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A Comparative Analysis of the Advantages and Disadvantages of Adult Mesenchymal Stem Cells and Induced Pluripotent Stem Cells in Bone Repair Applications

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Abstract. Bone defect repair remains a major clinical problem. Traditional bone grafting often faces practical limits such as donor site morbidity, limited availability, and immune rejection. Stem cell-mediated bone tissue engineering offers another route, and adult mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) have become the most widely discussed seed cells in this field. Work published over the past five years has compared these two cell types in terms of biological foundations, core application dimensions, and osteogenic repair efficacy, and has also tried to explain why each type runs into its own problems. MSCs have reliable safety profiles and are relatively easy to harvest, but their proliferation and differentiation capacities decline with donor age and passage number. This decline is often linked to senescence pathways such as p53/p21. iPSCs have near-unlimited proliferative capacity and tri-lineage differentiation potential, but they also face three core problems: tumorigenic risks from residual undifferentiated cells, epigenetic memory, and low differentiation efficiency. We compare these strengths and limits, propose a scenario-specific cell selection strategy for mild-to-moderate and severe bone defects, and discuss how genetic modification and culture optimization can enhance cell performance. This review offers a practical reference for choosing suitable seed cells and building tissue engineering frameworks in clinical bone repair.

Keywords: adult mesenchymal stem cells, induced pluripotent stem cells, bone defects, osteogenic differentiation, cell therapy

1. Introduction

Bone defects caused by trauma, tumor resection, or congenital malformations have long been a major clinical challenge. Autologous bone grafting is regarded as the standard approach, but it often brings donor site morbidity, insufficient bone volume, and the need for secondary surgery. Allografts and synthetic bone substitutes face their own barriers, including high risks of immune rejection, weak osteogenic potential, and limited availability [1]. Stem cell-mediated bone tissue engineering combines seed cells, scaffold materials, and growth factors; these components work together and open a new way for bone regeneration [2]. The most widely discussed seed cells generally fall into two categories. MSCs have become the most widely used adult stem cells in bone tissue engineering

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because of their multilineage differentiation potential, immunomodulatory functions, and relatively easy access [3]. Their proliferation and osteogenic differentiation capacities weaken with donor aging and in vitro passaging, however, and the highly heterogeneous cell population limits stable application [4]. iPSCs are produced through somatic cell reprogramming. They have unlimited self-renewal capacity and the potential to differentiate into cells across all three germ layers, which provides an almost inexhaustible and customizable cell source for bone regeneration [5]. They still cannot avoid two major problems: safety and efficiency. Tumorigenic risks from residual undifferentiated cells, low reprogramming efficiency, impure differentiated products, and potential immunogenicity all bring significant hurdles [6, 7]. Most existing studies focus on a single cell type and rarely conduct side-by-side, multidimensional comparisons, so they do not provide specific cell selection strategies tailored to different severities of bone injury. We set out to compare the pros and cons of adult MSCs and iPSCs in bone repair, explain the molecular mechanisms behind their core differences and inherent defects, and discuss how to select appropriate cells for different scenarios and how to optimize their performance.

2. Comparison of the biological basis and bone repair applications of the two types of stem cells

2.1. Overview of basic biological characteristics

Adult mesenchymal stem cells (MSCs) are widely found in bone marrow, adipose tissue, synovium, and dental pulp. As multipotent stromal cells, they can differentiate into osteoblasts, chondrocytes, and adipocytes. Bone marrow-derived mesenchymal stem cells (BMSCs) are the most studied subtype. Their osteogenic differentiation depends on several signaling pathways working together, including BMP, Wnt/β-catenin, and TGF-β [8]. As the donor ages, MSC stemness drops. Proliferation slows and osteogenic capacity weakens, while senescence markers such as p16 and p21 rise clearly [4, 9]. Developmental origin also matters. Because the jaw comes from the neural crest, jaw-derived BMSCs outperform iliac-derived BMSCs in proliferation, anti-senescence, and osteogenic capability [9].

iPSCs are pluripotent stem cells generated by introducing reprogramming factors such as Oct4, Sox2, and Klf4 into already differentiated somatic cells [5]. They resemble embryonic stem cells biologically. They express pluripotency markers like Nanog and Oct4, can proliferate without limit, and can differentiate into derivatives of all three germ layers in vivo and in vitro [7]. Compared with embryonic stem cells, iPSCs have two clear advantages. Because they come from the patient's own adult cells, they avoid ethical controversies and the risk of immune rejection, which makes personalized bone repair possible [6]. Their unlimited self-renewal also allows large-scale in vitro expansion, so they can provide plenty of seed cells for bone tissue engineering [7]. They can differentiate into all cell types across the three germ layers, including osteoblasts and chondrocytes, which makes them a customizable cell source for bone regeneration [5]. Maintaining iPSC pluripotency depends on a complex epigenetic regulatory network, however. Donor differences and different reprogramming methods also lead to clear variation in the pluripotency and differentiation potential of the resulting iPSCs [7, 10].

2.2. Cross-comparison of core application dimensions

Table 1 sets out a cross-comparison of the two stem cell types across four core application dimensions; the main findings are outlined below.

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Table 1. Cross-comparison of core dimensions for bone repair applications of the two stem cell types

Comparison Criteria	Adult Mesenchymal Stem Cells (MSCs)	Induced Pluripotent Stem Cells (iPSCs)
Materials and Sources	MSCs are widely available and can be extracted from bone marrow, adipose tissue, synovium, and other tissues through minimally invasive procedures, with relatively few ethical concerns. Preparation is straightforward, which can reduce costs while maintaining final efficacy [3].	Starting materials such as skin fibroblasts or peripheral blood are not overly difficult to acquire. The preparation stage, however, involves complex reprogramming and characterization procedures that require higher financial investment and are highly time-consuming [1].
Immunogenicity and Risk of Rejection	Autologous MSC transplantation theoretically does not trigger host immune rejection. Allogeneic MSCs, owing to their relatively low immunogenicity, can also evade immune surveillance and recognition to a certain extent [3].	Personalized treatment can be achieved by transplanting autologous differentiated cells, but some studies indicate that iPSC-derived cells might still trigger immune responses due to mitochondrial DNA mutations or abnormal antigen expression [6].
Carcinogenicity Risk	To date, no reports have suggested that adult MSCs spontaneously form tumors in vivo or in vitro, so they are generally regarded as a safe option [3].	Residual undifferentiated cells are the main hidden risk. Once these enter the body, they can form teratomas, and even a tiny number of residual cells could potentially induce tumors [5, 6].
Clinical Development Progress	Clinical research on MSC-based therapies has been conducted for nearly 20 years, and numerous clinical trials have confirmed the safety and preliminary efficacy of these cells in bone regeneration and related conditions [3].	iPSC-related therapies have entered the clinical trial stage in fields such as ophthalmology, but the vast majority of research in bone repair remains at the preclinical stage; translation to actual human application is still relatively slow [5].

We read the four dimensions as a practical separation between the two cell types. MSCs are easy to obtain and raise few ethical concerns; their preparation is simple and cheap. iPSCs do not require hard-to-get starting materials, but reprogramming and characterization cost a lot and take a long time. That difference helps account for why MSCs move toward clinical translation much faster [1, 3]. Immune rejection also favors MSCs. Autologous MSC transplants rarely trigger immune responses, and even allogeneic MSCs largely avoid immune surveillance because of their low immunogenicity. iPSCs can support customized therapy, but their differentiated cells may still cause immune reactions through mitochondrial DNA mutations or abnormal antigen expression [3, 6]. Safety is where the contrast is sharpest. No study has reported MSCs forming tumors in vivo or in

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vitro, whereas residual undifferentiated iPSCs can directly form teratomas once they enter the body [3, 5, 6]. Clinical progress differs as well. MSC research has run for nearly 20 years, and many trials have confirmed its safety and preliminary efficacy. Most iPSC work in bone repair is still at the preclinical stage [3, 5]. These differences define which scenario fits each cell type and provide the core basis for choosing cells according to bone injury severity.

2.3. Analysis of differences in osteogenic repair effects in vitro and in vivo

In vitro work has shown that culturing adult mesenchymal stem cells (MSCs) in an osteogenic induction medium containing dexamethasone, ascorbic acid, and β-glycerophosphate leads to strong expression of osteogenic markers such as Runx2, ALP, and OCN, and mineralized nodules also form [8, 11]. The overall osteogenic efficiency depends heavily on donor age, passage number, and culture conditions. For example, the STRO-1-positive subpopulation within bone marrow mesenchymal stem cells (BMSCs) shows clearly stronger osteogenic differentiation than other ordinary cells [4].

iPSCs follow two main pathways for osteogenic differentiation. They can first convert into MSCs and then differentiate, or they can directly become osteoblasts. The indirect route mimics natural development and gives relatively higher efficiency [5, 7]. Direct differentiation is faster, but it requires much more precise control of signaling pathways. Animal studies support this. When researchers implant iPSC-derived osteoblasts or MSCs into cranial or femoral defects in rats and mice, clear new bone formation appears [5, 12]. Kato et al. first converted peripheral blood-derived iPSCs into osteoblasts and implanted them into rat cranial defects, which confirmed their in vivo osteogenic capability [12]. Some studies also note that if the implantation period is too long, the in vivo survival rate and bone-forming efficacy of iPSC-derived MSCs may fall below expectations [13]. Gene editing has already shown promising signs for boosting iPSC osteogenic potential [14]. Three-dimensional osteogenic differentiation systems have also revealed that TGF-β signaling plays a key role in the transition from osteoblasts to osteocytes [15].

3. Application challenges and underlying molecular mechanisms of two types of stem cells

3.1. Inherent limitations and underlying regulatory mechanisms of adult mesenchymal stem cells

Replicative senescence is the main limitation of MSCs. Their function drops as donor age and passage number rise. At the molecular level, activation of pathways such as p53/p21 and p16/pRB stops the cell cycle [9]. Telomeres also shorten with each passage, and DNA damage keeps building up. The self-secreted inflammatory factors (SASP) further worsen the aging of the surrounding microenvironment, and age-related epigenetic changes suppress the transcription of key osteogenic genes such as Runx2 [9]. A separate problem is the high inherent heterogeneity of MSCs. This is the main reason why therapeutic outcomes fluctuate. Screening out highly active subpopulations may be a viable way to raise overall efficacy [4].

3.2. Safety risks and underlying mechanisms of induced pluripotent stem cells

Tumorigenic propensity and genetic instability are the main practical concerns for iPSCs. Incompletely differentiated residual cells are the central issue; once they enter the body, they can directly form teratomas [5, 6]. The genome and epigenome are prone to errors during

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reprogramming and long-term culture. The reprogramming process itself may cause gene mutations or copy number variations. Long-term in vitro culture also gradually selects for mutant clones with growth advantages [7].

Epigenetic memory means that iPSCs tend to retain the epigenetic traits of their source cells. This has long-term consequences for bone repair. It disrupts osteogenic differentiation in several ways. The original DNA methylation patterns of the source cells do not fully reset after reprogramming. These residual methylation marks suppress the promoter activity of osteogenic genes such as Runx2 and Osterix, which lowers osteogenic efficiency [7, 10]. Unremoved histone modification patterns (such as H3K27me3 and H3K4me3) also interfere with chromatin accessibility. This makes it harder for key osteogenic transcription factors to bind to the regulatory regions of target genes, which blocks directed differentiation toward the osteogenic lineage [7]. Epigenetic memory also gives iPSCs the biases of their source cells. Fibroblast-derived iPSCs, for example, tend to lean toward the fibroblast lineage instead of committing to osteoblasts, which directly reduces osteogenic efficiency in bone repair [7]. It may also change the immunogenicity of iPSCs, so differentiated cells express abnormal antigens and trigger immune responses [6]. Epigenetic memory therefore not only reduces osteogenic efficiency, but also creates hidden risks for the safety and long-term stability of bone repair.

3.3. Common limitations of existing studies

Current research still faces several practical hurdles. Differentiation protocols lack standardized criteria and have low overall efficiency. Long-term follow-up data on in vivo safety is also scarce. Most experiments still use serum with poorly defined components or culture systems with feeder layers, which creates large variation in the final data and makes exact replication very difficult [16]. In vivo studies also rely heavily on immunodeficient animals, which makes it hard to accurately mimic how the human immune system responds to transplanted cells. Observation periods are often too short, so long-term tumorigenic risks are not evaluated thoroughly [12].

4. Stem cell optimization strategies and recommendations for selection based on specific scenarios

4.1. Performance optimization pathways for two types of stem cells

For replicative senescence and heterogeneity, the two main shortcomings of MSCs, three routes are available. Gene editing can raise anti-senescence genes such as SATB2 or suppress differentiation-blocking genes such as HOXA10, which boosts MSC proliferation and osteogenic differentiation [9]. Hypoxic culture, 3D scaffolds, and specific growth factors help preserve MSC stemness and improve osteogenic differentiation [8, 11]. Screening for highly active subpopulations such as STRO-1-positive cells gives a purer population and higher osteogenic efficiency [4].

For iPSCs, safety and osteogenic efficiency can be addressed together. Non-integrating reprogramming systems such as the Sendai virus or episomal vectors avoid genomic integration mutations and lower tumorigenic risk from the start [12]. The stages of Wnt, BMP, and TGF-β signaling can be regulated precisely to guide cells toward the osteogenic lineage and improve differentiation efficiency [5, 7]. CD271 sorting and SSEA-4 negative screening remove incompletely differentiated residual cells and reduce the hidden risk of teratomas [6]. Epigenetic modifiers such as DNA methylation inhibitors and histone deacetylase inhibitors may reset epigenetic memory and improve osteogenic differentiation [7, 10]. Gene editing can directly

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enhance osteogenic potential, for example by precisely regulating key genes such as RUNX1 [14]. A 3D osteogenic differentiation system can optimize the culture environment [15], and iPSC-loaded scaffold materials used in vivo can further improve bone regeneration outcomes [13].

4.2. Selection strategies for different severities of bone injury

Drawing on the characteristics summarized above, we suggest a preliminary scenario-based strategy for cell selection:

• Mild-to-moderate bone defects or localized repairs such as alveolar ridge augmentation and minor fractures usually fit adult MSCs first. They are safe, relatively easy to operate, and low cost. The local microenvironment also supports their survival and function well. Direct local application of autologous bone marrow concentrates or adipose-derived MSCs is therefore a promising approach [3, 4].

• Extensive or complex bone defects, such as maxillofacial reconstruction and segmental long bone defects, usually need a large supply of osteoblasts and fit iPSCs better. Their unlimited proliferative capacity and strong differentiation potential meet this need. Researchers can engineer iPSC-derived MSCs through genetic modification, such as BMP-6 overexpression, or differentiate them directly into osteoblasts. Pairing these cells with custom 3D-printed bioactive scaffolds may offer an effective solution for these difficult bone defects [7, 16].

5. Conclusion

MSCs and iPSCs bring different strengths to bone repair. MSCs have a high safety profile and a solid clinical foundation. They have already entered clinical applications, and their main weaknesses are cell heterogeneity and age-related functional decline. iPSCs can provide an almost inexhaustible cell source and strong differentiation capabilities, but they still have to deal with tumorigenicity and genetic instability. We note several limits in this review. It does not include a systematic head-to-head comparison of the two cell types, and it lacks long-term in vivo safety data. Future work could move in several directions. A side-by-side comparison under identical conditions would help test proliferation, osteogenic differentiation, in vivo survival, and bone regeneration capacity. A safety monitoring system with observation periods of 12 months or longer would clarify the long-term tumorigenic risks and immune responses of iPSCs and their differentiated products. Epigenetic memory needs further study; single-cell sequencing, ATAC-seq, and ChIP-seq can reveal how epigenetic markers shift during reprogramming. Humanized animal models would better replicate how the human immune system reacts to transplanted cells. 3D printing and microfluidics could support smart responsive materials and personalized scaffolds that release growth factors and signaling molecules in a spatiotemporally controlled way. Combining gene editing, biomaterials, and developmental biology will likely produce safer and more effective ready-to-use iPSC-based bone repair products and support personalized bone regeneration therapies.

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