

Exploring Immunomodulatory Approaches in Dentistry: A Comprehensive Review

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ABSTRACT

Immunomodulators alter immune responses and are becoming important therapeutic agents in dentistry that may help treat various oral conditions. They fall into two categories: immunostimulants, which improve immunological function, and immunosuppressants, which lower immune activity. Immunomodulators are essential for regulating inflammation, preventing bone loss, and encouraging tissue regeneration in periodontics. While antibacterial therapy targets harmful bacteria without upsetting the beneficial microbiome, probiotic therapy, on the other hand, aids in restoring microbial equilibrium. Drug therapies, including both pharmacological agents and natural compounds, regulate immune cell function to reduce inflammation and tissue damage. Stem cell-based treatments-especially those using mesenchymal stem cells-help to promote periodontal repair. Gene therapy is a promising approach to modifying immune-related genes to enhance healing and reduce inflammation. These developments demonstrate the important role that immunomodulation plays in treating periodontal disease and provide fresh approaches to enhancing patient outcomes and promoting tissue regeneration.

Introduction to Immunomodulators in Dentistry

Immunomodulators are substances that can alter the body's immune response by either suppressing it or enhancing it for therapeutic purposes ¹. Currently, they are becoming immensely popular in the fields of dentistry, owing to their potential to manage numerous oral diseases and conditions. They can be utilized in the treatment of autoimmune disorders like Oral Lichen Planus, healing following surgical procedures, and even in the management and regulation of periodontitis. Since they control the inflammatory response, immunomodulators play a vital role in improving patient outcomes and overall health.

Classification

Immunomodulators can be chiefly classified into two main categories:

Immunosuppressants: They suppress the body's immune response. For instance, Cyclosporine, Azathioprine, Prednisolone, Sirolimus, Adalimumab and others ^{1,2}.

Immunostimulants: They enhance the body's immune response to help it fight infections and diseases. For instance, Vaccines, Cytokines, Lipopolysaccharides, etc. ^{1,2}.

Mechanism of Action

Immunomodulators have a complex mechanism of action including suppression of innate immune cells ¹, inhibition of gene expression ², neutralization of cytokines ², modulation of adaptive immune response involving activation of B-cells and T-cells to target specific pathogens, and enhancement of immune surveillance.

Approaches

Immunomodulation can be utilized in various ways by changing the physical properties like porosity and surface roughness or by adding minerals that lead to M1-M2 transition promoting neovascularization and healing ³.

Role in Dentistry

Immunomodulators play a very varied and diverse role in all fields of dentistry. They promote faster healing, minimize risk of post-surgical complications, help in reducing pain and inflammation, aid in the integration of implants with surrounding tissues and prevent the body from rejecting a new tissue or grafts ³. They promote tissue regeneration by modulating the immune response, act as adjuncts to mechanical debridement procedures such as scaling and root planning, reduce bacterial load in the periodontal pocket, and help prevent progression of periodontal diseases ¹. They control inflammation in the peri-apical region and can be used alongside traditional endodontic treatments.

Applications of Immunomodulators in Periodontics

Periodontics has come a long way, blending traditional dental care with modern medical advancements. One exciting area of progress is the use of immunomodulators—substances that help regulate the immune system—in treating oral health issues ^{1,2}. Immunomodulators help reduce bone loss by controlling the osteolytic and inflammatory processes, preventing or slowing the progression of periodontal diseases. The immune microenvironment in periodontitis plays a vital role in disease progression, where a delicate balance between inflammation and healing is crucial. Innovative approaches such as immunomodulatory drugs, stem cell therapy, and gene therapy offer promising avenues to not only reduce inflammation but also promote the regeneration of periodontal tissues ³.

Probiotic Therapy: Balancing the Microbial Ecosystem

Microbial therapies, particularly probiotic therapy, are emerging as innovative approaches in periodontics, focusing on restoring balance to the oral microbiome and managing periodontal diseases. By introducing beneficial microorganisms, probiotics help counteract harmful bacteria, reduce inflammation, and support tissue healing. This therapy can improve microbial metabolism and modulate local immune responses, potentially preventing conditions such as periodontitis and caries. While promising, the effectiveness of probiotics depends on factors like strain selection, dosage, and delivery method. Continued research is essential to understand their long-term benefits, positioning microbial therapies as a potential complement to traditional periodontal treatments ¹.

Antibacterial Therapy

Antibacterial therapy, a well-established treatment in medicine, is gaining renewed focus in periodontics, with a shift toward more precise targeting to avoid damaging beneficial bacteria and

to tackle antibiotic resistance. In periodontal care, antibiotics are used to eliminate bacteria that remain after mechanical treatments, helping to strengthen the body's defenses against infection. These therapies play an important role in managing oral infections and preventing the progression of periodontal diseases by specifically targeting harmful bacteria that cause inflammation and tissue damage. New approaches, such as targeted antimicrobial peptides, aim to neutralize these harmful bacteria while preserving the delicate balance of the oral microbiome, offering a more refined method of treating periodontal issues. Low-dose antibiotics, particularly doxycycline, have emerged as effective agents in modulating the immune response in periodontal disease. By inhibiting matrix metalloproteinase-8 (MMP-8) and reducing inflammatory markers such as interleukin-1 β , these treatments can lead to significant improvements in clinical outcomes, such as reduced pocket depths and enhanced clinical attachment levels. Additionally, studies such as the one by Ryan et al. on chemically modified tetracycline-3 further support the role of these therapies in promoting healing and managing inflammation in periodontal care ³.

Drug Therapy

Immunomodulators are increasingly recognized as valuable tools in managing periodontitis by influencing the body's immune response to infection and inflammation. In periodontal disease, immune cells such as neutrophils, macrophages, and T lymphocytes play central roles in driving inflammation and tissue damage. Neutrophils, while crucial in fighting infection, can also contribute to tissue harm through excessive oxidative stress, with natural compounds such as resveratrol and quercetin showing potential in mitigating this damage. Similarly, modulating the activity of monocytes and macrophages, which are involved in chronic inflammation and bone loss, can help control the inflammatory process. For example, agents such as proanthocyanidins and metformin have been found to regulate these cells and reduce the production of harmful cytokines. Additionally, certain compounds, including Astragaloside IV and curcumin can influence T lymphocyte activity, potentially restoring the balance between inflammatory and regulatory immune cells. Overall, immunomodulatory therapies offer a promising adjunctive approach to treating periodontitis by helping to regulate immune responses, reduce inflammation, and support tissue healing ¹.

Stem Cell-Based Therapies in Periodontal Regeneration and Immunomodulation

Mesenchymal stem cells (MSCs) have shown significant promise in the regenerative treatment of periodontal disease due to their ability to modulate inflammation and promote tissue repair. Various types of oral MSCs, such as periodontal ligament stem cells (PDLSCs), gingival mesenchymal stem cells (GMSCs), and dental pulp stem cells (DPSCs), are capable of reducing inflammation and enhancing healing through immunomodulatory actions. These cells adapt to the surrounding inflammatory environment, shifting from pro-inflammatory to anti-inflammatory responses as needed ¹.

Gene Therapy in Periodontal Disease Management

Gene therapy has emerged as a promising approach in treating periodontitis, offering potential for both immune modulation and tissue regeneration. By modifying genes related to inflammation and immune response, such as the P2X7 receptor and TIRAP, studies have shown improved healing and reduced inflammation in periodontal tissues. Additionally, gene therapies targeting inflammatory cytokines, such as IL-6 and TNF- α , have demonstrated benefits in controlling inflammation and promoting bone regeneration. Recent advancements in molecular therapies have

introduced effective strategies for managing inflammation in periodontal disease. Notably, injecting plasmid DNA encoding miR-200c into the gingiva has been shown to prevent gingival inflammation. Additionally, cathepsin K (Ctsk) regulates inflammation and osteoclast activity by reducing pro-inflammatory cytokines, while the P2X7 receptor (P2X7R) promotes bone tissue regeneration. Furthermore, utilizing the TNF receptor and immunoglobulin Fc (TNFR: Fc) helps decrease inflammatory cytokines, highlighting the potential of these targeted therapies to improve periodontal health ¹.

Immunomodulators in Oral Mucosal Diseases

Oral mucosal diseases often involve dysregulation of the immune system, leading to chronic inflammation and tissue damage. Immunomodulators play a crucial role in managing these conditions by either suppressing excessive immune responses or enhancing deficient ones. This section explores the application of immunomodulatory agents in the treatment of various oral mucosal diseases, including their mechanisms of action, therapeutic benefits, and limitations ¹.

Mechanism of Action of Immunomodulators

Immunomodulators exert their effects by modifying immune system activity, which can be broadly classified into immunosuppressive agents, immunostimulatory agents, and biologic agents. Immunosuppressive agents suppress hyperactive immune responses and are commonly used in autoimmune and inflammatory oral diseases ¹. Immunostimulatory agents enhance immune activity, though their application in oral mucosal diseases is less common. Biologic agents target specific immune pathways to modulate disease progression ⁴.

Immunomodulators in Specific Oral Mucosal Diseases

Oral Lichen Planus (OLP) is a chronic inflammatory disease with an autoimmune component. Immunomodulators used include topical and systemic corticosteroids such as dexamethasone and clobetasol, to reduce inflammation ¹¹. Calcineurin inhibitors, such as tacrolimus and cyclosporine serve as steroid-sparing agents, while biologic agents targeting TNF- α and IL-17 are emerging as potential treatments ^{4,12}.

Recurrent Aphthous Stomatitis (RAS) is characterized by recurrent ulcerations in the oral mucosa. Therapeutic options include thalidomide, which modulates TNF- α activity, colchicine, which reduces neutrophil migration, and topical corticosteroids to minimize inflammation and pain ⁶.

Pemphigus Vulgaris is an autoimmune blistering disorder involving antibody-mediated destruction of desmosomes. Immunomodulatory treatments include systemic corticosteroids as the first-line therapy ⁷. Rituximab, a CD20 monoclonal antibody, depletes B cells, while Azathioprine and Mycophenolate mofetil are used as steroid-sparing agents.

Mucous Membrane Pemphigoid is a chronic autoimmune condition characterized by subepithelial blistering. Treatment options include corticosteroids, both topical and systemic, to control inflammation, as well as immunosuppressants such as Dapsone and Cyclophosphamide to prevent disease progression ⁸.

Behçet's Disease is a multisystem inflammatory disorder with oral ulcers as a hallmark feature. Immunomodulatory therapies include interferon-alpha to regulate immune responses, colchicine for its anti-inflammatory effects, and TNF inhibitors, such as infliximab, for refractory cases ⁹.

Sjögren's Syndrome is an autoimmune disorder affecting salivary glands, leading to xerostomia (dry mouth). Immunomodulatory treatments include hydroxychloroquine for immune modulation,

biologic agents such as Belimumab targeting B cells, and Pilocarpine to stimulate saliva production¹⁰.

Advantages and Limitations of Immunomodulators

Immunomodulators are effective in controlling chronic inflammation and autoimmune responses. They improve patients' quality of life by reducing symptoms and preventing disease progression. Emerging biologic therapies offer targeted treatment with fewer systemic side effects. However, potential adverse effects include immunosuppression-related infections, and high costs, particularly for biologic agents, limit accessibility. Additionally, limited long-term data on newer immunomodulators necessitates further research¹.

Future Directions

The field of immunomodulation in oral mucosal diseases is rapidly evolving. Future research focuses on personalized medicine through genetic and biomarker-based treatment approaches, the development of novel biologic agents that provide more specific and safer immunomodulatory drugs, and nanotechnology-based drug delivery to enhance therapeutic efficacy while reducing side effects⁵.

Role of Immunomodulators in Endodontics and Caries Management

Endodontics

Antimicrobial medications currently being used in endodontics are becoming more and more resistant. Use of more effective antimicrobials can compromise healing and hence the outcome of the treatment as well. Therefore a good way of addressing this issue is to modify the inflammatory response of the body while using these highly effective medicines. The use of a different type of antimicrobials like peptides, propolis and nanomaterials is also an option which do not damage the tissue.

Recently, several studies reported that endodontic sealers exhibit immunomodulatory effects on inflammation and osteogenesis^{19,20}. This immunomodulatory effect can influence the behavior of immune cells and regulate the release of chemokines and cytokines through various immunological pathways. Root canal sealers (endodontic materials) commonly upregulate inflammatory cytokines, such as IL-6, IL-8, IL-12, and TNF- α , in the early stages of inflammation, leading to inhibition of cell growth and high cytotoxicity²¹. However, endodontic sealers can also downregulate the inflammatory cytokines, including IL-6 and TNF- α , induced by LPS, exhibiting a positive immunomodulatory effect²³. In addition, endodontic sealers promote fibroblast proliferation and tissue regeneration²². Moreover, calcium silicate-based sealers, such as MTA Fillapex, can also promote osteogenic differentiation ability and calcium nodule formation, which may help reduce bone resorption caused by inflammation²⁴. Therefore, endodontic sealers with immunomodulatory effects could be a promising strategy for promoting the healing and tissue regeneration process for regenerative medicine.

Caries Management

Immunomodulation plays a significant role in managing dental caries by modifying the immune response to oral bacteria. Various approaches, including vaccines, probiotics, and other immunotherapeutic strategies, have been explored to control and prevent caries.

Vaccines targeting dental caries have been developed using cell-surface antigens derived from oral bacteria. These vaccines have demonstrated protective effects in animal studies; however, only a limited number of studies have assessed their efficacy in humans. While active immunization presents potential benefits, local passive immunization may offer a safer alternative with fewer risks^{1,2,25}.

Probiotics have emerged as a promising and safe treatment for managing periodontitis and dental caries. They contribute to improved disease outcomes, reducing the need for antibiotics while also exhibiting preventive effects. By enhancing the balance of the oral microbiome, probiotics play a crucial role in caries management and overall oral health².

Anti-cytokine therapeutics have shown potential in limiting pulp inflammation and facilitating pulp healing. The topical application of anti-cytokine molecules is particularly advantageous, as it minimizes systemic adverse effects, making it a safer and more targeted approach for dental treatments²⁶.

Immunomodulatory biomaterials, such as iron oxide nanoparticles, have been explored for their ability to regulate the decomposition of hydrogen peroxide, a property that has been utilized in caries treatment. These biomaterials, along with other microbial therapies like targeted antibiotics, help restore microbial balance in the oral cavity, preventing oral diseases and promoting tissue regeneration. Integrating immunomodulators with microbial therapies provides a comprehensive approach to maintaining oral health and enhancing the effectiveness of caries management².

Applications of Immunomodulators in Dental Implantology and Bone Regeneration

Immunomodulators show encouraging results when it comes to integrating dental implants and accelerating wound healing following surgery¹. Although several studies have shown that immune reactions are unavoidable after biomaterial implantation, standard biomaterials are usually designed to reduce them. As a result, traditional biomaterials have frequently performed below expectations, which could result in immunological rejection and implant failure. As osteoimmunology has emerged, more and more data points to the immune system's crucial involvement in controlling the local microenvironment and affecting osteoblast activity, providing fresh perspectives on bone regeneration. With the goal of changing the design paradigm from conventional bioinert materials to functionalized biomaterials with immunoregulatory qualities, immunomodulatory biomaterials have become a viable tactic.

Numerous modification strategies that encourage osteogenesis through immune regulation have been compiled based on a review of the most recent literature. Although the majority of current research focuses mostly on macrophages as the primary immune cell target in regeneration techniques, these strategies exhibit encouraging findings and have potential implications in bone tissue engineering. The significance of macrophage-related growth factors and cytokines, as well

as studies of macrophage phenotypic transitions, in promoting osteogenesis has been investigated. Although bone immunomodulation is the result of the combined activity of various immune cells, the roles of other immune cells, such as neutrophils, T cells, and B cells, are still poorly understood in relation to their impact on bone biomaterials and functions. Future implant designs should take into account the holistic regulation of multiple immune cell types. Furthermore, a lot of research has simply detailed the phenotypic modifications in immune cells brought on by biomaterials without thoroughly clarifying the underlying mechanisms. In order to create better tissue-specific immunomodulatory implants, a more thorough investigation of the distinct functions and mechanisms of these immune cells in tissue regeneration processes is necessary.

Through chemical and physical changes or the addition of bioactive molecules, biomaterials have demonstrated early effectiveness in immune regulation and bone repair. Surface topography, stiffness, pore size, porosity, wettability, surface charge, chemical groups, and the delivery of bioactive compounds are some examples of these changes. Combining various modification techniques and building composite scaffolds may be the main path for creating next-generation implants in regenerative medicine because of the complexity of the immune cascade that occurs after biomaterial implantation, which means that a single biomaterial or modification strategy may not fully satisfy the requirements for effective bone immunomodulation.

Furthermore, it is still very difficult to properly control and manage the immune system to promote tissue repair. For example, under various inductive situations, macrophages can change their phenotypes, and the prompt transition of phenotypes is essential for tissue regeneration and effective wound healing. In a similar vein, the accurate administration of bioactive compounds is crucial. By combining immune-targeting technologies with carriers like lipids, microspheres, or nanoparticles, it is possible to deliver anti-inflammatory or osteogenic substances to specific locations with great efficacy, resulting in bone immunomodulatory effects. Additionally, new immunomodulatory techniques including gene editing, cell treatments, immunosuppressants, and regulators have a lot of potential to provide more accurate and efficient treatment methods in the field of bone tissue engineering. These forward-thinking strategies might more effectively address the multistage requirements of bone regeneration by integrating biomaterials with the dynamic interactions of the immune milieu²⁸

By controlling the immune response at the site of bone damage and enabling a balanced inflammatory phase that stimulates osteoblast activity and eventually aids in the development of new bone tissue, immunomodulators play a significant role in bone regeneration. Strong evidence points to MSCs playing a significant role in bone repair, mostly because of their capacity to modulate the immune system through the release of paracrine substances. Their safety, efficacy, and prospective application in cell therapy for bone illnesses with an underlying inflammatory state have all been confirmed by clinical trials. The selection of donors and/or subpopulations with strong osteogenic capacity is important to assess the osteogenic potential of MSCs for bone healing and inflammatory management, notwithstanding the significant advancements since their discovery and characterization²⁷

Future Perspectives

Precision medicine, gene and stem cell therapy, drug delivery via nanotechnology, microbiome modification, and bioengineered materials represent promising opportunities for immunomodulators in dentistry. By increasing tissue regeneration, decreasing inflammation, and improving treatment results, these developments have the potential to revolutionize periodontal therapy, implantology, and caries management ¹. But there are challenges to be addressed, including safety issues, ethical and legal barriers, exorbitant expenses, and the need for standard clinical guidelines. To include immunomodulatory therapies into general dentistry and provide safe, efficient, and easily accessible treatments for better patient care, further research and interdisciplinary cooperation are necessary.

CONCLUSION

In conclusion, immunomodulators play a crucial role in managing oral mucosal diseases, including periodontal diseases, dental implantology, endodontics, and caries management. Immunomodulators regulating immune responses, reducing chronic inflammation, and promoting tissue healing. The use of immunomodulatory agents, such as corticosteroids, calcineurin inhibitors, biologic agents, and probiotics, has shown promising results in treating specific oral mucosal diseases like Oral Lichen Planus, Recurrent Aphthous Stomatitis, Pemphigus Vulgaris, Mucous Membrane Pemphigoid, Behçet's Disease, and Sjögren's Syndrome. In periodontics, immunomodulators aid in reducing bone loss, modulating the oral microbiome, and promoting tissue regeneration through innovative approaches like stem cell therapy, gene therapy, and targeted antimicrobial peptides. Furthermore, in dental implantology, immunomodulators enhance osseointegration, prevent peri-implantitis, and improve bone regeneration through the use of growth factors, mesenchymal stem cells, and nanomedicine-based drug delivery. In endodontics, immunomodulatory effects of endodontic sealers have been reported to influence the behavior of immune cells, regulate the release of cytokines, and promote tissue regeneration. Additionally, immunomodulation plays a role in caries management through vaccines, probiotics, anti-cytokine therapeutics, immunomodulatory biomaterials, and microbial therapies. Overall, the application of immunomodulators in oral health care presents a promising avenue for personalized and targeted treatment strategies, potentially leading to improved patient outcomes and enhanced quality of life.

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