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Application and Prospects of Cell Therapy in Avascular Necrosis of the Femoral Head

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ABSTRACT

Avascular necrosis of the femoral head is a serious condition that leads to joint dysfunction and pain, with traditional treatment methods proving to be limited in their effectiveness. In recent years, cell therapy has emerged as a promising therapeutic approach, drawing significant attention within the medical community. This review comprehensively examines the current status of cell therapy in the treatment of avascular necrosis, focusing on the therapeutic effects of various cell types, their underlying mechanisms, advancements in clinical research, and future directions in this field. By analysing existing literature, this paper aims to provide insights for clinical practice and discuss the potential advantages and challenges associated with cell therapy.

Keywords: Cell Therapy; Avascular Necrosis; Femoral Head; Stem Cells; Clinical Research; Therapeutic Effects

Abbreviations: AVN: Avascular Necrosis; MSC: Mesenchymal Stem Cells; BMSC: Bone Marrow Mesenchymal Stem Cells; FHN: Femoral Head Necrosis; ADSC: Adipose-Derived Stem Cells; ESC: Embryonic Stem Cells; IPSC: Induced Pluripotent Stem Cells; BMP: Bone Morphogenetic Proteins; VEGF: Vascular Endothelial Growth Factor; IHF: Ischemic Heart Failure; B-ALL: B-Cell Acute Lymphoblastic Leukaemia; MCID: Minimum Clinically Important Difference; ANFH: Avascular Necrosis of the Femoral Head; IL-6: Interleukin-6; TNF- α: Tumor Necrosis Factor-Alpha

Introduction

Avascular necrosis (AVN), also known as osteonecrosis, is a pathological condition characterized by the death of bone tissue due to a lack of blood supply [1,2]. Traditional treatment methods for AVN, including core decompression and total hip arthroplasty, have shown limited effectiveness, particularly in the early stages of the disease. These methods often fail to address the underlying pathophysiological processes and do not promote true regeneration of the necrotic bone [3]. In recent years, there has been a significant shift towards exploring innovative treatment strategies, particularly cellular therapies. These therapies leverage the regenerative potential of various cell types, including mesenchymal stem cells (MSCs), to promote bone repair and regeneration. Cellular therapy holds great promise in the orthopaedic field, as it offers a more targeted approach to treatment, potentially addressing both the symptoms and the underlying causes of AVN [4,5]. This review aims to discuss the definitions, epidemiology, limitations of traditional treatments, and the emerging role of cellular therapies in managing AVN of the femoral head.

Overview of Cellular Therapy

Basic Concepts of Cellular Therapy

Definition and Classification: Cellular therapy refers to the administration of living cells to treat various diseases and conditions. It encompasses a wide range of therapeutic strategies, including stem cell therapy, immune cell therapy, and tissue engineering. In the context of bone repair, cellular therapy primarily involves the use of stem cells, which are undifferentiated cells capable of self-renewal and differentiation into specialized cell types [6]. The use of MSCs, particularly those derived from bone marrow or adipose tissue, has gained traction due to their ability to differentiate into osteoblasts and pro-

mote bone regeneration. Furthermore, MSCs exert paracrine effects, releasing bioactive factors that modulate inflammation and enhance the healing process [7,8].

Role of Cellular Therapy in Bone Tissue Repair: Cellular therapy's role in bone tissue repair is multifaceted. It not only aims to replace lost or damaged tissue but also to create a conducive environment for healing through the secretion of growth factors and cytokines. Studies have shown that MSCs can enhance angiogenesis, reduce inflammation, and stimulate the proliferation and differentiation of local progenitor cells, thereby facilitating the repair of osteonecrotic lesions [5,9]. In addition to MSCs, other cell types such as immune cells and genetically modified cells (e.g., CAR-T cells) are being investigated for their potential roles in treating AVN. These innovative approaches may provide synergistic effects, combining the regenerative capabilities of stem cells with the targeted action of immune therapies [10,11]. Overall, cellular therapy represents a promising frontier in the treatment of AVN, with the potential to improve outcomes significantly compared to traditional methods. Through this review, we will further explore the mechanisms, applications, and future directions of cellular therapy in the management of avascular necrosis of the femoral head.

Cell Types and Their Application in Femoral Head Necrosis

Bone Marrow Mesenchymal Stem Cells (BMSC): Bone marrow mesenchymal stem cells (BMSCs) are increasingly recognized for their potential in the treatment of femoral head necrosis (FHN) due to their unique regenerative properties. BMSCs possess the ability to differentiate into various cell types, including osteoblasts, which are crucial for bone formation and repair. Recent studies have demonstrated that BMSCs can enhance angiogenesis and promote osteogenesis in the context of avascular necrosis, particularly when combined with biomaterials such as hydrogels. For instance, injectable hydrogels incorporating angiogenesis-stimulating peptides have shown to boost the proliferation and differentiation of BMSCs, leading to improved outcomes in animal models of FHN [12]. Moreover, the paracrine effects of BMSCs, such as the release of growth factors and cytokines, play a significant role in modulating the local microenvironment, thereby facilitating tissue repair and regeneration [13]. The therapeutic application of BMSCs in FHN is further supported by their ability to mitigate oxidative stress and apoptosis, which are critical factors in the pathogenesis of necrosis [14]. Overall, BMSCs represent a promising cell type for regenerative strategies aimed at treating femoral head necrosis.

Adipose-Derived Stem Cells (ADSC): Adipose-derived stem cells (ADSCs) have emerged as a viable alternative to BMSCs in the treatment of femoral head necrosis due to their abundance and ease of harvest. ADSCs possess similar multipotent capabilities, allowing them to differentiate into osteogenic and chondrogenic lineages, which are essential for bone healing [15]. Recent research highlights the role of ADSC-derived exosomes in enhancing the regenerative process. These exosomes are rich in growth factors and have been shown to promote angiogenesis and inhibit apoptosis in osteoblasts, thereby improving bone regeneration in FHN models [16]. Moreover, studies have indicated that ADSCs can be preconditioned to enhance their therapeutic efficacy, particularly through the modulation of signalling pathways that govern cell proliferation and differentiation [17]. The potential of ADSCs in FHN treatment is further underscored by their ability to secrete anti-inflammatory cytokines, which can help mitigate the inflammatory response associated with necrosis [18]. As such, ADSCs represent a promising avenue for therapeutic intervention in femoral head necrosis.

Embryonic Stem Cells (ESC) and Induced Pluripotent Stem Cells (iPSC): Embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC) hold significant promise for regenerative medicine, including the treatment of femoral head necrosis. ESCs are characterized by their ability to differentiate into any cell type, providing a versatile platform for tissue engineering applications [19]. Recent advancements in stem cell technology have enabled the generation of iPSCs from somatic cells, which can also differentiate into osteoblasts and other relevant cell types for bone regeneration [20]. The application of iPSCs in FHN is particularly appealing due to their potential for autologous transplantation, minimizing the risk of immune rejection [21]. Furthermore, studies have shown that both ESCs and iPSCs can be engineered to enhance their regenerative capabilities through genetic modifications or by optimizing their culture conditions [22]. The ability of these pluripotent stem cells to secrete a variety of growth factors also contributes to their therapeutic potential by promoting angiogenesis and reducing apoptosis in surrounding tissues [23]. In conclusion, ESCs and iPSCs represent a cutting-edge approach to address the challenges associated with femoral head necrosis, offering new avenues for research and clinical application.

Mechanisms of Cell Therapy

Biological Mechanisms Promoting Bone Regeneration: Bone possesses a remarkable ability to regenerate, a characteristic that has been extensively studied in the context of cell therapy. The biological mechanisms underlying this regenerative capacity involve a complex interplay between various cell types, signalling pathways, and extracellular matrix components. Specifically, mesenchymal stem cells (MSCs) play a pivotal role in bone healing by differentiating into osteoblasts, which are essential for new bone formation. Additionally, these stem cells secrete a variety of cytokines and growth factors that modulate the local microenvironment, promoting angiogenesis and recruiting other cell types necessary for tissue repair [24].

Recent studies have highlighted the significance of the immune response in bone regeneration. Immune cells, particularly macrophages, have been shown to switch between pro-inflammatory and

anti-inflammatory states, which can either promote or inhibit osteogenesis. This dynamic balance is crucial for creating a favourable environment for bone healing [25].

Furthermore, the presence of bioactive materials, such as calcium-phosphate compounds and nanomaterials, can enhance the mechanical and biological properties of scaffolds used in bone tissue engineering, thereby facilitating better integration and regeneration of bone tissue [26]. The cellular and molecular mechanisms involved in bone regeneration are also influenced by mechanical stimuli. Research indicates that applying mechanical forces can enhance the proliferation and differentiation of osteoblasts, contributing to improved bone formation. This mechanotransduction process is critical, especially in the context of scaffold design for bone regeneration [27]. Overall, understanding these biological mechanisms is essential for optimizing cell therapy strategies aimed at enhancing bone regeneration.

Role of Cytokines and Growth Factors: Cytokines and growth factors are pivotal in orchestrating the complex processes involved in bone regeneration. These signaling molecules facilitate communication between cells and play crucial roles in cell proliferation, differentiation, and survival. Among the various cytokines, bone morphogenetic proteins (BMPs) have garnered significant attention for their ability to induce osteogenesis and enhance bone healing. BMPs stimulate the differentiation of MSCs into osteoblasts, thereby promoting new bone formation [28]. Additionally, vascular endothelial growth factor (VEGF) is essential for angiogenesis, which is critical for supplying nutrients and oxygen to the regenerating bone tissue. The interplay between VEGF and BMPs is particularly important, as adequate vascularization is necessary for effective bone healing [29]. Other cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), can modulate the inflammatory response during the healing process, influencing the balance between bone formation and resorption [25]. The therapeutic application of these cytokines and growth factors has been explored in various preclinical and clinical settings. For instance, local delivery of BMPs in combination with scaffolds has shown promise in enhancing bone regeneration in critical-sized defects [30]. However, challenges remain regarding the optimal dosing, timing, and delivery methods for these bioactive molecules to maximize their therapeutic potential while minimizing adverse effects [27]. Future research should focus on refining these approaches to harness the full capabilities of cytokines and growth factors in cell therapy for bone regeneration.

Clinical Research Progress

Existing Clinical Trial Results: Recent clinical trials have provided significant insights into various medical conditions and their treatment modalities. For instance, the study on the efficacy of intracoronary cell-based therapy in acute myocardial infarction revealed insufficient effects, prompting further investigation into alternative delivery methods of reparative cells in ischemic heart failure (iHF) patients. A meta-analysis encompassing individual patient data demonstrated that percutaneous transendocardial cell therapy significantly improved survival rates and cardiac performance, indicating its potential as a safe and effective treatment for patients with chronic iHF [31]. Similarly, the use of mesenchymal stem cells (MSCs) in treating perianal fistulizing Crohn's disease has shown promising results, with a significant odds ratio for remission compared to controls, suggesting MSCs could be a viable adjunct therapy [32]. Moreover, a systematic review of CAR T-cell therapy for relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL) indicated high rates of minimal residual disease-negative complete remission, although concerns about adverse events such as cytokine release syndrome remain [33]. These findings collectively underscore the dynamic landscape of clinical research, highlighting both the advancements and challenges in evolving treatment modalities.

Treatment Efficacy Assessment Standards: The evaluation of treatment efficacy is crucial for determining the success of clinical interventions and guiding future research. Various standards have emerged to assess treatment outcomes, notably the minimum clinically important difference (MCID), which quantifies the smallest change in outcomes that patients perceive as beneficial. For instance, in knee osteoarthritis, the variability in MCIDs across guidelines complicates treatment recommendations, emphasizing the need for consensus on defining clinically significant outcomes [34]. Additionally, the use of standardized reporting criteria, such as the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guidelines for intratympanic steroid treatment of sudden sensorineural hearing loss, has been advocated to ensure consistency in outcome assessment across studies [35]. Furthermore, systematic reviews and meta-analyses have become essential tools in synthesizing data from multiple studies to provide a comprehensive evaluation of treatment efficacy, as seen in the analysis of CAR T-cell therapy for acute myeloid leukemia, which highlighted the importance of stratifying outcomes based on treatment regimens and patient characteristics [36]. These standards not only enhance the reliability of clinical findings but also facilitate informed decision-making in patient care.

Safety and Efficacy Analysis of Cell Therapy: Cell therapy has gained traction as a promising treatment modality across various medical fields, yet its safety and efficacy remain subjects of ongoing research. A systematic review of stem cell therapy for advanced heart failure demonstrated significant improvements in left ventricular ejection fraction and end-systolic volume, suggesting that this approach may enhance cardiac function without increasing mortality risk [37]. However, concerns about safety profiles persist, particularly regarding adverse events associated with treatments like CAR T-cell therapy, where the incidence of cytokine release syndrome and neurotoxicity can complicate patient outcomes [33]. The meta-analysis of MSCs for perianal fistulizing Crohn's disease indicated that while the

therapy is effective, the occurrence of treatment-emergent adverse events remains comparable to control groups, underscoring the necessity for rigorous safety monitoring [32]. Furthermore, the analysis of various delivery methods for cell-based therapies emphasizes the need for tailored approaches that consider patient-specific factors and the underlying pathology to optimize therapeutic outcomes while minimizing risks [31]. As research progresses, establishing robust safety and efficacy profiles will be essential for integrating cell therapy into standard clinical practice effectively.

Future Directions and Challenges

Technological Advances and Innovations: The landscape of medical technology is rapidly evolving, driven by advancements in genomics, artificial intelligence, and digital health applications. These innovations hold the potential to transform patient care by facilitating personalized medicine, enhancing diagnostic accuracy, and streamlining treatment protocols. For instance, the integration of genomic sequencing into routine clinical practice allows for the identification of actionable mutations in cancer patients, enabling targeted therapies tailored to individual genetic profiles. However, despite the promise of precision medicine, the clinical application of such technologies remains limited to a small fraction of patients due to challenges in accessibility and the need for further validation of these approaches in diverse populations [38]. Moreover, the implementation of artificial intelligence in radiology and other specialties is still in its infancy, facing hurdles related to regulatory approval and ethical considerations surrounding patient data privacy [39]. As technology continues to advance, it is crucial for healthcare systems to adapt and integrate these innovations effectively to maximize their potential benefits for patient outcomes.

Ethical Issues and Regulatory Challenges: With the rapid pace of technological advancement in healthcare, ethical and regulatory challenges have emerged as critical areas of concern. The development of new therapies, particularly those involving genetic manipulation and biobanking, raises significant ethical questions regarding informed consent, the moral status of biological materials, and potential misuse of genetic information [40]. Furthermore, the regulatory landscape is often lagging behind technological progress, leading to uncertainties around approval processes and compliance requirements for novel therapies [40]. As healthcare providers and researchers navigate these complexities, it is essential to establish robust ethical frameworks and regulatory guidelines that ensure patient safety while fostering innovation. This requires ongoing dialogue among stakeholders, including ethicists, regulators, and the scientific community, to address the multifaceted challenges posed by emerging technologies and to develop policies that promote responsible research and clinical practice [41].

Individualization of Cell Therapy and Precision Medicine: The shift towards personalized medicine is particularly evident in the field of cell therapy, where treatments are increasingly tailored to the individual characteristics of patients. This approach not only enhances therapeutic efficacy but also minimizes adverse effects by considering the unique genetic and phenotypic profiles of patients. For example, advancements in stem cell research have opened new avenues for regenerative medicine, allowing for the development of personalized therapies for conditions such as cancer and rare genetic disorders [42]. However, the realization of fully individualized therapies faces several challenges, including the need for standardized protocols for cell sourcing, processing, and application, as well as the ethical implications of manipulating human cells [43]. Furthermore, the integration of precision medicine into clinical practice necessitates a multidisciplinary approach, involving collaboration between geneticists, clinicians, and bioethicists to ensure that treatments are both effective and ethically sound. As the field continues to evolve, addressing these challenges will be crucial for unlocking the full potential of personalized cell therapies in improving patient outcomes and advancing healthcare as a whole [44].

Discussion

In conclusion, the current landscape of cell therapy for avascular necrosis of the femoral head (ANFH) presents a promising yet complex picture. As highlighted throughout this review, cell therapy, particularly utilizing stem cells, shows significant potential in promoting cartilage regeneration and enhancing the healing process within the affected bone. The advantages of such therapies include their ability to not only alleviate symptoms but also address the underlying pathological mechanisms of ANFH, thereby potentially offering a more durable solution compared to traditional treatment modalities. However, the field still faces challenges, including variability in patient responses and the need for standardized protocols. Discrepancies in research findings, particularly regarding the types of stem cells used and their methods of administration, underscore the necessity for further investigations. This complexity necessitates a balanced approach to interpreting the available evidence, as differing perspectives can lead to confusion in clinical practice and patient management [45-49].

Future research must prioritize large-scale, multicentric clinical trials that not only validate the efficacy of various cell therapy approaches but also explore the optimal conditions for their application. Additionally, it is essential to investigate the long-term outcomes of these treatments, as well as their cost-effectiveness compared to existing interventions. To promote the advancement of cell therapy in the clinical setting, collaboration between researchers, clinicians, and regulatory bodies is crucial. Establishing clear guidelines and benchmarks for cell therapy applications can help standardize treatment protocols and improve patient outcomes. Furthermore, educating healthcare professionals about the potential and limitations of cell therapies will be vital in integrating these innovative approaches into routine practice.

Conclusion

In summary, while cell therapy for ANFH holds substantial promise, concerted efforts are needed to address the existing gaps in research and clinical application. By fostering a collaborative environment and prioritizing rigorous scientific inquiry, we can pave the way for more effective and widely accepted treatment options for patients suffering from this debilitating condition.

Self-Assessment Questions

1. The role of cell therapy in bone tissue repair: The role of cell therapy in bone tissue repair is multifaceted. It aims not only to replace lost or damaged tissue but also to create a healing environment by secreting growth factors and cytokines.

2. The application prospects of cell therapy in avascular necrosis of the femoral head Cell therapy has great potential in the field of orthopedics as it offers a more targeted treatment approach that may address both the symptoms and underlying causes of AVN.

3. Clinical research progress in cell therapy: Cell therapy, as a promising treatment method, has gained attention across various medical fields and is being applied clinically.

4. How do different cell types affect treatment outcomes? The regenerative potential of different cell types varies, and further research is needed to determine how to select the appropriate cell therapy for specific diseases.

5. Future directions of cell therapy: Research in cell therapy has opened new avenues for regenerative medicine, enhancing treatment efficacy, but further efforts are needed to address the gaps in research and clinical application.

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Data availability

Data were included in article/referenced in article. No new data were generated or analysed in support of this research.

Conflict of Interest Statement

The authors declare that they have no competing financial interests or personal relationships that may have influenced the work reported in this study.

Ethics Declarations

Review and/or approval by an ethics committee was not needed for this study because animal experiments or clinical studies are not required for this study.

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