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International Journal of Surgery & Surgical Techniques
ISSN: 2578-482X

Application of Induced Pluripotent Stem Cells in Bone Tissue Engineering: Current Status and Prospects

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Review Article
Volume 9 Issue 2
Received Date: November 24, 2025
Published Date: December 18 2025
DOI: 10.23880/ijsst-16000228

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Abstract

Induced pluripotent stem cells (iPSCs) have attracted widespread attention in the field of bone tissue engineering in recent years due to their unique self-renewal ability and multi-directional differentiation potential. Bone tissue engineering, as an important component of regenerative medicine, aims to repair and reconstruct damaged bone tissue to address clinical issues such as bone defects and fractures. Currently, research on iPSCs has shown significant potential in bone regeneration; however, there are still many challenges in their application, such as cell differentiation efficiency, immune rejection reactions, and ethical issues. This article reviews the current application status of iPSCs in bone tissue engineering, including their sources, differentiation mechanisms, and roles in bone regeneration, and discusses comparisons with other cell sources. By analyzing the latest research findings, this article aims to provide new perspectives on the potential and future development directions of iPSCs in clinical applications, promoting research and practice in bone tissue engineering.

Keywords: Induced Pluripotent Stem Cells; Bone Tissue Engineering; Cell Differentiation; Bone Regeneration; Clinical Applications

Abbreviations

iPSCs: Induced Pluripotent Stem Cells; ESCs: Embryonic Stem Cells; RA: Retinoic Acid; BMP-4: Bone Morphogenetic Protein; TGF-β: Transforming Growth Factor β; ECM: Extracellular Matrix; NAC: N-Acetylcysteine; hPSCs; Human Pluripotent Stem Cells; MSCs: Mesenchymal Stem Cells.

Introduction

Induced pluripotent stem cells (iPSCs) are cells obtained through the reprogramming of somatic cells, possessing pluripotency similar to that of embryonic stem cells, and capable of differentiating into various cell types. The breakthrough in this technology originated from the research of Japanese scientists Shinya Yamanaka and Kazutoshi Takahashi in 2006, who successfully reprogrammed adult cells into pluripotent stem cells for the first time, overcoming the ethical issues associated with the use of embryonic stem cells [1]. The discovery of iPSCs has not only advanced stem cell research but also provided new possibilities for regenerative medicine, disease model construction, and drug screening.

Compared to embryonic stem cells, iPSCs have several advantages. First, iPSCs can be sourced from a variety of somatic cells, including skin fibroblasts and blood cells, making their acquisition relatively simple and free from

ethical controversies [2]. Second, iPSCs exhibit strong proliferation capabilities in vitro and can differentiate into various cell types under appropriate conditions, demonstrating characteristics similar to those of embryonic stem cells [3]. However, iPSCs still face certain challenges regarding genomic stability and differentiation potential, which need to be addressed in future research [3].

Bone tissue engineering is an interdisciplinary research field aimed at repairing or regenerating damaged bone tissue using biomaterials, cells, and growth factors. With the aging population and the increasing number of patients with bone diseases, the importance of bone tissue engineering is becoming more pronounced. The potential application value of iPSCs in bone tissue engineering is gradually gaining attention, with studies indicating that iPSCs can effectively provide a cellular source for bone defects and play a crucial role in bone regeneration [4]. By combining iPSCs with biocompatible scaffolds, the regeneration and repair of bone tissue can be promoted [5]. Therefore, exploring the application prospects of iPSCs in bone tissue engineering is of great significance for advancing the development of regenerative medicine.

Main Body

Sources and Characteristics of iPSCs

Cell Reprogramming Technology

Induced pluripotent stem cells (iPSCs) are stem cells with pluripotent characteristics generated by reprogramming mature somatic cells using reprogramming technology. The earliest reprogramming method involved the use of viral vectors to introduce four key transcription factors (OCT4, SOX2, KLF4, and c-MYC), which act on the genome of somatic cells to help them regain pluripotency [6]. In recent years, researchers have explored various non-viral reprogramming strategies, such as using small molecule compounds, chemical inducers, and physical methods, which have shown good potential in improving reprogramming efficiency and reducing the risk of tumor formation [7]. Additionally, the sources of iPSCs have gradually diversified; besides traditional skin fibroblasts, non-invasive somatic cells such as urine cells and blood mononuclear cells are also widely used in the generation of iPSCs, providing convenience for clinical applications [8].

Self-Renewal and Multidirectional Differentiation Ability of iPSCs

iPSCs not only have the ability to self-renew indefinitely but also possess the capability for multidirectional differentiation, allowing them to differentiate into all cell types in the body. This characteristic demonstrates the enormous application potential of iPSCs in regenerative medicine, disease models, and drug screening [9]. Research indicates that the self-renewal ability of iPSCs is closely related to their epigenetic status, and the epigenetic memory of the source cells may influence the differentiation direction of iPSCs [10]. For example, iPSCs derived from cardiac sources exhibit a stronger ability to differentiate into cardiomyocytes, which is related to the epigenetic characteristics of their source cells [11]. Furthermore, when cultured in vitro, iPSCs can effectively produce functional cells under appropriate induction and culture conditions, providing new possibilities for clinical treatment [12].

Ethical Issues and Clinical Translation Potential of iPSCs

Although iPSCs show broad prospects in regenerative medicine, their ethical issues remain an important topic of discussion. Compared to embryonic stem cells (ESCs), the generation of iPSCs does not involve the destruction of embryos, making them a more ethically acceptable choice [13]. However, the clinical translation of iPSCs still faces several challenges, including issues related to genetic stability, tumor formation risk, and differentiation efficiency [14]. To ensure the safety of iPSCs in clinical applications, researchers need to conduct rigorous analyses of genomic integrity and functional validation [7]. Nevertheless, the application prospects of iPSCs in personalized medicine, drug screening, and disease models are still widely optimistic, with an increasing number of clinical trials underway aimed at exploring their potential in the treatment of various diseases [15].

Mechanisms of Osteogenic Differentiation of iPSCs

Role of Differentiation Inducers

Inducers play a crucial role in the process of inducing human induced pluripotent stem cells (iPSCs) to differentiate into osteoblasts. Studies have shown that small molecules such as retinoic acid (RA) can effectively promote the osteogenic differentiation of iPSCs. By applying RA to iPSCs, researchers found that mature osteoblasts could be induced within just 10 days, significantly enhancing the osteogenic potential of iPSCs. Furthermore, the mechanism of action of RA may be related to the activation of the Wnt/β-catenin signaling pathway, which plays an important role in the process of osteogenesis [16]. Other inducers such as bone morphogenetic protein (BMP-4) and transforming growth factor β (TGF-β) have also been confirmed to play important roles in promoting the differentiation of iPSCs into osteoblasts, especially in three-dimensional rotating culture systems, where the regulation of BMP-4 and FGF-2 signaling pathways

can effectively accelerate the differentiation of iPSCs towards the osteogenic lineage [17]. The effective combination and use of these inducers provide new strategies and methods for bone tissue engineering and regenerative medicine.

Role of Extracellular Matrix in Differentiation

The extracellular matrix (ECM) plays an important role in the osteogenic differentiation of iPSCs. The ECM not only provides necessary physical support for the cells but also influences cell behavior and fate through its composition and structure. Research has shown that biophysical properties of the ECM, such as stiffness, composition, and topological structure, can significantly affect the mechanosensing and differentiation pathways of stem cells. For example, synthetic polymer scaffolds that mimic the physical properties of natural ECM can promote the osteogenic differentiation of iPSCs, primarily by regulating intracellular signaling pathways [18]. In addition, the interaction between cells and ECM is mediated by receptors such as integrins, which are crucial for cell proliferation, migration, and differentiation due to their connection to the intracellular cytoskeleton [19]. Therefore, optimizing the properties of ECM and designing corresponding scaffold materials will help improve the application effectiveness of iPSCs in bone tissue engineering.

Regulatory Mechanisms of Signaling Pathways

Signaling pathways play a central regulatory role in the osteogenic differentiation of iPSCs. Multiple signaling pathways, including Wnt/β-catenin, TGF-β/BMP, and PI3K/Akt, are involved in this complex biological process. The Wnt signaling pathway is considered a key regulatory factor in osteogenic differentiation, as its activation can promote the expression of osteogenic-related genes, thereby driving the differentiation of iPSCs into osteoblasts [16]. At the same time, TGF-β and BMP signaling pathways further influence the formation and function of osteoblasts by regulating the activity of downstream SMAD proteins [20]. Additionally, studies have found that the metabolic state within cells, such as enhanced aerobic glycolysis, may promote osteogenic differentiation by regulating these signaling pathways [21]. Therefore, a deeper understanding of the interactions among these signaling pathways and their mechanisms in the osteogenic differentiation of iPSCs will provide new therapeutic strategies and research directions for bone tissue regeneration.

The Application of iPSCs in Bone Regeneration Research

Application Examples in Animal Models

The application of induced pluripotent stem cells (iPSCs) in bone regeneration has been validated in various animal models. For example, studies have shown that rapid osteogenesis can be achieved by using retinoic acid (RA) to induce iPSCs, resulting in the formation of osteoblasts within just 10 days. In the experiment, researchers created a 5 mm mandibular defect in rats and used a 3D printed Ti6Al4V scaffold combined with iPSC-induced osteoblasts for repair. The results indicated that rapidly induced iPSCs significantly enhanced the ability of bone regeneration and bone integration, suggesting that using iPSCs for bone defect repair is a safe, effective, and reproducible method [16]. Additionally, another study utilized a mouse model to investigate the role of vascular networks generated by iPSC-derived endothelial cells in bone regeneration, finding that these networks could integrate with host blood vessels, although their promoting effect on bone regeneration was limited, providing new ideas for future bone regeneration strategies [22]. These studies demonstrate that the application of iPSCs in animal models offers new potential and directions for bone regeneration.

Progress in Preclinical Research

In preclinical studies, the application of iPSCs has shown great potential in bone regeneration therapy. Research indicates that iPSCs can effectively differentiate into osteoblasts and exhibit good regenerative capabilities in bone defect models. For example, one study successfully induced osteoblasts from iPSCs derived from peripheral blood mononuclear cells and transplanted them into a rat bone defect model, with results showing significantly better bone formation in the transplant group compared to the control group [23]. Furthermore, iPSCs can accelerate differentiation towards chondrogenic lineage through a three-dimensional rotating culture system, thereby promoting bone regeneration [17]. The progress of these preclinical studies not only validates the application potential of iPSCs in bone regeneration but also lays the foundation for future clinical translation.

Composite Application Research Combining Biomaterials

The combined application of iPSCs and biomaterials has shown promising prospects in bone regeneration research. By combining iPSCs with various biomaterials, more ideal scaffolds can be constructed to promote the regeneration of bone tissue. For example, researchers developed a biomimetic nanofiber scaffold loaded with N-acetylcysteine (NAC), which not only improved mechanical properties but also effectively promoted the osteogenic differentiation of iPSC-derived mesenchymal stem cells [22]. Additionally, synthetic nanofiber scaffolds prepared by electrospinning have also been shown to support the osteogenic differentiation of iPSCs, thereby enhancing the effectiveness of bone regeneration [24]. These composite application studies indicate that the combination of iPSCs and biomaterials can not only improve

the outcomes of bone regeneration but also provide new strategies and methods for bone tissue engineering.

Challenges and Issues Faced

Stability of Cell Proliferation and Differentiation

The stability of cell proliferation and differentiation is a key issue that needs to be addressed in regenerative medicine. Research shows that the proliferation and differentiation of stem cells are regulated by various internal and external factors, including the cellular microenvironment, signaling pathways, and gene expression. Taking human pluripotent stem cells (hPSCs) as an example, the application of chemical regulators can effectively control their differentiation into cardiac progenitor cells, ensuring stability during the proliferative state. This chemical regulation method can not only temporarily prevent cells from differentiating in a specific direction but also restore their proliferative capacity after the removal of the regulators, thus providing new possibilities for cardiac regeneration [25]. Additionally, the stability of microtubules plays an important role in the differentiation of mesenchymal stem cells (MSCs), as the stability of microtubules can enhance the chondrogenic differentiation ability of these cells, suggesting that regulating microtubules may be an effective strategy to improve differentiation efficiency in cell therapy [26].

Risk of Immune Rejection

Immune rejection is one of the most common complications in transplantation surgeries, especially in high-risk corneal and kidney transplants, where the incidence of rejection significantly increases. Studies show that the occurrence of immune rejection is closely related to the HLA matching between the donor and recipient. Although matching ABO blood types and gender can reduce the risk of rejection, this matching has not significantly lowered the incidence of rejection in high-risk corneal transplants [27]. For high-risk patients, the efficacy of local immunosuppressive agents such as tacrolimus (FK506) and steroids has also been confirmed, with these drugs demonstrating superior performance in reducing the incidence of rejection [28]. Furthermore, with the application of immune-checkpoint inhibitors in cancer treatment, the risk of rejection in kidney transplant patients has also drawn attention. Although early data indicate a reduction in rejection risk, further research is needed to optimize immunosuppressive strategies [29].

Ethical and Regulatory Limitations

In stem cell research and clinical applications, ethical and regulatory limitations pose a significant challenge. With the rapid development of stem cell technology, how to promote scientific research while protecting the rights of subjects has become an urgent issue to be resolved. Many countries have strict regulations regarding the use of embryonic stem cells, leading to slow research progress. For example, in some countries, the ethical review process for stem cell research is complex and time-consuming, affecting the enthusiasm of researchers [30]. At the same time, there are significant differences in public awareness and acceptance of stem cell research, which poses challenges for the formulation and implementation of related policies. To promote the development of stem cell research, it is essential to establish a clearer and more reasonable ethical framework to facilitate the coordinated development of science and ethics [31].

Future Development Directions

Integration of New Biomaterials

The integration of new biomaterials has shown great potential in the fields of medicine and bioengineering. In recent years, researchers have been dedicated to developing various new biomaterials, including nanofibers and composite hydrogels. These materials not only possess excellent biocompatibility but also effectively promote tissue regeneration and wound healing. For example, a study pointed out that microcapsules prepared by combining natural polysaccharides with sodium alginate exhibited outstanding drug loading capacity and biocompatibility, significantly enhancing the bioavailability of drugs [32]. Additionally, the use of self-assembling peptides as biomaterials has demonstrated good bioactivity in food and biomedical applications, further advancing the multifunctional development of biomaterials [33]. In the future, with the continuous progress of materials science, it is expected that more innovative biomaterials will be developed and widely applied in clinical therapeutics and regenerative medicine.

Application of Gene Editing Technology

The rapid development of gene editing technology has opened new directions for medical research and clinical treatment. The emergence of gene editing tools such as CRISPR/Cas9 has made precise editing of specific genes possible, providing new solutions for treating genetic diseases and cancers. Research has shown that gene editing technology has made certain progress in the application of hematopoietic stem cells, where gene modification of stem cells can effectively treat immunodeficiency diseases and hereditary blood disorders [33]. However, gene editing technology still faces several challenges in clinical applications, including issues of editing efficiency and safety. Therefore, future research needs to focus on how to improve the efficiency of gene editing, reduce potential side effects, and explore its application in a broader range of diseases

[34]. With the continuous maturation of technology, gene editing technology is expected to play a greater role in personalized medicine.

Prospects and Outlook of Clinical Translation

Clinical translation is an important link in medical research, involving the process of applying laboratory research results to actual treatments. With the rapid development of biomedical technology, the construction and optimization of preclinical models have become particularly important. For example, patient-derived organoid technology has shown good prospects in tumor microenvironment research and personalized drug screening, providing new ideas for clinical treatment [35] Prospects and Outlook of Clinical Translation.

Clinical translation is an important link in medical research, involving the process of applying laboratory research results to actual treatments. With the rapid development of biomedical technology, the construction and optimization of preclinical models have become particularly important. For example, patient-derived organoid technology has shown good prospects in tumor microenvironment research and personalized drug screening, providing new ideas for clinical treatment [36]. In the future, with multidisciplinary collaboration and continuous technological advancements, the efficiency and success rate of clinical translation are expected to be significantly improved, providing patients with more effective treatment options.

In this review, we explore the potential applications and challenges of induced pluripotent stem cells (iPSCs) in bone tissue engineering. With the continuous development of regenerative medicine, iPSCs have become ideal candidates for bone regeneration therapy due to their unique differentiation capabilities and self-renewal properties. However, despite numerous studies demonstrating the feasibility of iPSCs in bone tissue regeneration, there are still many technical and ethical issues that need to be addressed.

From an expert's perspective, it is crucial to balance different viewpoints and findings from various studies. Some research indicates that the differentiation efficiency and functional stability of iPSCs may be influenced by various factors, such as culture medium composition, cell source, and their genome characteristics. Therefore, future research should focus on optimizing culture conditions and differentiation protocols to enhance the application performance of iPSCs. Meanwhile, with the development of gene editing technologies, scientists hope to enhance the safety and efficacy of iPSCs through precise genetic modifications, providing stronger support for clinical applications.

Ethically, while the use of iPSCs avoids the ethical controversies associated with embryonic stem cells, there is still a need to establish a clear ethical framework regarding cell sources, clinical applications, and long-term observations to ensure public trust and support. Therefore, multidisciplinary collaborative research will be an important strategy to promote the application of iPSCs in bone tissue engineering.

In summary, research on induced pluripotent stem cells in the field of bone tissue engineering is rapidly developing. Despite facing technical and ethical challenges, through continuous research and technological innovation, iPSCs show great promise in future bone regeneration therapies. It is hoped that this article can provide guidance and reference for researchers in related fields, promoting the application process of iPSCs in bone tissue engineering and ultimately achieving clinical translation.

Funding

National Key Research and Development Program (2024YFA1108600).

This work was funded by the Natural Science Foundation of Beijing (ID:L242042).

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