Stem Cell Therapy: The Future of Medicine and its Wide-Ranging Applications.

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Abstract. Stem cell therapy, while offering promise for once-intractable diseases, faces safety concerns due to unchecked private clinic treatments. This review provides a comprehensive overview of stem cell-based therapies in human and veterinary medicine. Tracing stem cell therapy's evolution from its 1930s inception to today's groundbreaking induced pluripotent stem cells (iPSCs), it highlights iPSCs' potential for diseases like Parkinson's and multiple sclerosis. Examining various stem cell types—embryonic stem cells (ESCs), tissue-specific progenitor stem cells (TSPSCs), mesenchymal stem cells (MSCs), and iPSCs—it explores their advantages and challenges. Adult stem cells, ethically sourced from specialized tissues, shine in hematopoietic transplants. Directed differentiation, critical for specific cell lineage transformation and teratoma prevention, is discussed. Strategies like culture manipulation and molecular cues are outlined, with acknowledged in vivo challenges. Stem cell therapy's potential is evident in addressing neurodegenerative diseases, spinal cord injuries, ocular disorders, and diabetes. However, realizing its full potential mandates further research and rigorous clinical trials. In veterinary medicine, stem cell therapy is relevant, especially for equine and canine injuries and joint issues, relying on mesenchymal stem cells from bone marrow and adipose tissue. While stem cell therapy holds promise, challenges persist in differentiation, safety, and the need for well-structured clinical trials. Continued research and development are crucial to unlock its full regenerative potential.

Keywords. Stem cell, diseases, treatment, pluripotent, degenerative, ESCs, TSPSCs, MSCs, iPSCs, transplants, research, clinical trial, regenerative.

1. Introduction

The approval of cancer immunotherapies in the US and mesenchymal stem cell (MSC) treatments in Europe has made regenerative medicine more prominent. Cell-based therapies, especially using stem cells, offer hope for patients with incurable diseases. Stem cell therapy aims to improve the body's natural repair processes by stimulating or replenishing stem cells. These unique cells, capable of self-renewal and differentiation, have undergone extensive research and are considered potential therapeutic tools. [1]

Regenerative medicine focuses on tissue regeneration and cell replacement, utilizing various stem cell types such as human pluripotent stem cells (hPSCs), multipotent stem cells, and progenitor cells. However, concerns have arisen due to private clinics promoting stem cell therapy as a cure-all, leading to safety issues. Notably, injecting cells from lipoaspirate into the eyes of macular degeneration patients resulted in vision loss. [1]

As regenerative medicine advances and dispels the notion of these cells, this review provides a concise overview of stem cell-based therapies for treating diseases.

2. History

Stem cell therapy is an innovative medical approach harnessing the remarkable capabilities of stem cells—self-renewal and differentiation—to repair damaged tissues in the human body. It involves introducing either a patient's own cells (autologous) or cells from a healthy donor (allogeneic) to replace damaged or dysfunctional cells. The term "stem cell" was first introduced in 1868 by German biologist Ernst Haeckel to describe the unique potential of fertilized eggs to develop into all types of cells in an organism. [2]

The history of stem cell therapy dates back to 1939 when the first bone marrow transplant was reported for treating aplastic anemia. Subsequently, in 1958, French oncologist George Mathe performed the first stem cell transplant to aid radiation-exposed researchers. Later, in 1963, Mathe achieved success with a leukemia patient. However, early allogeneic hematopoietic stem cell transplantations (HSCT) faced challenges, and it wasn't until 1972 when the discovery of cyclosporine significantly improved outcomes. [2]

Throughout the 1960s and 1970s, research by Friendenstein and colleagues revealed the potential of a minor bone marrow cell population, distinct from hematopoietic cells, capable of rapid proliferation and differentiation into various cell types. This marked the emergence of mesenchymal stem cells, a term coined in 1991 by Caplan. [2]

Over the past six decades, stem cell therapy has evolved into a potent tool of regenerative medicine, offering hope for treating a wide range of previously incurable conditions. These include neurological disorders, pulmonary issues, metabolic and endocrine related diseases, reproductive disorders, skin burns, and cardiovascular conditions. [2]

3. Different types of stem cell therapy: approved by the FDA (USA and others) and unapproved

Let's start by dividing them into two main categories of stem cell therapies: approved (by the FDA, Food and Drug Administration) and unapproved, and this distinction greatly affects their scientific validity, effectiveness, and safety. [2]

Currently, only a handful of FDA-approved stem cell therapies exist. The most well-known is the blood stem cell transplant, used to treat blood cancers like leukemia. This procedure involves chemotherapy to eliminate cancer cells and the subsequent infusion of healthy stem cells. FDA-approved treatments like this one result from extensive, years-long research and testing. Recently, numerous clinics across the country claim to offer various forms of stem cell therapy, targeting conditions from Parkinson's disease to common joint pain. However, many of these therapies don't actually use stem cells. Instead, they harvest tissues believed to contain adult stem cells from one part of the body and inject them into another. [2]

4. What are stem cell-based therapies?

Stem cell-based therapies encompass treatments utilizing various viable human stem cell types, such as embryonic stem cells (ESCs), iPSCs (induced pluripotent stem cells), and adult stem cells, for both autologous and allogeneic therapies. These stem cells offer a promising avenue for tissue and organ transplantation because of their capacity to develop into specific cell types needed to repair damaged tissues. [3]

Nevertheless, the intricacy of stem cell-based therapies prompts researchers to seek a dependable, safe, and readily accessible source of stem cells with the potential to differentiate into various cell lineages. Therefore, it becomes paramount to make careful choices regarding the appropriate stem cell type for clinical applications. [3]

5. Types of stem cells

5.1 Hierarchy of stem cells

Three main types of stem cells exist, each with unique abilities. Stem cells can renew themselves and transform into various cell types, but they differ in developmental stages. First, totipotent stem cells are the most basic and can form a complete embryo and extra-embryonic tissue from a fertilized ovum. However, this ability is short-lived, lasting until the embryo reaches the four to eight cell stage. [3] Next, embryonic stem cells emerge at the blastocyst stage, losing totipotency and becoming pluripotent. These cells can differentiate into all embryonic germ layers (ectoderm, mesoderm, and endoderm). As they divide further, they become multipotent adult stem cells, which can only differentiate into specific cell types related to their tissue of origin. Adult stem cells are found in a dormant state in various specialized tissues, maintaining the body's balance throughout life, including in bone marrow, oral tissues, and dental tissues. [3]

5.2 Standard in stem cell-based therapy

Several authors regard adult stem cells as the preferred choice for stem cell therapies. Adult stem cells have shown promising results, particularly in hematopoietic transplants. Unlike ESCs, adult stem cells don't raise contentious debates about their source. The ethical and religious concerns surrounding ESCs arise from their derivation, which involves the destruction of human embryos, making them unacceptable to a substantial portion of the population. [3]

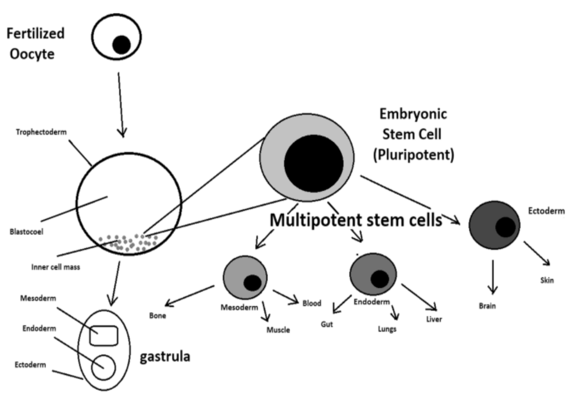

Figure 1. The development of oocytes leads to the creation of stem cells within the blastocoel. This blastocoel contains embryonic stem cells that subsequently specialize into mesodermal, ectodermal, or endodermal cells. Eventually, the blastocoel transforms into the gastrula. [4]

6. Directed differentiation

For effective therapy, stem cells must transform into specific cell types, preventing issues like teratoma formation from undifferentiated cells. Guided differentiation is key in regenerative medicine, replicating natural developmental signals. Manipulating culture conditions helps control differentiation pathways in vitro but faces challenges in vivo. Hwang et al. highlighted the need for defined, feeder-free culture methods for large-scale hESC maintenance in cell and tissue therapy. [4]

Most differentiation methods mimic gastrulation's inner cell mass development. Molecular cues, like FGFs, Wnt, TGFβ, and BMP, induce stem cells into germ layer progenitors, but precise concentrations and timings vary. Various protocols exist for generating specific cell types from germ layers. Directed differentiation, e.g., into hepatocytes, aids research in molecular liver development and drug toxicity testing. [4]

Small molecules offer cost-effective alternatives to recombinant factors, enhancing reprogramming efficiency. Hedgehog pathway antagonists and agonists, as well as endogenous molecules like retinoic acid, are used in these methods. Efficient differentiation relies on functional maturity, effectiveness, and in vivo compatibility. Biophysical factors like topography, shear stress, and substrate rigidity influence cell phenotype. Properly controlled biophysical and biochemical signals, along with guided hESC differentiation, are vital for successful stem cell culture. [4]

7. Applications of stem cell therapy in regenerative human medicine

Regenerative medicine focuses on restoring damaged tissues and organs in patients where the body's natural regenerative processes fall short. Stem cells, with their ability to divide and transform into various cell types, have become a crucial resource in regenerative medicine. They play vital roles in disease progression, development, and tissue repair. Stem cells fall into four categories based on their transformation potential: unipotent, multipotent, pluripotent, and totipotent. [5]

Among these, zygotes are the sole totipotent stem cells capable of giving rise to an entire organism. Cells from the inner cell mass (ICM) of an embryo are pluripotent, able to differentiate into cells from the three germ layers but not extraembryonic tissue. Stem cell characteristics and transformation capabilities depend on pluripotency factors like OCT4, cMYC, KLF44, NANOG, and SOX2. [5]

Induced pluripotent stem cells (iPSCs) are generated by restoring pluripotency factors in differentiated cells. Stem cells for regenerative use include embryonic stem cells (ESCs), tissue-specific progenitor stem cells (TSPSCs), mesenchymal stem cells (MSCs), umbilical cord stem cells (UCSCs), bone marrow stem cells (BMSCs), and iPSCs. [5]

Stem cell transplantation can be autologous (from the patient), allogenic (from a donor), or syngeneic (from a genetically identical donor). To prevent host-versus-graft rejections, tissue typing of human leukocyte antigens (HLA) and immune suppressants are recommended. Stem cells express low levels of major histocompatibility complex (MHC) receptors and secrete chemokines that recruit immune cells, promoting tissue tolerance. [5]

Current regenerative medicine approaches often involve tissue engineering, combining cell transplantation, material science, and microengineering to create organoids for restoring damaged tissues and organs. Ideal scaffolds support cell adhesion, mimic target tissue mechanics, promote angiogenesis and neovascularization, and are nonimmunogenic. [5]

The success of stem cell transplantation relies on factors like the number of transplanted stem cells, their survival, proliferation, site-specific differentiation, and integration into the host circulatory system. [5]

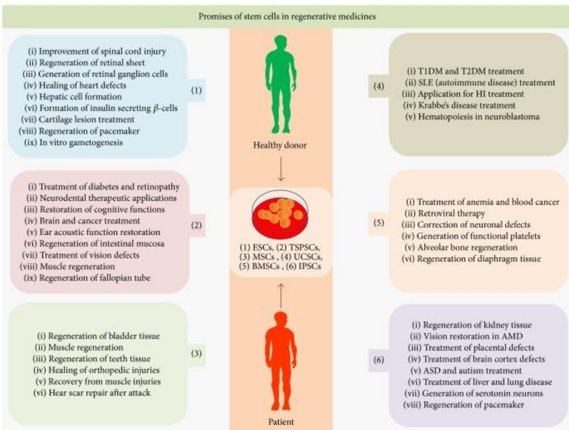

Figure 2. Stem cells offer significant potential in the field of regenerative medicine and the treatment of various diseases. These promises are evident across the six categories of stem cells: embryonic stem cells (ESCs), tissue-specific progenitor stem cells (TSPSCs), mesenchymal stem cells (MSCs), umbilical cord stem cells (UCSCs), bone marrow stem cells (BMSCs), and induced pluripotent stem cells (iPSCs). [5]

Stem cell-based clinical trials are advancing in the treatment of neurodegenerative diseases like Parkinson's, Alzheimer's, ALS, and multiple sclerosis. These trials aim to halt disease progression and achieve complete recovery. For Parkinson's disease, both embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) show promise in generating dopaminergic neurons for treatment. Clinical trials using iPSCs have begun, demonstrating safety. [3]

In the case of multiple sclerosis (MS), initial trials using placental-derived mesenchymal stem cells (MSCs) did not improve the condition. Immunoablative therapy, which involves replacing the immune system with hematopoietic stem cells, has shown potential but also complications like infertility. [3]

ALS treatment trials are ongoing, with positive results in mice using MSCs. However, clinical success remains elusive, possibly due to using autologous transplantation. [3]

Stem cell therapies for spinal cord injuries have shown potential in animal models, but clinical proof of functional recovery is lacking. Japan has approved stem cell treatment for spinal cord injuries based on promising early results. [3]

Ocular diseases are a major focus of stem cell-based clinical trials due to the eye's immune-privileged status. These trials often use ESCs and have shown positive results, including iPSC-based treatments for macular degeneration. [3]

For diabetes, pluripotent stem cells (PSCs) are a top choice for beta cell replacement. Clinical trials involving encapsulated insulin-producing beta cells derived from ESCs are in progress, showing potential for glycemic correction. [3]

Overall, stem cell-based therapies hold promise across various diseases, but more research and clinical trials are needed to establish their effectiveness fully.

8. Applications of stem cell therapy in veterinary medicine

Over the past two decades, significant attention has been dedicated to researching stem cell biology, leading to a better understanding of their properties and therapeutic potential across various fields. While human stem cell applications remain largely experimental, except for specific cases like bone marrow transplants and skin regeneration, veterinary medicine has already treated numerous animals, offering valuable insights into cell therapy's effectiveness for a range of diseases. [6]

Stem cells have shown the ability to repair or regenerate almost all types of animal tissues, possessing remarkable potential for growth and differentiation. Efforts have focused on uncovering how adult stem cells renew tissues and the conditions supporting this process in diseased organisms. Adult stem cells, primarily sourced from bone marrow and adipose tissue, have been utilized worldwide for animal disease treatment. [6]

Mesenchymal stem cells (MSCs), derived from different germ layers and found in various adult tissues, hold significant regenerative capabilities. MSCs are naturally multipotent, generating cells specific to their tissue location, influenced by growth factors and hormones. These cells play a vital role in tissue repair and maintenance in response to specific cues, making them valuable in cell therapy protocols.[6]

In veterinary medicine, minimally manipulated MSCs from bone marrow or adipose tissue have shown clinical relevance in treating tendon, ligament injuries, and joint diseases in animals like horses and dogs, particularly in orthopedic conditions. However, more research is needed to fully understand these cells' fundamental characteristics and properties. [6]

9. Conclusion

In conclusion, the field of regenerative medicine, particularly stem cell-based therapies, has witnessed significant advancements and promises for both human and veterinary medicine. Stem cells, with their unique ability for self-renewal and differentiation, offer hope for the treatment of various diseases and tissue regeneration. The historical evolution of stem cell therapy, from its early roots in bone marrow transplants to the exploration of different stem cell types, demonstrates the remarkable progress made over the years. [2]

In human medicine, ongoing clinical trials are targeting neurodegenerative diseases like Parkinson's, Alzheimer's, ALS, and multiple sclerosis, with the aim of halting disease progression and achieving full recovery. Promising results have been observed, especially in the use of induced pluripotent stem cells (iPSCs) for Parkinson's disease. Additionally, stem cell-based approaches for spinal cord injuries and ocular diseases, which leverage the immune-privileged status of the eye, are showing great potential. However, more research and clinical trials are required to establish their effectiveness fully. [5]

In veterinary medicine, the application of stem cell therapy has already provided insights into its efficacy for treating a wide range of animal diseases. Mesenchymal stem cells (MSCs) derived from sources like bone marrow and adipose tissue have shown promise in treating injuries and joint diseases in animals such as horses and dogs. This underscores the potential of stem cell-based therapies in veterinary care, although further research is needed to better understand their fundamental properties. [6]

Both in human and veterinary medicine, stem cell-based therapies offer a promising avenue for regenerating damaged tissues and organs, but the intricacies of stem cell differentiation, safety concerns, and the need for well-designfed clinical trials highlight the ongoing challenges in realizing their full potential. As research continues to advance, stem cell-based therapies hold the potential to revolutionize the treatment of various diseases and contribute to the field of regenerative medicine.

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