modeling genetic disorders and infectious diseases to high-throughput drug screening and personalized medicine.

The foundation of organoid technology lies in the use of stem cells, particularly pluripotent stem cells (PSCs) such as embryonic stem cells (ESCs) and induced pluripotent stem cells [1] [2] (iPSCs), as well as adult tissue-specific stem cells. These cells possess intrinsic self-organizing and differentiation capacities that, under appropriate culture conditions, allow them to form organ-like structures. For example, intestinal organoids [13] can be derived from adult intestinal stem cells isolated from patient biopsies, while cerebral or retinal organoids [14] are typically generated from iPSCs differentiated along neural lineages. The use of patient-derived iPSCs enables the generation of genetically matched organoids for disease modeling, offering unprecedented insights into disorders such as cystic fibrosis, Parkinson's disease, and microcephaly. Moreover, gene editing tools like CRISPR/Cas9 can be applied to stem cell-derived organoids to dissect gene function or test gene therapies. As such, stem cell-based organoids not only complement tissue engineering in regenerative strategies but also serve as transformative platforms for advancing biomedical research and translational applications.

7. Conclusion

Stem cells hold a unique and transformative place in biology and medicine due to their ability to self-renew and differentiate into diverse cell types. A thorough understanding of the hierarchy of stem cell potency—from totipotent to unipotent—forms the basis for their clinical and experimental use. Advances in stem cell biology have laid the groundwork for a wide range of therapeutic applications, including hematopoietic stem cell transplantation, mesenchymal stem cell therapy, and the generation of patient-specific induced pluripotent stem cells. Coupled with breakthroughs in tissue engineering, stem cells now offer the potential to regenerate damaged tissues, repair diseased organs, and reduce reliance on donor transplants. In parallel, the emergence of organoid systems derived from stem cells provides unprecedented opportunities to model human development, study disease pathogenesis, and test therapeutic strategies in a physiologically relevant context. While several challenges remain—including issues of safety, standardization, and scalability—the continuous evolution of stem cell and organoid technologies promises to revolutionize personalized medicine and deepen our understanding of human health and disease.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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