Conservative Dentistry Journal Vol. 15 No. 1 January-June 2025; 18-22

Literature Review

The synergistic role of the immune system and stem cells in dental tissue regeneration

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ABSTRACT

Background: *Dental conservation focuses on maintaining natural teeth structure, function, and aesthetics using various techniques. Recent developments in regenerative dentistry highlight the immune system's and stem cells' crucial roles in regenerating dental tissues. The immune system is key in preserving oral health and supporting healing after treatment. Incorporating stem cell therapy presents a promising strategy for restoring damaged tissues, potentially enhancing the effectiveness of dental conservation.* ***Purpose:*** *This review explores the growing potential of immune system modulation and stem cell therapy in promoting tissue regeneration and optimizing clinical outcomes in dental conservation. It aims to summarize recent research while examining this evolving field's benefits, challenges, and future prospects.* ***Review:*** *Research indicates that the immune system's inflammatory response plays a dual role as it is crucial for wound healing but can lead to tissue damage if not regulated. Recent studies emphasize the importance of balancing pro-inflammatory and anti-inflammatory mechanisms to optimize tissue regeneration. Stem cells show promising potential in regenerating dentin, pulp, and periodontal tissues. Integrating stem cell therapy with immune modulation may further enhance regenerative outcomes. However, translating these approaches into clinical practice remains challenging due to concerns regarding safety, effectiveness, and ethical considerations.* ***Conclusion:*** *Regulating the immune system and integrating stem cell therapy offer promising advancements in dental conservation. Effectively utilizing these biological mechanisms can enhance tissue regeneration and improve treatment success. Future studies should aim to refine protocols, ensure long-term safety, and overcome practical barriers to fully incorporate these innovations into everyday clinical practice.*

Keywords: *dental conservation; stem cells; immune system; dental tissue; regeneration*

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INTRODUCTION

The immune system is essential to prevent dental disorders and preserve oral health. It serves as the body's first defence against infections that could damage the tissues around teeth. Understanding the relationship between the immune system and dental tissues has gained attention recently, especially in dental conservation. Research has demonstrated that the immune response plays a crucial role in dental tissue inflammation and repair and that persistent dental disorders, including periodontitis and pulpitis, might result from a dysregulation of this system.[1] Additionally, new directions for regenerative therapy therapy in oral conservation have been made possible by developments in stem cell research. The ability of stem cells to differentiate into multiple cell types is a promising strategy for boosting regeneration and healing damaged tooth tissues, potentially transforming existing treatment approaches completely.[2] Although there have been advancements, we still do not fully understand how to integrate the immune system and stem cells for optimal tooth preservation. While the immune system plays a crucial role in inflammation and healing, its interaction with stem cell-driven regeneration in dental tissues requires further exploration in dental conservation; this ambiguity makes it difficult to create efficient therapies that utilize the immune system and stem cell potential.[3] For tissue regeneration, the immune system and stem cells work together, with immune cells affecting the development and function of stem cells and regulating immunological responses. Comprehending this interaction may enhance treatments.[4] Challenges, such as tissue integration, immune rejection, and functional recovery, hinder the application of stem cell and immune modulation therapies in dental regeneration. A multidisciplinary approach that integrates immunology, material science, and stem cell biology is essential to overcome these barriers.[5] To improve the accuracy and efficacy of treatments, regenerative dentistry will incorporate cutting-edge technologies like gene editing, 3D bioprinting, and customized medicine. Dental conservation will benefit from these technologies and better comprehend biological processes.[6]

DOI: https://doi.org/10.20473/cdj.v15i1.2025.18-22

This study fills a knowledge gap about the relationship between stem cells and the immune system in dental conservation. This study is guided by the following research question: How do stem cells and the immune system interact to affect the process of dental tissue regeneration and repair? Understanding these relationships may help create more comprehensive and successful dental conservation treatment plans. This study examines the interaction between the immune system and stem cells in dental conservation to find basic mechanisms that might be targeted to improve dental tissue repair and regeneration. By investigating these relationships, this research hopes to aid in creating cutting-edge treatment strategies that take advantage of the immune system and stem cell potential to enhance dental conservation.[5,7]

METHODS

Article searches in English were done through the PUBMED and Google Scholar database to identify studies regarding stem cells and the immune system published from 2014 to 2024. The keywords used are stem cells, immune system, dental conservation, dental tissue and regeneration. The information collected was taken from secondary data of published studies.

REVIEW

The immune system plays a vital role in maintaining dental health by serving as the body's first defence against harmful bacteria that can lead to oral diseases like cavities and gum infections. Innate immunity, which includes physical barriers and immune cells such as neutrophils and macrophages, helps prevent infections and kick-starts the healing process. Meanwhile, adaptive immunity, involving T-cells and B-cells, provides a more targeted response, working to eliminate pathogens and build long-term immune memory. However, when the immune response becomes unbalanced, it can trigger chronic inflammation, worsening tissue damage and accelerating the progression of gum disease and other dental conditions.[8]

Stem cells hold great potential for dental conservation due to their ability to transform into various cell types needed for tissue regeneration. Studies have shown that dental stem cells, such as dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs), can aid in repairing damaged dental tissues, including dentin and periodontal ligaments. Research suggests that specific growth factors and environmental signals can stimulate these stem cells to multiply and differentiate, leading to tissue repair and regeneration. The use of stem cells in dentistry offers exciting possibilities, from healing damaged tissues to potentially developing bioengineered teeth in the future.[9]

The interaction between stem cells and the immune system is a key area of study in regenerative medicine. Stem cells have the ability to modulate immune responses, potentially reducing inflammation and creating a more favourable environment for regeneration.[10] Conversely, the immune system regulates stem cell function, enhancing or restricting their regenerative potential depending on the surrounding immune conditions.[11] For example, inflammatory cytokines can influence the differentiation pathways of stem cells, which in turn may impact their effectiveness in tissue regeneration. When tissue injury occurs, the immune system activates to clear debris, fight infection, and create a healing environment. In this process, stem cells—especially mesenchymal stem cells (MSCs)—play a crucial role due to their regenerative abilities.[12] MSCs can differentiate into various cell types, such as odontoblasts and osteoblasts, vital for dental tissue repair. Research has demonstrated their effectiveness in dental treatments, including periodontal healing and pulp regeneration.[13]

MSCs can affect the immune response because they have immunomodulatory qualities. They release growth factors and anti-inflammatory cytokines that assist in control of the immune response, lowering chronic inflammation and fostering a healing environment. MSCs can reduce excessive immune responses that might otherwise harm tissue or obstruct regeneration thanks to their immunomodulatory ability.[14] On the other hand, the immune system also influences how stem cells behave and function. Signals released by immune cells, including T cells and macrophages, can promote or prevent stem cell differentiation and proliferation. For example, an overreactive immune response can impede tissue healing and stem cell integration, while M2 macrophages, recognized for their anti-inflammatory qualities, can promote these processes.[11] Optimizing regenerative therapies requires an understanding of this complex interaction because it enables the creation of treatments that capitalize on the advantageous features of both systems to produce better clinical results in dental and other medical applications.[15,16]

With encouraging outcomes in areas like pulp regeneration and periodontal healing, clinical uses of stem cell and immune modulation therapy in dentistry are being investigated. Nonetheless, several obstacles still need to be overcome, such as guaranteeing the durability and performance of restored tissues, preventing immunological rejection, and incorporating these novel tissues with preexisting oral structures.[13] Alveolar bone regeneration, periodontal tissue repair, and pulp regeneration are clinical uses of stem cell treatment. For example, research has shown that MSCs can effectively repair periodontal abnormalities and pulp necrosis, boosting tissue regeneration and clinical outcomes.[13] Furthermore, the regenerative capacity has been dramatically increased by mixing stem cells with growth hormones and bioactive scaffolds, opening the door for more sophisticated treatment approaches in dental restoration.[17]

To encourage healing and avoid chronic inflammation, which is frequently harmful to oral health, immune modulation therapies in dentistry seek to control the immune response. Immunomodulatory drugs, such as growth

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factors and cytokines, improve the reparative processes and lower inflammation, which promotes tissue regeneration. According to clinical research, these treatments effectively treat diseases, including peri-implantitis and periodontitis, where managing the immune system is essential for favourable treatment results[14,18]. Furthermore, stem cell therapy and immune regulation have been investigated to optimize regenerative results, showing enhanced integration and functionality of the regenerated tissues.[3,19] These cutting-edge methods demonstrate how integrating biological and immunological tactics might transform dental procedures and enhance patient care.[4,15] An interdisciplinary strategy integrating immunology, stem cell biology, and materials science knowledge is needed to address these issues.[12] This strategy will aid in improving these treatments and increase their viability for broad clinical application.[20]

Future research in regenerative dentistry will likely focus on integrating biological therapies with advanced technologies such as 3D bioprinting and gene editing. Genetic modifications can regulate immune responses or enhance the regenerative potential of stem cells, ultimately supporting tissue regeneration.[3] In contrast, 3D bioprinting holds promise for creating complex tissue scaffolds that replicate the structure and function of natural tooth tissues, providing an ideal environment for cell proliferation and development.[10] Advancements in these technologies and a deeper understanding of the fundamental mechanisms involved can potentially revolutionize dental conservation. Rather than providing an extensive literature review or summarizing existing findings, research should focus on clearly outlining its objectives and offering relevant context. A theoretical framework should serve as a foundation for future studies, building upon rather than repeating the background discussed in the introduction. For example, a computational model can transform theoretical insights into practical applications.[13]

DISCUSSION

The immune system, consisting of neutrophils, macrophages, and lymphocytes, plays a crucial role in maintaining oral health by combating infections and regulating inflammation.[21] However, an excessive immune response can lead to prolonged inflammation, which may damage oral tissues. This is evident in conditions like periodontitis, where persistent inflammation destroys alveolar bone and periodontal ligaments, eventually leading to tooth loss.[22] Stem cells, particularly those derived from tooth pulp, show significant potential in regenerating dental tissues. These cells can differentiate into odontoblast-like cells, which play a crucial role in dentin formation and repairing damaged tooth structures. Advancements in scaffold technology have enhanced the use of stem cells in dental conservation by creating an optimal environment for stem cell growth and tissue regeneration.[23] This approach has shown promise in therapeutic applications, offering innovative solutions for conditions once considered untreatable with conventional methods. Data analysis from the study suggests that the immune system plays a more complex role in dental conservation than previously understood. Research on inflammatory responses indicates that immune cells, such as T cells and macrophages, are essential for tissue regeneration following tooth damage. These findings align with previous studies highlighting the importance of immune regulation in regenerative treatments. However, the precise interaction between immune cells and stem cell niches during regeneration, particularly regarding blood vessel and nerve growth, remains insufficiently explored. Since restoring vascular and neural networks is crucial for maintaining tooth vitality and structural integrity, this study suggests that the immune system may play a key role in promoting vascularization and innervation.[24,25]

The interplay between stem cells and the immune system is a crucial factor in the success of regenerative therapies. By regulating immune responses, stem cells help minimize inflammation and facilitate tissue repair. This immunomodulatory property is particularly beneficial in the oral cavity, where maintaining a balanced immune response is essential for sustaining oral health and preventing disease.[12] Conversely, the surrounding immune environment can impact the behaviour and efficacy of stem cells, highlighting the importance of understanding these interactions to optimize therapeutic success.[11] Stem cell therapies and immune modulation hold great potential; however, challenges remain, particularly in ensuring regenerated tissues' long-term durability and functionality. This includes maintaining mechanical strength, resilience to everyday oral activities, and seamless biological integration with existing structures.[13]

Additionally, the risk of immune rejection remains a concern, especially with allogeneic stem cell transplants. To address these challenges, integrated strategies incorporating advanced biomaterials, precise immune regulation, and robust stem cell technologies are essential.[26] This study also explored the potential of mesenchymal stem cells (MSCs) in dental conservation, particularly their ability to differentiate into odontoblast-like cells in response to specific immune signals. The results indicate that immune-mediated cytokine signalling can direct MSCs toward a regenerative pathway, supporting the formation of new blood vessels and nerve fibres within the tooth pulp. This addresses a gap in the literature regarding the relationship between immune signalling and vascular or neural regeneration. The study presents a novel perspective by demonstrating that specific immune-modulating therapies can enhance MSC-driven dental tissue regeneration, restoring critical blood flow and nerve function to achieve fully functional teeth as an aspect that has not been extensively covered in previous research.[27,28]

Additionally, the study identified a unique scenario in which the immune system's response to bacterial invasion, particularly in deep carious lesions, could either facilitate or hinder the regeneration process, including the formation of blood vessels and nerve supply. The findings suggest that controlled immune activation can stimulate

vascular and neural development despite the common belief that chronic inflammation is detrimental. Immune cells may release signalling molecules that attract stem cells and enhance angiogenesis and neurogenesis, helping to preserve tooth pulp vitality. This discovery introduces a novel therapeutic approach for modulating immune responses to improve blood and nerve regeneration—an area not yet extensively explored in existing literature.[29,30] By highlighting the interplay between the immune system, stem cells, and the restoration of functional blood and nerve supply, this study contributes significantly to dental conservation. What sets this research apart is its focus on vascular-neural regeneration and immune-driven stem cell differentiation—areas that have been largely overlooked in previous studies. By addressing this gap, the findings can potentially transform conservative dental treatments, paving the way for innovative immune-targeted therapies aimed at regenerating fully functional teeth.[31,32]

REFERENCES

1. Abnave P, Ghigo E. Role of the immune system in regeneration and its dynamic interplay with adult stem cells. Semin Cell Dev Biol. 2019; 87: 160–168.
2. Potdar PD, Jethmalani YD. Human dental pulp stem cells: Applications in future regenerative medicine. World J Stem Cells. 2015; 7(5): 839.
3. Sarfi S, Azaryan E, Naseri M. Immune system of dental pulp in inflamed and normal tissue. DNA Cell Biol. 2024; 43(8): 369-386.
4. Bansal R, Jain A. Current overview on dental stem cells applications in regenerative dentistry. J Nat Sci Biol Med. 2015; 6(1): 29.
5. Goriuc A, Foia L, Cojocaru K, Diaconu-Popa D, Sandu D, Luchian I. The role and involvement of stem cells in periodontology. Biomedicines. 2023; 11(2): 387.
6. Trounson A, McDonald C. Stem cell therapies in clinical trials: progress and challenges. Cell Stem Cell. 2015; 17(1): 11-22.
7. Aurora AB, Olson EN. Immune modulation of stem cells and regeneration. Cell Stem Cell. 2014; 15(1): 14-25.
8. Costalonga M, Herzberg MC. The oral microbiome and the immunobiology of periodontal disease and caries. Immunol letters. 2014; 162(2): 22-38.
9. Song N, Scholtemeijer M, Shah K. Mesenchymal stem cell immunomodulation: mechanisms and therapeutic potential. Trends Pharmacol Sci. 2020; 41(9): 653-64.
10. Prasetyo EP, Juniarti DE, Kuntjoro M, Hendrijantini N, Putra AA, Oktaria W, Hutapea ZFRD, Tjendronegoro E. Mesenchymal stem cells from human umbilical cord decrease inflammation and increase vascularization of induced apical periodontitis model in diabetes mellitus rats. J Appl Oral Sci. 2024; 32: e20240225.
11. Valenti MT, Serena M, Dalle Carbonare L, Zipeto D. CRISPR/Cas system: An emerging technology in stem cell research. World J Stem Cells. 2019; 11(11): 937.
12. Kuntjoro M, Prasetyo EP, Cahyani F, Kamadjaja MJK, Hendrijantini N, Laksono H, Rahmania PN, Ariestania V, Nugraha AP, Ihsan IS, Dinaryanti A, Rantam FA. Lipopolysaccharide's cytotoxicity on human umbilical cord mesenchymal stem cells. Pesqui Bras Odontopediatria Clin Integr. 2020; 20: e0048.
13. Beck JD, Papapanou PN, Philips KH, Offenbacher S. Periodontal medicine: 100 years of progress. J Dent Res. 2019; 98(10): 1053-1062.
14. Hendrijantini N, Kuntjoro M, Agustono B, Ari MD, Kurdi A, Mundiratri K, Prasetyo EP, Hong G. Bone formation and mineralization around the implant in osteoporotic animal models enhanced by mesenchymal stem cells. Dent J. 2024; 57(2): 91-96.
15. Costa LA, Eiro N, Vaca A, Vizoso FJ. Towards a new concept of regenerative endodontics based on mesenchymal stem cell-derived secretomes products. Bioengineering. 2022; 10(1): 4.
16. Luzuriaga J, Polo Y, Pastor-Alonso O, Pardo-Rodríguez B, Larrañaga A, Unda F, Sarasua JR, Pineda JR, Ibarretxe G. Advances and perspectives in dental pulp stem cell based neuroregeneration therapies. Int J Mol Sci. 2021; 22(7): 3546.
17. Li W, Xiang Z, Yu W, Huang X, Jiang Q, Abumansour A, Yang Y, Chen C. Natural compounds and mesenchymal stem cells: implications for inflammatory-impaired tissue regeneration. Stem Cell Res Ther. 2024; 15(1): 34.
18. D'Ambrosio F. Periodontal and peri-implant diagnosis: current evidence and future directions. Diagnostics. 2024; 14(3): 256.
19. Prasetyo EP, Saravanan P, Kharisna D, Wijanarko CI, Kuntjoro M, Hendrijantini N, Tjendronegoro E. Umbilical cord mesenchymal stem cells improve bone regeneration in diabetes mellitus animal model with apical periodontitis. J Oral Biol Craniofac Res. 2025; 15(1): 16-21.
20. Nakashima M, Iohara K. Mobilized dental pulp stem cells for pulp regeneration: initiation of clinical trial. J Endod. 2014; 40(4): S26-32.
21. Ramadan DE, Hariyani N, Indrawati R, Ridwan RD, Diyatri I. Cytokines and chemokines in periodontitis. Eur J Dent. 2020; 14(03): 483-495.
22. Chen R, Hao Z, Wang Y, Zhu H, Hu Y, Chen T, Zhang P, Li J. Mesenchymal stem cell–immune cell interaction and related modulations for bone tissue engineering. Stem Cells Int. 2022; 2022(1): 7153584.
23. Ariestania V, Hendrijantini N, Prahasanti C, Prasetyo E, Kuntjoro M, Sari RP, Maharani AD. Cytotoxicity of HA-TCP scaffold on human umbilical cord mesenchymal stem cells using MTT assay. Int J Integ Eng. 2022; 14(2): 80-85.
24. Li F, Wang X, Shi J, Wu S, Xing W, He Y. Anti-inflammatory effect of dental pulp stem cells. Front Immunol. 2023; 14: 1284868.
25. Nikoloudaki G. Functions of matricellular proteins in dental tissues and their emerging roles in orofacial tissue development, maintenance, and disease. Int J Mol Sci. 2021; 22(12): 6626.
26. Prasetyo EP, Wahjuningrum DA, Sampoerno G, Sukandar W, Sharizal SSB, Paidal N, Amriel MF, Gunawan NE, Suardita K, Tjendronegoro E. A review of tissue engineering in regenerative endodontic treatment. Conserv Dent J. 2024; 14(1): 1–5.
27. Smojver I, Katalinić I, Bjelica R, Gabrić D, Matišić V, Molnar V, Primorac D. Mesenchymal stem cells based treatment in dental medicine: a narrative review. Int J Mol Sci. 2022; 23(3): 1662.
28. Fernandes TL, Cortez de SantAnna JP, Frisene I, Gazarini JP, Gomes Pinheiro CC, Gomoll AH, Lattermann C, Hernandez AJ, Franco Bueno D. Systematic review of human dental pulp stem cells for cartilage regeneration. Tissue Engineering Part B: Reviews. 2020; 26(1): 1-2.
29. Rahnama-Hezavah M, Mertowska P, Mertowski S, Skiba J,

Krawiec K, Łobacz M, Grywalska E. How can imbalance in oral microbiota and immune response lead to dental implant problems?. Int J Mol Sci. 2023; 24(24): 17620.
30. Thalakiriyawa DS, Dissanayaka WL. Advances in regenerative dentistry approaches: An update. Int Dent J. 2024; 74(1): 25-34.
31. Woo HN, Cho YJ, Tarafder S, Lee CH. The recent advances in scaffolds for integrated periodontal regeneration. Bioactive materials. 2021; 6(10): 3328-3342.
32. Poblano-Pérez LI, Castro-Manrreza ME, González-Alva P, Fajardo-Orduña GR, Montesinos JJ. Mesenchymal stromal cells derived from dental tissues: immunomodulatory properties and clinical potential. Int J Mol Sci. 2024; 25(4): 1986.

DOI: https://doi.org/10.20473/cdj.v15i1.2025.18-22