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Literature Review

Human dental pulp mesenchymal stem cells regenerative potential

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ABSTRACT

***Background**: Stem cells can be divided into mono-potent, oligopotent, multipotent, pluripotent, and totipotent. Dental and oral stem cells are stem cells found in the teeth and mouth that has the potential to develop into various cell types. The rapid development of regenerative dentistry has resulted in the exploration of stem cells, including dental pulp mesenchymal stem cells. Mesenchymal stem cells, have important regenerative potential in repairing dental and surrounding tissues. One of dental stem cells source that have been discovered is dental pulp mesenchymal stem cells. **Purpose**: This article aims to review the regenerative potential of human dental pulp mesenchymal stem cells (HDPMSCs). **Review:** HDPMSCs are potential for regenerative dentistry, including regenerative endodontics due to their multipotency, ease of collection, and ability to support tissue repair, immunomodulation, and regeneration across dental, orthopedic, neurological, and cardiovascular applications**. **Conclusion**: The regenerative potentials of HDPMSCs on various treatments are vastly explored by many studies.*

***Keywords:** regenerative potential; dental pulp; stem cells; mesenchymal stem cell; medicine*

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INTRODUCTION

Stem cells can be found in the human body. These stem cells have the capability to not only self-renew but also differentiate into every other kind of cell found in the body. To a certain extent, stem cells may be found in both embryonic and adult cells.[1] It is possible to categorize these cells as pluripotent, totipotent, oligopotent, unipotent, or multipotent based on their tendency to develop into certain cell types. In animal and human models of regenerative medicine and regenerative dentistry, mesenchymal stem cells (MSCs), which are also often referred to as multipotent stromal cells, have shown a remarkable capacity to produce innovative therapies.[2-7] Cells that exhibit the presence of CD90, CD73, and CD105 markers, but lacking the presence of CD34 and CD45 markers, are categorized as MSCs.[8-12] A notable feature of MSCs is their enhanced ability to transform into multiple types of cells, such as chondrogenic, myogenic, osteogenic, adipogenic, and neurogenic-like cells.[13]

Human dental pulp mesenchymal stem cells (HDPMSCs) are adult mesenchymal stem cells obtained from dental pulp. These cells are derived from the neural crest and have shown potential for various regenerative therapies. These cells, including stem cells from exfoliated primary teeth (SHEDs) and human dental pulp stem cells (HDPSCs), have been used in regenerative dentistry for applications such as regenerating dentin-pulp complexes, periodontal tissues, and alveolar bone.[14] HDPMSCs are known for their relative genomic stability during in vitro expansion and their ability to differentiate into various cell lineages such as osteocytes, chondrocytes, myocytes, adipocytes, and neurons. They have been considered as a promising source for tissue repair and regenerative medicine due to their multipotency and ease of isolation through non-invasive procedures.[15]

HDPMSCs are increasingly recognized for their significant regenerative potential in various medical applications, particularly in dental and periodontal tissue regeneration. Their exceptional features, including the capability to differentiate into multiple lineages, make them a valuable resource in regenerative medicine.[14] Therefore, this article purposed to review the regenerative potency of HDPMSCs.

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METHODS

For the purpose of this study, we investigated the English-language literature on regenerative potential of HDPMSCs by using the databases of Science Direct, PUBMED, and Google Scholar. Research and literary studies conducted between 2019 and 2024 were included. It was determined that regenerative potential, medical treatments, and mesenchymal stem cells derived from human dental pulp were the search parameters.

REVIEW

Human Dental Pulp Mesenchymal Stem Cells

HDPMSCs are a type of MSCs gained from human pulp tissue. These cells are thought to originate from neural crest cells that migrate during early development.[16] Isolating HDPMSCs is relatively non-invasive, as they can be derived from teeth extracted for various reasons, such as periodontal disease, tooth decay, or orthodontic procedures. This accessibility offers a key advantage over bone marrow-derived stem cells, which require more invasive extraction methods.

MSC-like cells from dental pulp exhibit typical MSC properties, including the ability to form colonies, express specific surface markers, and differentiate in multiple directions.[17] Similar to other MSCs, HDPMSCs have a fibroblast-like shape, show strong adhesion to solid surfaces, and are capable of colony formation in vitro. They express mesenchymal stem cell markers, while hematopoietic markers are absent. Additionally, HDPMSCs express several pluripotency markers, such as Nanog, Oct4, SSEA, Sox2, and c-Myc. Besides these stemness markers, they also express bone-related proteins, including dentin matrix protein-1 (DMP-1), alkaline phosphatase (ALP), osteopontin (OPN), osteocalcin (OCN), type I collagen, dentin sialophosphoprotein (DSPP), and osterix (Osx). Through a range of factors, including extracellular matrix proteins, transcription factors, growth factors, and receptors, HDPMSCs can differentiate into both mesodermal and non-mesodermal cell types, such as adipocytes, osteoblasts, odontoblasts, corneal epithelial cells, cardiomyocytes, chondrocytes, hepatocytes, neurons, and melanocytes.[18] Dental pulp stem cells, commonly sourced from the third molars, are the most common dental mesenchymal stem cells.[19] However, recent findings indicate that tooth germ may actually be a richer source of dental mesenchymal stem cells.

Regenerative Potential

MSCs are a type of adult stem cell with significant regenerative potential, making them a focal point in regeneration. They are characterized by their capacity to differentiate and self-renew into various specialized cell types, including chondrocytes, osteoblasts, and adipocytes. This versatility, combined with the immunomodulatory capacity, places MSCs as promising candidates for therapeutic applications across a range of medical conditions.[20]

DISCUSSION

HDPMSCs are adult stem cells obtained from dental pulp tissue, originating from neural crest. These cells, which include hHDPSCs and SHEDs, have demonstrated potential in regenerative dentistry for applications such as the regeneration of dentin-pulp complexes, periodontal tissues, and alveolar bone.[14] HDPMSCs are valued for their genomic stability during in vitro expansion and their capacity to differentiate into diverse cell types, including chondrocytes, osteocytes, adipocytes, myocytes, and neurons. Due to their multipotency and ease of non-invasive isolation, they are regarded as a promising source for tissue repair and regenerative medicine.[15] Increasingly, HDPMSCs are recognized for their extensive regenerative capabilities across various medical applications, especially in dental and periodontal tissue regeneration. Their capacity to differentiate into multiple cell types highlights their value as a resource for regeneration.[14]

HDPMSCs exhibit remarkable differentiation capabilities and regenerative potential, making them a focal point in regenerative medicine. These cells are derived from tooth pulp and possess high proliferation potency along with multilineage differentiation abilities, allowing them to transform into many cell types, including chondrocytes, osteoblasts, and adipocytes. The osteogenic differentiation pathway is particularly significant as it enables HDPMSCs to form bone tissue, which is crucial for applications in bone repair and regeneration. Studies have demonstrated that HDPMSCs can be influenced by their microenvironment; for instance, co-culturing with other stem cells can enhance their osteogenic differentiation and mineralization potential significantly compared to monoculture conditions.[21] Furthermore, HDPMSCs have been shown to express key osteogenic markers such as ALP and OPN, indicating their capability to contribute to bone formation.[22]

The regenerative potential of HDPMSCs is augmented by their immunomodulatory properties, which allow them to interact favorably with the immune system, reducing inflammation and promoting healing in damaged tissues. Their accessibility, due to the ease of obtaining dental pulp tissue, along with their ability for cryogenic preservation, positions HDPMSCs as a valuable resource in regenerative therapies for conditions like periodontitis and other maxillofacial disorders. Recent research has explored the use of pharmacological agents like acetylsalicylic acid (aspirin) to further stimulate the osteogenic differentiation of HDPMSCs, showing promising results in enhancing bone regeneration in experimental models.[23] Overall, the unique characteristics of HDPMSCs not only underscore their potential in tissue engineering but also highlight their role in advancing therapeutic strategies across various medical fields.

The secretome of HDPMSCs plays crucial role in their regenerative potential, comprising a complex mixture of bioactive molecules that facilitate various therapeutic effects. This secretome includes a variety of cytokines, chemokines, growth factors, and extracellular

vesicles (EVs) that contribute to the cells' paracrine signaling capabilities. Notably, HDPMSCs secrete higher concentrations of key factors such as vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1), RANTES, and granulocyte-macrophage colony-stimulating factor (GM-CSF) compared to other stem cell sources like adipose and bone marrow derived stem cells. These factors are instrumental in promoting anti-apoptotic effects and enhancing neuroprotection, particularly in neurodegenerative conditions. Additionally, proteins such as alpha-2-macroglobulin (A2M) and neprilysin are involved in modulating neuroinflammatory responses and degrading amyloid-beta plaques, which are significant in Alzheimer's disease pathology. The presence of neurotrophic factors like glial cell-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) further underscores the neuroprotective capabilities of HDPMSCs, aiding in neuronal survival and recovery following injuries. The secretome also influences various signaling pathways, including the PI3K/Akt and MAPK pathways, enhancing neuronal protection and promoting recovery in models of spinal cord injury. Furthermore, the composition of the secretome can be influenced by the microenvironment, such as hypoxic conditions, which can enhance the production of angiogenic and anti-inflammatory mediators. Overall, the diverse array of molecules presents in the HDPMSC secretome not only facilitates tissue repair and regeneration but also positions these cells as valuable resources in regenerative medicine applications across multiple domains, including neurology and orthopedics.[24]

HDPMSCs are increasingly recognized for their significant potential in endodontic treatments, particularly for regeneration of dental tissues and the management of pulp-related diseases. One of the primary applications of HDPMSCs in endodontics is the regeneration of pulp-dentine complex, which is crucial for maintaining tooth vitality after trauma or carious lesions have compromised the pulp tissue. The regenerative capabilities of HDPMSCs stem from their ability to differentiate into odontoblast-like cells, which can produce dentin-like matrix, thereby facilitating the repair and regeneration of damaged dental structures. Additionally, the secretome derived from HDPMSCs contains a rich array of cytokines and growth factors, such as VEGF and transforming growth factor-beta (TGF-β), which promote angiogenesis and stimulate the proliferation and differentiation of surrounding cells. This secretome not only enhances the healing process but also exerts anti-inflammatory effects that are beneficial in managing periapical inflammation and promoting tissue regeneration. Furthermore, HDPMSCs can be employed in treating necrotic teeth through regenerative endodontic procedures, where they are used to replace damaged pulp tissue with a biologically active substitute that supports natural healing processes. Recent studies have highlighted their effectiveness in clinical settings, showing promising outcomes in terms of tooth vitality and structural integrity following treatment. Overall, the incorporation of HDPMSCs into endodontic therapies represents a paradigm shift towards more biologically-based approaches that aim to restore not just function but also the natural architecture and vitality of dental tissues.[14]

HDPMSCs hold immense potency in endodontic treatments, particularly when coupled with the regulation of dentin sialophosphoprotein (DSPP). DSPP is crucial for the formation and mineralization of dentine, which is essential for tooth repair and regeneration after pulp damage or caries lesions. The integration of HDPMSCs into endodontics leverages their ability to differentiate into odontoblast-like cells, thereby facilitating the production of new dentinal matrix rich in DSPP. This process mimics natural dentinogenesis, where undifferentiated stem cells mature into specialized odontoblasts capable of secreting proteins necessary for dentin formation.[14]

In regenerative endodontic procedures aimed at treating immature permanent teeth with necrotic pulps, HDPMSCs play a pivotal role. These stem cells can replace damaged pulp tissue with biologically active substitutes that support continued root development and restoration of functional pulpal tissue. By promoting angiogenic differentiation through growth factors like VEGF in secretome, these cells enhance blood vessel formation around the injured area, providing a conducive environment for healing and regeneration. Additionally, the anti-inflammatory properties of the hDPSC-secretome help manage periapical inflammation, ensuring a stable microenvironment favorable for tissue repair.[18]

HDPMSCs exhibit remarkable neuroprotective properties that are increasingly being recognized as beneficial in endodontic treatments, particularly for managing conditions involving pulp necrosis and trauma. The neuroprotection offered by HDPMSCs is primarily attributed to their secretome, which is rich in neurotrophic factors such as glial cell derived neurotrophic factor (GDNF), brain derived neurotrophic factor (BDNF), and nerve growth factor (NGF). These factors play a pivotal role in reducing apoptosis, promoting neuronal survival, and facilitating neural tissues regeneration. In endodontics, where the dental pulp is often compromised due to caries or trauma, the application of HDPMSCs can help restore the vitality of the pulp tissue by enhancing its regenerative capacity. For instance, studies have shown that the secretome from HDPMSCs can significantly reduce apoptosis in neuronal cells and promote their proliferation through modulation of critical signaling mechanisms such as MAPK and PI3K/Akt. This is particularly relevant in cases of pulp necrosis, where the preservation of remaining healthy nerve tissues is crucial for maintaining tooth sensitivity and function. Furthermore, the anti-inflammatory properties of HDPMSCs contribute to their neuroprotective effects by mitigating the inflammatory response that often accompanies pulpitis and other dental pathologies. This dual action—promoting neuronal health while simultaneously reducing inflammation—positions HDPMSCs as a valuable resource in regenerative endodontics, potentially leading to improved clinical outcomes such as enhanced healing of apical periodontitis and continued root formation in immature permanent teeth.

Overall, the integration of HDPMSCs into endodontic therapies not only aims at repairing damaged tissues but also emphasizes the importance of neuroprotection in achieving long-term success and functionality of dental structures.[25]

HDPMSCs are increasingly recognized for their significant role in bone protection and regeneration within medical treatments, particularly in the context of orthopedic and dental applications. These stem cells possess a remarkable capacity for osteogenic differentiation, which is essential for the repair and regeneration of bone tissue. The unique properties of HDPMSCs allow them to secrete a variety of bioactive molecules, including growth factors such as bone morphogenetic proteins (BMPs) and VEGF, which play critical roles in promoting bone healing and enhancing the formation of new bone tissue. Recent studies have demonstrated that when HDPMSCs are combined with ceramic nanocomposites—such as hydroxyapatite, titania, and calcium silicate—their osteogenic potential is significantly augmented. This combination not only provides a supportive scaffold for the HDPMSCs but also enhances their capability to differentiate into osteoblasts, as the cells in charge for bone formation. In experimental models, such as rabbit tibial defects, the application of HDPMSCs impregnated within these nanocomposites has shown promising results, including accelerated bone healing and improved osseointegration compared to control groups. Histological analyses reveal significant new bone formation in defect areas treated with HDPMSC-based therapies, highlighting their potential in clinical settings for treating bone defects or fractures. Furthermore, the paracrine effects of HDPMSCs—mediated through their secretome—contribute to a favorable microenvironment that promotes angiogenesis and reduces inflammation, both of which are vital for effective bone regeneration. This multifaceted approach positions HDPMSCs as a powerful tool in regenerative medicine, particularly for enhancing bone protection and repair in various medical treatments, thereby improving patient outcomes in orthopedic and dental practices.[26]

HDPMSCs are gaining popularity for their potency in cardiovascular repair, especially in the context of treating ischemic heart disease and myocardial infarction. These stem cells possess unique regenerative properties that enable them to contribute to cardiac tissue repair through several mechanisms. Upon transplantation, HDPMSCs can secrete many growth factors, including VEGF and hepatocyte growth factor (HGF), which are crucial for promoting the formation of new blood vessels or angiogenesis. This is particularly crucial in ischemic conditions where blood flow to the heart muscle is compromised, as enhanced angiogenesis can restore perfusion and support the survival of cardiomyocytes. Moreover, HDPMSCs have demonstrated the ability to modulate the immune response, reducing inflammation that often accompanies cardiac injury. By creating a more favorable microenvironment, these stem cells not only help in the repair of damaged myocardial tissue but also prevent further degeneration of cardiac function. Experimental studies shown that HDPMSCs can differentiate into cardiomyocyte-like cells under certain conditions, although their primary role appears to be more about paracrine signaling rather than direct differentiation into heart muscle cells. Additionally, HDPMSCs can enhance the recruitment and activation of endogenous stem cells within the heart, further supporting tissue regeneration. Clinical trials involving HDPMSC therapy have reported improvements in left ventricular ejection fraction and overall cardiac function in patients with heart failure or post-myocardial infarction, highlighting their therapeutic potential. Overall, the application of HDPMSCs in cardiovascular repair represents a promising strategy in regenerative medicine, aiming to improve outcomes for patients suffering from various forms of heart disease by leveraging the body's intrinsic healing processes.[27]

HDPMSCs are characterized by their non-immunogenic nature, meaning they do not provoke a significant immune response when transplanted into a recipient. This characteristic is crucial in regenerative medicine, especially for allogeneic transplants, where cells from a donor are used. The non-immunogenicity of HDPMSCs reduces the risk of rejection and allows for easier integration into the host tissue.[28] In addition to being non-immunogenic, HDPMSCs exhibit potent immunosuppressive properties. They can modulate the immune response by inhibiting the proliferation of T cells, particularly CD4+ T cell subsets. Studies have shown that HDPMSCs significantly reduce the activation and expansion of these T cells, which are critical players in the immune response. This immunomodulation helps create a favorable environment for tissue regeneration by minimizing inflammation and promoting healing.[29] HDPMSCs utilize paracrine signaling to exert their immunomodulatory effects. They secrete various cytokines and growth factors that influence neighboring cells and modulate immune responses. For instance, the secretion of factors like IL-10 can skew T cell polarization towards regulatory T cells (Tregs), which further suppresses inflammatory responses and promotes a healing environment. This ability to communicate with other cells enhances their therapeutic potential in regeneration.[30,31]

Conclusion

HDPMSCs hold immense potential in regenerative dentistry and regenerative medicine due to their unique properties, including multipotency, immunomodulatory capabilities, and ease of non-invasive collection. Derived from the neural crest, HDPMSCs can differentiate into multiple cell types such as chondrocytes, osteoblasts, and neurons and are increasingly recognized for their applications in dental, orthopedic, neurological, and cardiovascular therapies. In dental and periodontal regeneration, HDPMSCs contribute significantly to the repair of the pulp-dentin complex, bone tissue, and periodontal structures, supported by their robust osteogenic and angiogenic potential. The secretome of HDPMSCs, rich in cytokines, growth factors, and neurotrophic factors, plays a key role in their regenerative

effects, offering anti-inflammatory, neuroprotective, and healing-promoting benefits. These stem cells also demonstrate strong immunomodulatory functions, reducing T cell activation and inflammation, which fosters a favorable environment for tissue repair. Their paracrine signaling, enhanced by factors like IL-10 and VEGF, enhances angiogenesis, neuroprotection, and cellular repair processes across diverse medical applications. Collectively, HDPMSCs offer a promising avenue for regenerative therapies in various fields by leveraging their unique characteristics and biological activities.

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