International Clinical and Medical Case Reports Journal
Research Article (ISSN: 2832-5788)

Immunomodulation in Endodontics: Bridging Inflammation Control and Tissue Regeneration

Rupam Kaur*, Reader, Kanwalpreet Kaur Bhullar, Sagar Arora, Tajdeep Kaur, Jagteshwar Singh Kanwar, Gaurvika Bibra

Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar, India

Citation: *Rupam Kaur, Reader, Kanwalpreet Kaur Bhullar, Sagar Arora, Tajdeep Kaur, Jagteshwar Singh Kanwar, et al. Immunomodulation in Endodontics: Bridging Inflammation Control and Tissue Regeneration. Int Clinc Med Case Rep Jour. 2026;5(7):1-13.*

Received Date: 02 July 2026; **Accepted Date:** 09 July 2026; **Published Date:** 10 July 2026

***Corresponding author:** Rupam Kaur, Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar, India

ABSTRACT

Immunomodulation in endodontics focuses on how bioactive materials, stem cells and pharmacological agents regulate pulp and periapical healing. A narrative review of contemporary literature was conducted using relevant experimental studies and review articles describing bioactive materials, dental stem cells and therapeutic agents in pulpitis and apical periodontitis. Bioactive materials, including calcium silicates and engineered chitosan nanoparticles, promoted M2 macrophage polarization and suppressed pro-inflammatory cytokines such as TNF-α and IL-1β. Mesenchymal stem cells derived from dental tissues enhanced these effects by upregulating regulatory T cells, creating an environment conducive to regeneration. Immunotherapeutic agents, including resolvins and anti-cytokine therapies, effectively resolved periapical inflammation and stimulated bone repair. Evidence indicated a shift from passive disinfection toward the active biological management of host immune responses. The integration of immunomodulatory strategies into endodontic protocols demonstrated significant potential to improve vital pulp therapy and regenerative outcomes. Future clinical validation is necessary to support broader therapeutic application.

Keywords: Apical periodontitis, Bioactive materials, Immunomodulation, Pulpitis, Regenerative endodontics

INTRODUCTION

Traditional endodontic treatment has primarily focused on mechanical and chemical disinfection followed by sealing the root canal with inorganic materials [1]. However, the high incidence of persistent apical periodontitis and the physical limitations of non-vital teeth have driven a paradigm shift toward regenerative endodontics [2]. Immunomodulation serves as a vital component of this evolution, targeting the manipulation of the host's innate and adaptive immune responses to resolve chronic inflammation [2]. By harnessing the therapeutic potential of dental pulp-derived stem cells (DPSCs) and engineered bioactive materials, this biological approach seeks to transition the local environment from a destructive state to one that promotes tissue repair and regeneration[3]. Transitioning from mere disinfection to active biological management is essential for improving clinical

outcomes for the nearly 50% of the global adult population affected by periapical disease [2].

THE CONCEPT OF IMMUNOMODULATION IN ENDODONTICS

It refers to the deliberate targeting or manipulation of the host's innate and adaptive immune responses to resolve inflammation and promote tissue healing [4]. This represents a significant paradigm shift from traditional root canal therapy - high focuses on mechanical disinfection - toward active biological management aimed at regenerating the dentine-pulp complex [2]. A central mechanism of this approach is macrophage polarization, specifically shifting these cells from a destructive, pro-inflammatory M1 phenotype to a pro-healing, anti-inflammatory M2 phenotype to create a microenvironment conducive to repair [1]. Clinicians can harness this through the use of dental pulp-derived stem cells (DPSCs), which mediate immune tolerance by secreting soluble factors like TGF- beta1 and IDO, or through engineered bioactive materials like bioceramics and nanoparticles that actively suppress pro-inflammatory cytokines while stimulating regenerative markers [3]. Ultimately, immunomodulation seeks to transition the local environment from a state of tissue destruction to one of regeneration and homeostasis, potentially restoring original tooth anatomy and sensitivity [2].

Clinical Significance

The clinical significance of immunomodulation in endodontics lies in its potential to transition treatment from a focus on mere disinfection to the active biological management of the host's immune response to resolve inflammation and promote tissue regeneration [2]. By utilizing engineered bioactive materials—such as bio-ceramic sealers and chitosan nanoparticles (CSNP)—clinicians can guide macrophage polarization, shifting cells from a destructive M1 phenotype to a pro-healing M2 phenotype to resolve apical periodontitis and prevent external root resorption [1]. This biological approach is vital for improving the predictability of Vital Pulp Therapy (VPT) and Regenerative Endodontic Treatment (RET), as it creates a stable immune microenvironment that facilitates the survival and differentiation of dental pulp stem cells (DPSCs) and stem cells from the apical papilla (SCAP) into new, functional tissues [5]. Furthermore, the adjunctive use of anti-cytokine therapies and immunomodulatory antibiotics like Azithromycin offers a targeted means to dampen chronic inflammation and accelerate periapical bone healing [6]. Ultimately, these immunomodulatory strategies seek to preserve natural dentition and restore sensory functions, providing a more effective and holistic alternative to traditional endodontic procedures [2].

THE INFLAMMATORY MILIEU OF THE DENTINE-PULP COMPLEX

Innate and Adaptive Recognition

In the context of endodontics, the host identifies and responds to microbial invasion through the coordinated actions of innate and adaptive recognition[2]. Innate recognition serves as the immediate first line of defense, where structural cells like odontoblasts and resident immune cells utilize Pattern Recognition Receptors (PRRs) - primarily Toll-like receptors (TLRs) and NOD receptors - to detect highly conserved microbial components known as Pathogen-Associated Molecular Patterns (PAMPs)[2]. This binding triggers the activation of the NF-kappaB and MAPK signaling pathways, resulting in the rapid release of antimicrobial peptides, pro-inflammatory cytokines, and chemokines[2]. If the infection persists or becomes irreversible, the host transitions

to adaptive recognition, a highly specific response[1]. This process relies on Dendritic Cells (DCs) and macrophages to capture microbial antigens and migrate to regional lymph nodes, where they present these antigens to naïve CD4+ T cells[7]. Successful activation of these T cells requires a dual signaling process involving the CD3 receptor and a co-stimulatory signal from CD28, leading to their differentiation into specialized subsets like Th1, Th2, or Th17 cells to coordinate a targeted immune attack[7]. While these recognition systems are essential for defense, sustained adaptive recognition and the resulting chronic inflammation are the primary drivers of pulp necrosis and periapical bone destruction[1].

Cytokine Cascade

The cytokine cascade in endodontics is initiated when Pattern Recognition Receptors (PRRs), such as Toll-like receptors (TLRs) and NOD receptors on pulp cells, detect microbial antigens, triggering the activation of the NF- kappaB and MAPK signaling pathways [7]. This process results in the rapid release of an initial wave of pro-inflammatory mediators, including TNF- alpha, IL-1alpha, IL-1beta, IL-6, and IL-8 [7]. TNF-alpha serves as a critical upstream regulator of this cascade, inducing the production of IL-1, which can stimulate its own synthesis through a positive feedback loop to intensify the inflammatory response [8]. As the disease progresses, the cascade drives the differentiation of CD4+ T cells into specialized subsets; for instance, the IL-17/IL-23 axis stimulates Th17 cells to produce IL-17, which further recruits' neutrophils and amplifies inflammation [7]. Sustained high levels of these pro-inflammatory cytokines eventually activate the RANK/RANKL/OPG axis, shifting the balance toward osteoclastogenesis and causing the pathologic bone resorption seen in periapical lesions [1]. To prevent unchecked tissue destruction, the cascade also includes immunoregulatory cytokines such as IL-10 and TGF-beta, which function to inhibit immune overactivation and create a microenvironment suitable for tissue repair and regeneration[8].

Macrophage polarization

It is the process by which key innate immune cells differentiate into distinct functional phenotypes, primarily the pro-inflammatory M1 and anti-inflammatory M2 in response to specific local environmental signals [3]. The M1 phenotype is classically activated by microbial components like lipopolysaccharide (LPS) and cytokines such as interferon-gamma (IFN- gamma), resulting in the secretion of bone-destructive mediators (e.g, TNF-alpha, IL-1, and IL-6) and reactive oxygen species that drive tissue necrosis and pathologic bone resorption in periapical lesions [6]. Conversely, the M2 phenotype is triggered by cytokines like IL-4, IL-10, and IL-13, and is characterized by the production of pro-healing factors (e.g., IL-10 and TGF-beta) that resolve inflammation, clear necrotic debris via efferocytosis, and establish a microenvironment suitable for tissue repair and regeneration [3]. Chronic endodontic pathologies, such as apical periodontitis, are often defined by a persistent M1/M2 imbalance where destructive pro-inflammatory signals overwhelm pro-healing ones [1]. Modern immunomodulatory strategies aim to correct this by actively guiding the macrophage shift toward the M2 phenotype through the use of dental pulp stem cells (DPSCs), bio-ceramic sealers, engineered chitosan nanoparticles, and pharmacological agents like azithromycin [6]. Ultimately, these interventions resolve the local inflammatory state to promote successful Regenerative Endodontic Treatment (RET) and periapical bone healing [9].

Dental-Derived Stem Cells: Mechanisms of Immunomodulation

Dental Pulp Stem Cells (DPSCs)

They are a unique population of postnatal mesenchymal stem cells (MSCs) primarily located within the pulp of human teeth [3]. First discovered in 2000 from young impacted molars, these multipotent cells originate from migrating neural crest cells and possess a higher proliferative capacity than bone marrow-derived MSCs [3]. DPSCs are critical to immunomodulation in endodontics because they mediate immune tolerance through low immunogenicity - expressing low levels of MHC class I and being negative for MHC class II, and the active manipulation of host immune cells [3]. They exert these effects via the secretion of soluble factors, such as TGF-beta1, IL-10, IDO, and PGE2, which suppress excessive T-cell and B-cell proliferation and promote the conversion of pro-inflammatory T-cells into CD4+CD25+Foxp3+ regulatory T-cells (Tregs) [3]. Furthermore, DPSCs utilize direct surface-mediated interactions, including the Fas/FasL and PD-1/PD-L1 pathways, to induce apoptosis in activated T-cells and maintain local homeostasis [3]. Their ability to shift macrophages from a pro-inflammatory M1 phenotype to a pro-healing M2 phenotype makes them essential for Regenerative Endodontic Treatment (RET) and a promising tool for treating systemic immune-mediated diseases such as Sjögren's syndrome and Type 1 Diabetes [3].

Surface-Mediated Interactions

It involves direct **cell-to-cell contact** or physical engagement between stem cells, biomaterials, and the host's immune system to regulate inflammation [3]. **Dental Pulp Stem Cells (DPSCs)** utilize critical pathways such as **Fas/FasL** (binding to the CD95 receptor) to induce apoptosis in activated T lymphocytes and maintain local immune homeostasis [3]. Additionally, the **PD-1/PD-L1 axis** allows DPSCs to bind to receptors on activated T cells and counteract activation signals, suppressing hyperactive immune responses that could lead to irreversible tissue damage[3]. For **Stem Cells from the Apical Papilla (SCAP)**, physical contact is the dominant mechanism during the early stages of interaction (the first 24 hours) for promoting the conversion of pro-inflammatory T cells into **CD4+CD25+Foxp3+ regulatory T cells (Tregs)** [5]. Beyond cellular
interactions, **engineered bioactive materials** like cationic chitosan nanoparticles leverage surface-mediated effects through **electrostatic interaction** with negatively charged mammalian cell membranes, facilitating rapid cellular uptake via macropinocytosis and phagocytosis [9]. These direct physical interactions are essential for established regenerative treatments, as they help create a stable, "pro-healing" microenvironment early in the repair process [9].

Stem Cells from the Apical Papilla (SCAP)

They are a resilient population of mesenchymal stem cells located in the apical papilla of immature permanent teeth [10]. These multipotent cells are uniquely capable of surviving and maintaining their stemness even in environments of advanced pulpal necrosis and apical periodontitis, making them the primary cell source for achieving root lengthening, wall thickening, and apex closure during Regenerative Endodontic Treatment (RET) [5].

SCAPs possess low immunogenicity and powerful immunomodulatory properties, specifically the ability to suppress pro-inflammatory T-cell proliferation and promote the conversion of these cells into CD4+CD25+Foxp3+ regulatory T cells (Tregs) [5]. This conversion process is time-dependent: direct cell-to-cell contact is the dominant mechanism during the first 24 hours (upregulating CD25), while soluble (paracrine) factors become involved after 72 hours to establish the stable Foxp3 expression necessary for a "pro-healing" microenvironment [5]. Additionally, their regenerative capacity can be significantly enhanced by engineered biomaterials, such as dexamethasone-functionalized chitosan nanoparticles (CS-DEX), which promote higher alkaline phosphatase activity and calcified matrix deposition[9].

Sensitivity to TLR Agonists

The immunomodulatory properties of Dental Pulp Stem Cells (DPSCs) are highly sensitive and susceptible to activation by Toll-like receptor (TLR) agonists, which can significantly alter their biological behavior depending on the specific receptor engaged [3]. Treatment with a TLR3 agonist, such as poly(I:C), has been shown to augment the suppressive potential of DPSCs, nearly doubling their secretion of TGF-beta and stimulating the release of IL-6 [11]. Conversely, sensitivity to TLR4 agonists like lipopolysaccharide (LPS) can abrogate their immunosuppressive activity by inhibiting TGF- beta production and downregulating the expression of Indoleamine 2,3-dioxygenase (IDO-1) [11]. Furthermore, LPS exposure can enhance TLR4 expression itself and promote Wnt5a expression through the TLR4/MyD88/PI3-kinase/AKT pathway, highlighting the complex signaling outcomes triggered by these agonists [3]. Ultimately, this sensitivity means the local inflammatory milieu—containing various microbial and host-derived TLR ligands—plays a decisive role in whether DPSCs maintain immune tolerance or adopt a more pro-inflammatory profile [11].

BIOCOMPATIBILITY AND IMMUNOMODULATION OF ENDODONTIC MATERIALS

Calcium Hydroxide

It is a gold standard intracanal dressing in endodontics, valued for its antimicrobial and mineralizing properties[12]. Its primary mechanism of action involves creating a highly alkaline environment that disrupts microbial cell membranes and inhibits bacterial enzymes, metabolism, and growth[12]. Despite its broad spectrum of activity, resilient pathogens such as Enterococcus faecalis and Candida albicans have shown resistance to its high alkalinity[12]. Beyond disinfection, research suggests calcium hydroxide can act as a pro-inflammatory agent by up-stimulating the production of cytokines like TNF-α, IL-6, IL-12, and MCP-1, potentially contributing to an exaggerated response and tissue damage[12]. Furthermore, while it is considered biocompatible at low concentrations, it can be highly cytotoxic at the elevated levels required to inhibit resistant bacteria[12].

Clinically, it is extensively used to disinfect root canal systems and facilitate healing in treatments such as Vital Pulp Therapy (VPT) and Regenerative Endodontic Treatment (RET)[2].

Endodontic Sealers

It plays a critical role in the success of root canal treatment, as their molecular biocompatibility directly influences the periapical immune microenvironment and tissue healing [13]. Traditional sealers, such as zinc

oxide eugenol (ZOE) and epoxy resin, are frequently linked to high levels of pro-inflammatory cytokines - specifically IL-1β, IL-6, and IL-8, which can contribute to chronic inflammation, tissue degradation, and poor fibroblast survival [13]. In contrast, calcium silicate-based bio-ceramic sealers exhibit exceptional cytocompatibility and bioactivity, actively promoting an anti-inflammatory environment by significantly upregulating IL-10 while suppressing inflammatory pathways like NF- kappaB [13]. Beyond their immunomodulatory effects, bio-ceramic sealers demonstrate superior regenerative capabilities by stimulating the expression of osteogenic markers such as ALP, RUNX2, and osteocalcin (OCN), which are vital for periapical bone formation and extracellular matrix maturation [13]. Ultimately, while ZOE remains the most cytotoxic and inflammatory option, bio-ceramic sealers represent a biological shift toward materials that support immune regulation and tissue regeneration, leading to improved treatment success rates and better long-term outcomes [13].

Bio-ceramic Sealers

They are calcium silicate-based materials that represent a biological advancement in endodontics due to their exceptional cytocompatibility and bioactivity [13]. Unlike traditional sealers, they actively modulate the immune response by upregulating anti-inflammatory IL-10 and significantly reducing pro-inflammatory cytokines such as IL-1beta, IL-6, and IL-8 via inhibition of the NF- kappaB pathway [13]. These sealers function by releasing calcium ions and maintaining a strong alkaline pH, which together establish an environment that promotes healing and suppresses chronic inflammation [13].

Furthermore, bio-ceramic sealers possess powerful osteoinductive capabilities, stimulating the expression of essential osteogenic markers - ALP, RUNX2, and Osteocalcin (OCN) to support periapical bone regeneration and extracellular matrix maturation. Because they demonstrate significantly higher metabolic cell viability than epoxy resin or zinc oxide eugenol sealers, bio-ceramics are clinically preferred for achieving predictable periapical outcomes and enhancing the long-term success of root canal treatments [13].

Host Defense Peptides (HDPs)

They are multifunctional biomolecules that act early in response to infections, possessing potent antimicrobial, immunomodulatory, and tissue repair properties [12]. Key examples researched for endodontic application include the human cathelicidin LL-37 and synthetic clavanins (such as A and MO), which exhibit a broad spectrum of activity at low concentrations and low levels of microbial resistance [12]. LL-37, in particular, has demonstrated superior antibacterial potential against Enterococcus faecalis compared to traditional medications like calcium hydroxide and is capable of inducing cell proliferation to aid in host defense [12]. Beyond direct antimicrobial action, HDPs exert significant immunomodulatory effects by neutralizing lipopolysaccharides (LPS), inhibiting pro-inflammatory signaling through Toll-like receptors (TLRs), and modulating cytokine production to favor a stable periradicular environment without stimulating the cytokines active in pathologic bone resorption. While traditional agents like calcium hydroxide can act as pro-inflammatory triggers that potentially cause tissue damage, HDPs offer a biological alternative that promotes healing and resolves persistent endodontic infections more predictably [12].

ADVANCED TECHNOLOGIES: NANOPARTICLES AND SCAFFOLDS

Engineered Nanoparticles: Chitosan nanoparticles (CSNP)

They are bioactive, biodegradable particles derived from chitin that offer unique therapeutic advantages due to their nanoscale size and high surface-area-to-mass ratio [9]. Because of their cationic nature, these nanoparticles leverage electrostatic interactions with negatively charged cell membranes to facilitate rapid cellular uptake via pathways like macropinocytosis and phagocytosis [9]. CSNPs serve as potent immunomodulatory agents, capable of resolving inflammation by significantly upregulating anti-inflammatory cytokines like IL-10 and TGF- beta1 while downregulating pro-inflammatory mediators such as TNF- alpha, IL-1 beta, and nitric oxide [9]. Research indicates they can completely inhibit the differentiation of macrophages into bone-destructive osteoclasts, effectively preventing external root resorption [9]. Furthermore, functionalised CSNPs - such as those conjugated with dexamethasone (CS-DEX) or Rose Bengal (CSRB), actively support tissue repair by stabilising the dentin matrix and promoting the expression of regenerative markers like periostin and alkaline phosphatase. Their combined antibacterial and antibiofilm efficacy makes them a transformative tool for root surface modification and biological disinfection in endodontics [9].

Scaffold Properties

They are fundamental to the success of tissue engineering because their physical and chemical characteristics directly manipulate immune cell behavior to guide regenerative outcomes [1]. Porosity and pore size are critical regulators; for instance, scaffolds with 40 µm pores have been shown to induce spontaneous M2-like polarization and macrophage elongation, whereas pores that are too small limit cell infiltration [1]. Surface wettability and chemistry also play decisive roles, with hydrophilic surfaces containing -COOH groups favoring anti-inflammatory cytokine production, while hydrophobic surfaces often exhibit a higher affinity for pro-inflammatory M1 differentiation [1].

Furthermore, surface charge significantly influences the local immune response; while cationic surfaces can activate the inflammasome, zwitterionic hydrogels (net neutral charge) are effective at shifting macrophages toward an M2 phenotype and resisting the foreign body reaction [1]. Finally, structural architecture—including fiber morphology (aligned vs. random) and pore curvature—further modulates cellular signaling pathways like YAP/TAZ to enhance angiogenesis and osteogenic differentiation[1].

Drug Delivery Systems

In endodontics are designed to provide localized, targeted, and controlled release of therapeutic agents to resolve inflammation and promote tissue healing [7]. These systems utilize various advanced carriers, including micro/nanoparticles, injectable hydrogels, and microspheres, which allow for direct application to the pulp or periradicular area while minimizing systemic side effects [1]. For instance, engineered chitosan nanoparticles (CSNP) can be functionalized for the sustained release of anti-inflammatory drugs like dexamethasone (CS-DEX) or antibiotics like doxycycline, leveraging their cationic nature for rapid cellular uptake via electrostatic interactions [9]. Additionally, injectable hydrogels are highly effective for filling complex root canal anatomies, while core/shell fibrous scaffolds can achieve the sequential release of growth factors, such as bFGF and BMP-

2, to coordinate angiogenesis and bone regeneration [2]. These technologies represent a significant shift toward biological management, offering a platform for delivering anti-cytokine therapies and other immunomodulators to create a stable microenvironment conducive to Vital Pulp Therapy (VPT) and regenerative endodontic procedures [7].

Innovative Strategies: Immunotherapy and Vital Pulp Therapy (Vpt)

Antibody-based drugs

Specifically anti-cytokines, are therapeutic agents designed to target or manipulate the host's immune response by blocking specific overactive cytokine networks that drive chronic inflammation [7]. These drugs have been successfully used to treat systemic inflammatory conditions such as rheumatoid arthritis, psoriasis, and inflammatory bowel diseases by utilizing mechanisms like direct cytokine neutralization, receptor blockade, or the use of soluble decoy receptors [7]. Primary targets for these therapies include TNF-alpha (e.g., infliximab and adalimumab), IL-1 (e.g., anakinra), IL-6 (e.g., tocilizumab), and the IL-17/IL-23 axis [7]. While traditionally administered systemically, there is significant potential for the direct topical application of anti-cytokines within the root canal system to manage pulpal inflammation more predictably during Vital Pulp Therapy (VPT) [7]. Delivering these drugs via advanced carriers like micro/nanoparticles or hydrogels could limit chronic inflammation and facilitate tissue repair while avoiding the systemic adverse effects associated with traditional administration [7].

Targeting the IL-17/IL-23 Axis

Represents a promising immunotherapeutic strategy for managing chronic pulpal and periapical inflammation by blocking the pathway that drives Th17 cell differentiation and subsequent tissue destruction[7]. In this axis, IL-23 stimulates the amplification of CD4+ T cells into Th17 cells, which secrete IL-17, a potent pro-inflammatory cytokine that triggers the release of further inflammatory mediators like IL-6, IL-8, and TNF- alpha from resident pulp cells. Because relatively high levels of both IL-17 and IL-23 have been identified in inflamed pulp tissue and chronic apical periodontitis, utilizing FDA-approved monoclonal antibodies such as ustekinumab (targeting IL-12/23) or secukinumab (targeting IL-17A), could effectively dampen the associated chronic inflammation. Clinically, these therapies could be applied through direct topical delivery or advanced carriers like nanoparticles and hydrogels to limit pulpal damage and create a more predictable environment for Vital Pulp Therapy (VPT) and tissue regeneration[7].

Macrolide modulation

Specifically, through the use of azithromycin (AZM), represents a potent immunomodulatory strategy in endodontics that leverages the antibiotic's unique chemical structure to resolve chronic inflammation [6]. AZM actively guides macrophage polarization, shifting the local environment from a destructive M1 phenotype to a pro-resolving M2 phenotype, which promotes the clearance of necrotic debris and the maturation of granulation tissue[6]. At the molecular level, azithromycin is distinct from other common antibiotics because it suppresses the NF- kappaB signalling pathway and subsequently inhibits the production of key pro-inflammatory mediators,

including TNF-alpha, IL-1, and IL-8 [6]. Furthermore, AZM possesses exceptional pharmacokinetics, concentrating within myeloid cells like neutrophils and macrophages to achieve sustained tissue-to-plasma ratios over 100 times higher than plasma at infection sites. In experimental models of periapical periodontitis, this targeted modulation has been shown to significantly attenuate bone loss and promote advanced wound healing and fibrosis, offering a superior biological advantage over traditional non-macrolide therapies[6].

Conclusion: Challenges and Future Directions

The standardization of isolation and cultivation techniques

It's a critical challenge for the clinical translation of dental pulp stem cell (DPSC) research[4]. Currently, significant variations exist in enzyme systems, growth media, and serum inclusion used across different studies, which result in inconsistent DPSC phenotypes[4]. This heterogeneity prevents different stem cell groups from being directly compared and contributes to ambiguous research methods that hinder the establishment of definitive clinical trial outcomes or commercial products[4]. To overcome these hurdles, a future consensus must be reached to enhance and unify protocols, data collection, and patient information. Establishing such standardized, innovative methodologies is essential to ensure that regenerative treatments are reproducible, effective, and ethically accessible for widespread medical use[4].

Diagnostic Tools

Current diagnostic tools in endodontics are considered rudimentary, primarily relying on clinical signs, symptoms, and radiographic evidence of bone loss, which often correlate poorly with the actual molecular and histological status of the pulp [7]. Clinicians frequently use the ability to achieve haemostasis as a functional indicator of pulp health, yet there are currently no commercially available chairside tests to quantitatively measure infection levels or cytokine profiles [7]. In research settings, advanced tools like micro-computed tomography (μCT) provide precise measurements of bone destruction, while immunofluorescence analysis and histological staining are utilized to identify specific inflammatory cell infiltration and markers such as Foxp3 for regulatory T cells or CD80/CD206 for macrophage polarization[9]. Future diagnostic advancements aim to utilize biomarker panels to identify and quantify specific cytokines and bacterial by-products, enabling clinicians to tailor immunomodulatory therapies to a patient's unique inflammatory profile for more predictable clinical outcomes[7].

The safety and efficacy of immunomodulatory therapies in endodontics

are underpinned by the low immunogenicity of Dental Pulp Stem Cells (DPSCs) and
Stem Cells from the Apical Papilla (SCAP), which express low levels of MHC molecules and successfully escape host immune rejection[3]. Numerous clinical studies have confirmed that DPSC-based therapies are both feasible and safe, demonstrating therapeutic efficacy in tissue regeneration and the treatment of inflammatory diseases[3]. Regarding biomaterials, bio-ceramic sealers exhibit superior safety profiles with significantly higher cell viability than traditional zinc oxide eugenol (ZOE) sealers, which are often linked to potent cytotoxicity and chronic inflammation[13]. While pharmacological agents like azithromycin effectively resolve periapical lesions

by concentrating within myeloid cells to minimize systemic side effects, the safety of engineered nanoparticles is highly dependent on particle size, composition, and surface charge, which must be carefully evaluated to avoid immunotoxicity[6]. Furthermore, while Host Defense Peptides (HDPs) like LL-37 are efficacious against resistant bacteria and promote healing, other synthetic peptides like clavanin MO can be potentially cytotoxic at therapeutic concentrations[12]. Finally, the direct topical application of anti-cytokine drugs offers a promising strategy to enhance local efficacy and reduce systemic adverse effects, although it may increase local susceptibility to opportunistic infections[7].

REFERENCES

1. Dal-Fabbro R, Swanson, WB, Capalbo, LC, Sasaki, H and Bottino, MC. 'Next-generation biomaterials for dental pulp tissue immunomodulation', Dental Materials, vol. 2023;39(4):333-349.
2. Murad AH. 'Immunomodulatory biomaterials in dental pulp regenera-tion: Towards enhancing endodontic Treatment Outcomes', Future Dental Research 2023;1(1):1-11.
3. Min, Q, Yang, L, Tian, H, Tang, L, Xiao, Z and Shen, J. 'Immunomodulatory mechanism and potential application of dental pulp-derived stem cells in immune-mediated diseases', International Journal of Molecular Sciences, 2023;24(9):8068.
4. Alshareef, SA. 'Therapeutic and Immunomodulatory Effects of Dental Pulp Stem Cells', J Regen Biol Med, 2024;6(1):348-364.
5. Liu, XM, Liu, Y, Yu, S, Jiang, LM, Song, B and Chen, X. 'Potential immunomodulatory effects of stem cells from the apical papilla on Treg conversion in tissue regeneration for regenerative endodontic treatment', International endodontic journal, vol. 2019;52(12):1758-1767.
6. Andrada, AC, Azuma, MM, Furusho, H, Hirai, K, Xu, S, White, RR and Sasaki, H. 'Immunomodulation mediated by azithromycin in experimental periapical inflammation', Journal of endodontics, 2020;46(11):1648-1654.
7. Arora, S, Cooper, PR, Friedlander, LT, Rizwan, S, Seo, B, Rich, AM and Hussaini, HM, 2021, 'Potential application of immunotherapy for modulation of pulp inflammation: opportunities for vital pulp treatment', International Endodontic Journal, 54(8):1263-1274.
8. Gazivoda, D, Dzopalic, T, Bozic, B, Tatomirovic, Z, Brkic, Z and Colic, M, 2009, 'Production of proinflammatory and immunoregulatory cytokines by inflammatory cells from periapical lesions in culture', Journal of oral pathology & medicine, 2009;38(7):605-611.
9. Siddappa, RHR, Bishop, E, Ali, A, Magalhaes, M and Kishen, A. 'Engineered immunomodulatory nanoparticles inhibit root resorption and ankylosis', Journal of Endodontics, 2024;50(11):1579-1592.
10. Tomic, S, Djokic, J, Vasilijic, S, Vucevic, D, Todorovic, V, Supic, G and Colic, M, 2011, 'Immunomodulatory properties of mesenchymal stem cells derived from dental pulp and dental follicle are susceptible to activation by toll-like receptor agonists', Stem cells and development, 2011;20(4):695-708.
11. Tomic, S, Djokic, J, Vasilijic, S, Vucevic, D, Todorovic, V, Supic, G and Colic, M, 2011,

'Immunomodulatory properties of mesenchymal stem cells derived from dental pulp and dental follicle are susceptible to activation by toll-like receptor agonists', Stem cells and development 2011;20(4):695-708.

12. Lima, SMF, Freire, MS, Gomes, ALO, Cantuária, APC, Dutra, FRP, Magalhães, BS, Sousa, MGC, Migliolo, L, et al. 'Antimicrobial and immunomodulatory activity of host defense peptides, clavanins and LL-37, in vitro: An endodontic perspective', Peptides, 2017;95:16-24.
13. Khan, MQ, Munawar, M, Moazzam, M, Karim, H and Ali, F. 'Immunomodulatory Roles of Interleukins in Root Canal Healing: A Molecular Perspective on Endodontic Sealer Biocompatibility', Pakistan Journal of Medicine and Dentistry, 2005;14(4).