IEJ
Iranian Endodontic Journal

# Beyond the Necrosis-first Model: Towards a New Integrated Biological Framework for Inflammation-mediated Apical Periodontitis

**Néstor Ríos-Osorio** [a,b*]

[a] Postgraduate Endodontics Department, School of Dentistry, CES University, Medellin, Colombia; [b] Faculty of Dentistry, Institución Universitaria Visión de las Américas, Medellín, Colombia

*Article Type*: **Review Article**

*Received*: 04 Sep 2026
*Accepted*: 12 Oct 2026
*Published*: 09 Nov 2026
*Doi*: *10.22037/iej.v21i1.52669*

***Corresponding author***: Néstor Ríos-Osorio, Endodontic Research Department, Universidad CES Medellín, Antioquia, Calle 10A #22-04, Colombia.

***E-mail***: dadopi1981@gmail.com

**Abstract**

Chronic apical periodontitis (AP) has traditionally been attributed to microbial infection and pulp necrosis. Emerging biological and clinical evidence supports the biological plausibility of chronic periapical disease arising from persistent pulpal inflammation through inflammation-mediated pathways. In this integrated model, pulpal inflammation initiated by infectious or non-infectious stimuli progresses corono-apically, potentially contributing to periapical inflammation and bone resorption without microbial colonisation. This review synthesises molecular, immunological, and clinical evidence supporting the biological plausibility of inflammation-driven pathways contributing to chronic AP. Pattern recognition receptors (PRRs), historically regarded as sensors of pathogen-associated molecular patterns (PAMPs), also respond to damage-associated molecular patterns (DAMPs) released by stressed or dying cells. PAMPs and DAMPs converge on innate immune pathways including toll-like receptors (TLRs), NOD-like receptors (NLRs), and inflammasomes amplifying inflammatory signalling. Neuropeptide release, elevated intrapulpal pressure, and apically directed chemotactic gradients may facilitate mediator transport beyond the pulp. In the periapical region, these signals may activate resident cells and promote osteoclastogenesis through interconnected inflammatory and immunological pathways. Collectively, these findings suggest that persistent pulpal inflammation may contribute to chronic AP even in the presence of pulp vitality. Collectively, these findings support inflammation-mediated pathways as a complementary biological mechanism that may contribute to chronic AP in selected clinical scenarios, while recognising microbial infection and pulp necrosis as the predominant drivers of disease.

**Keywords:** Apical Periodontitis; DAMPs; Inflammasome; Neurogenic Inflammation; Osteoclastogenesis; Pulpal Inflammation

## Introduction

Traditionally, apical periodontitis (AP) has been viewed as an infection-dependent condition sustained by toxins and bacterial by-products released from necrotic pulp tissue [1-3]. The interaction between these microbial derivatives and the host immune system underlies the chronic immunopathological response observed at the periapical tissues [3, 4]. However, emerging evidence suggests that persistent pulpal inflammation may also contribute to the development of chronic AP through interconnected molecular and cellular pathways [5, 6].

Mild but persistent noxious stimuli mechanical, chemical, or microbial can elicit sublethal pulpal inflammation sufficient to activate immune pathways that extend toward the periapical tissues [6]. Yamasaki *et al.* demonstrated that pulpal necrosis progresses apically over time. Importantly, periapical inflammatory infiltration was observed before complete pulp necrosis [7]. Similarly, Kovačević *et al.* [8] reported early osteoclastic activity and bone resorption in periapical tissues during initial pulpitis, indicating that AP with bone loss may develop during pulpal inflammation. Clinical evidence also supports the coexistence of irreversible pulpitis and chronic AP [9-17]. Cone-beam computed tomography (CBCT) examinations identified hypodense periapical lesions consistent with chronic AP in 13.7% (138 teeth) of teeth diagnosed with irreversible pulpitis [9]. Similarly, a multicentre, randomised, non-inferiority clinical trial including 407 vital molar teeth, in which pulpal vitality was confirmed by visual inspection of



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

pulpal haemorrhage and all teeth were diagnosed with irreversible pulpitis, reported the presence of periapical radiolucencies in 128 teeth (31%) [17]. Thus, radiographic evidence of chronic AP may reflect either pulpal necrosis or active pulpal inflammation [3, 5, 6]. Accordingly, an updated diagnostic approach identifies cases with periapical radiolucencies and a vital-inflamed pulp as pulpitis with either symptomatic or asymptomatic apical periodontitis, relying on percussion test results [6].

During pulpal inflammation, damaged cells release damage-associated molecular patterns (DAMPs) recognised by pattern recognition receptors (PRRs) [18-20]. DAMP-driven and inflammasome-mediated inflammatory signalling in pulp biology describes the propagation of host inflammatory responses through endogenous danger signals. Odontoblasts can activate PRRs/NF-κB/p38 MAPK signalling and the NLRP3 inflammasome, promoting IL-1β and IL-18-dependent responses that regulate and amplify pulpal inflammation [18].

Concurrently, neurogenic inflammation amplifies this response through vasodilation, increased vascular permeability, and cytokine release, establishing a self-perpetuating immune–neural feedback loop [21]. The immune–pathologic response may be acute or chronic, depending on the intensity of the stimulus and the reparative capacity of pulpal and periapical tissues [22]. As pulpal inflammation progresses into a chronic phase, several chemokines contribute to inflammatory cell infiltration, thereby maintaining a persistent, low-grade inflammatory infiltrate [23]. As inflammatory mediators generated within the persistently inflamed pulp propagate in a corono-apical direction and reach the periapical tissues, activation of the RANK/RANKL/OPG pathway may promote osteoclastogenesis, and thereby contribute to periapical bone resorption and chronic AP [24].

Within this framework, corono-apical progression reflects the spatiotemporal relay of inflammatory mediators along the pulp axis rather than solely the spread of microorganisms or their products. Although the initiating insult may be microbial, such as dental caries, persistent pulpal inflammation may contribute to periapical tissue responses through interconnected molecular and cellular pathways, providing a complementary biological perspective on the development of chronic AP. In clinically relevant caries-associated pulpitis, however, this host-derived inflammatory response is likely to coexist with diffusible microbial products originating from the infected coronal pulp, which activate many of the same innate immune pathways through PRRs [18-20]. The relative contribution of PAMP- and DAMP-mediated signalling probably varies according to disease stage and the spatial distribution of bacterial colonisation.

Recent culture-independent studies challenge the traditional view of healthy dental pulp as a microorganism-free tissue [25]. Using 16S rRNA gene sequencing, Widmer *et al.* [25] detected bacterial DNA in all vital pulps. However, because dental pulp is a low-biomass tissue, such signals are highly susceptible to contamination [26]. Using matched dentine samples, extensive negative controls, and spike-in calibrators, Bérard *et al.* [26] also detected bacterial DNA in all pulps but found profiles largely overlapping with controls and enriched for known reagent contaminants. These findings argue against a genuine core pulpal microbiome and indicate that bacterial DNA alone does not demonstrate microbial viability or infection [26]. If authentic, these low-level signals may represent human-associated symbionts with neutral or beneficial roles in host physiology [25, 26].

In contrast to the uncertain significance of bacterial signals in healthy pulps, histopathologic and histobacteriologic studies of deep caries-associated pulpitis define when clinically relevant infection occurs. Using serial sectioning and bacterial staining, Ricucci *et al.* [27] showed that pulpal inflammation remains localised and necrosis develops only after bacteria reach the pulp space. Bacterial colonisation initially occurs in small necrotic foci within the pulp horn adjacent to the lesion, whereas more apical tissue remains structurally intact, indicating that pulpal "irreversibility" is often segmental rather than global [27]. Consistent with this, Ricucci *et al.* [28] detected bacterial invasion of necrotic coronal tissue and blood vessels only in the coronal third, with no intravascular bacteria in the middle or apical pulp. Collectively, these findings indicate that bacteria in caries-exposed teeth are confined to focal coronal infection fronts, while more apical tissue frequently remains viable and comparatively bacteria-free [27, 28]. Collectively, these studies indicate that bacterial colonisation is initially confined to focal coronal regions, whereas the apical pulp frequently remains viable and shows no histological evidence of established bacterial invasion. These observations do not exclude biological effects of diffusible bacterial products originating from the infected coronal pulp but suggest that extensive apical bacterial colonisation is not a prerequisite for persistent host inflammatory signalling within the remaining vital pulp.

Accordingly, in this manuscript, the term "inflammation-mediated AP" is used operationally to denote periapical inflammatory processes presenting as chronic AP in teeth diagnosed with irreversible pulpitis triggered by infectious or non-infectious insults in the absence of evidence for bacterial colonisation and/or established necrosis in the apical portion of the dental pulp.



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

Recognition of pulp-to-periapical inflammatory pathways broadens the current understanding of endodontic disease without challenging the established role of microbial infection as the principal cause of apical periodontitis. Instead, this review synthesises evidence supporting inflammation-mediated AP as a complementary biological mechanism that may explain selected cases in which persistent pulpal inflammation coexists with pulp vitality and periapical bone resorption. Although periapical radiolucencies have been reported in teeth with vital pulps [9-14], no comprehensive model explains the mechanisms underlying osteolytic lesions secondary to pulpal inflammation. This review synthesises molecular, immunological, histopathologic, and clinical evidence consistent with an inflammation-mediated framework for apical periodontitis, whereby DAMP/PRR and inflammasome signalling, neuroimmune amplification, and RANK/RANKL/OPG-mediated osteoclastogenesis may drive periapical bone resorption without uniform intraradicular infection.

## Literature Search Methodology

A comprehensive literature search was conducted in MEDLINE (via PubMed), Web of Science, and Scopus from inception until January 2026. The search strategy combined free-text keywords and Medical Subject Headings (MeSH) relevant to the topic. Key search terms included: *"sterile inflammation" OR "non-infectious inflammation"*, *"pulpitis" OR "pulpal inflammation" OR "inflammation"*, *"danger signals" OR "DAMPs" OR "damage-associated molecular patterns"*, *"pulp" OR "dental pulp"*, *"vital pulp" OR "pulp vitality"*, and *"periapical radiolucency" OR "periapical lesion"*. Titles and abstracts were screened for relevance. Studies were included if they addressed cellular and molecular mechanisms linking pulpal inflammation to inflammation-mediated chronic AP, encompassing clinical trials, in vitro/in vivo/ex vivo research, human and animal tissue studies, and reviews on molecular and immune pathways. Clinical case reports were also considered to illustrate the clinical spectrum, given the limited direct evidence.

## Damp-mediated Immune Activation in Dental Pulp

Noxious stimuli are classified as acute or chronic according to their duration and intensity. Acute insults typically induce transient inflammation followed by repair, whereas persistent infectious, mechanical, or chemical stimuli promote chronic pulpal inflammation [22, 29-33]. Notably, established evidence has demonstrated that mechanical stimuli can activate inflammatory signalling in clinically healthy pulp. Experimental studies show that occlusal trauma and orthodontic forces increase the expression of substance P (SP), calcitonin gene-related peptide (CGRP), and vascular endothelial growth factor (VEGF), demonstrating that non-infectious stimuli can induce a neurogenic inflammatory phenotype without pulpal infection or necrosis [30-33].

Non-infectious insults can trigger neurogenic inflammation in the dental pulp, characterised by vasodilation, plasma extravasation, and recruitment of immune cells expressing neuropeptide receptors [18, 21, 33]. Infectious stimuli, such as chronic caries, similarly activate these pathways as metabolic by-products diffuse through dentine and disrupt pulp homeostasis without direct bacterial invasion [20]. A hallmark of both infectious and non-infectious pulpal inflammation is the release of DAMPs [18, 34, 35]. Both non-infectious and microbial stimuli can induce sublethal stress and/or cell death including apoptosis, pyroptosis, ferroptosis, and NETosis releasing DAMPs that activate innate immunity through extracellular toll-like receptors (TLRs) and intracellular nucleotide-binding oligomerisation domain-like receptors (NLRs), even in the absence of viable pathogens [18, 19, 34-36].

Key DAMPs include high mobility group box 1 (HMGB1), extracellular adenosine triphosphate (ATP), DNA, uric acid, heat shock proteins, and S100 proteins, signalling tissue distress. DAMPs engage TLRs and NLRs expressed by resident pulpal cells, including odontoblasts, fibroblasts, endothelial cells, Schwann cells, resident macrophages, dendritic cells, and other antigen-presenting cells, thereby initiating innate immune signalling within the dental pulp [20, 37-44]. Upon ligand binding, TLR2, TLR3, and TLR4 induce pro-inflammatory cytokines and chemokines, including CCL2 (MCP-1), CCL5, CCL7, CXCL8 (IL-8), and CXCL10 [41, 45]. Notably, TLR2 synergises with NOD2 to enhance fibroblast inflammatory mediator production and cooperates with histamine receptor 1, underscoring fibroblasts' role as active immunocompetent cells [38, 41]. These receptor-ligand interactions trigger intracellular signalling cascades that activate innate immunity, amplify pulpal inflammation through self-sustaining host-derived signalling mechanisms, and promote downstream adaptive immune responses [18, 19, 36, 46].

Although structurally distinct from pathogen-associated molecular patterns (PAMPs) derived from microbial components like lipopolysaccharides (LPS) or peptidoglycan, DAMPs often engage the same PRRs [18-20, 47]. This convergence enables DAMP-driven pulp inflammation to mimic the molecular and immunological profile of infection-induced pulpal and periapical responses.

Certain cytoplasmic PRRs detect DAMPs or PAMPs and assemble into inflammasomes [18, 19, 48]. Canonical inflammasomes comprise a sensor molecule, an adaptor protein



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

(ASC; apoptosis-associated speck-like protein containing a CARD domain), and the effector enzyme caspase-1. Upon sensing intracellular stress signals, sensor molecules, typically members of the NLR family, oligomerise, recruit ASC, and activate procaspase-1, leading to caspase-1-mediated maturation of IL-1β and IL-18 [18, 48]. Among these complexes, NLRP3 is the best-characterised inflammasome in the dental pulp [18, 46]. Its activation follows a two-step process: priming through TLR-mediated NF-κB signalling induces transcription of NLRP3, pro-IL-1β and pro-IL-18, whereas a second signal derived from cellular stress promotes inflammasome assembly, caspase-1 activation, and cytokine maturation, thereby amplifying pulpal inflammation [18, 49-51]. Consistent with its role in pulpal immunity, immunofluorescence studies have identified NLRP3 and caspase-1 in the odontoblast layer of healthy pulp, with markedly increased expression in damaged odontoblasts from irreversible pulpitis [38, 52].

As the primary sentinels of the dentine–pulp complex, odontoblasts detect thermal, mechanical, chemical, and microbial insults through PRRs [53]. Engagement of these receptors by PAMPs or DAMPs activates MAPK signalling, particularly p38, together with the transcription factors NF-κB and AP-1, promoting NLRP3 expression [18, 19, 54]. Once assembled, the NLRP3 inflammasome drives caspase-1-dependent cytokine maturation and gasdermin D cleavage, leading to pyroptotic cell death and extracellular release of DAMPs. By activating PRRs on neighbouring resident pulpal cells, these endogenous danger signals may trigger successive rounds of inflammasome activation, establishing a feed-forward inflammatory loop that amplifies and sustains pulpal inflammation independently of continued increases in bacterial burden [18, 19, 54].

Further, activated odontoblasts secrete pro-inflammatory cytokines and chemokines, including CCL2, CXCL1, CXCL2, CXCL8, CXCL10, and IL-6, which diffuse sub-odontoblastally to activate adjacent innate immune cells, such as fibroblasts, mesenchymal stem cells, and resident immune cells [19, 55]. Progressive infiltration of macrophages, neutrophils, and B lymphocytes parallels persistent pulpal inflammation [19, 55]. Activated resident cells amplify this milieu by secreting chemokines and cytokines, enhancing immune cell recruitment [56].

Collectively, these findings identify DAMP-mediated signalling as a central amplifier of persistent pulpal inflammation. Through coordinated activation of PRRs, the NF-κB/p38 MAPK pathways, and the NLRP3 inflammasome, endogenous danger signals establish autocrine and paracrine feed-forward inflammatory circuits that perpetuate and amplify host-derived inflammatory signalling independently of continued microbial burden [19, 55]. Pyroptotic release of additional DAMPs may further reinforce these circuits by activating neighbouring resident pulpal cells, thereby sustaining inflammasome activation and inflammatory propagation [18]. As persistent inflammatory signalling intensifies, the response may progressively extend from the coronal pulp towards the apical tissues, providing a biological basis for the proposed inflammation-mediated pathway linking chronic pulpitis to apical periodontitis [7, 20, 57].

## Neurogenic Inflammation of Dental Pulp: Pathophysiological Implications

Under microbial, mechanical, thermal, or chemical stress, sensory afferent neurons amplify pulpal inflammation through sustained neuropeptide release [21, 58]. Peripheral nociceptors express TLR2, TLR3, TLR4, TLR7, and TLR8, enabling PAMPs and DAMPs to activate MyD88/NF-κB and MAPK signalling, leading to the release SP, CGRP, vasoactive intestinal peptide (VIP), and neurokinin A (NKA) [21, 51, 59-64]. These mediators sensitise nociceptors, amplify PRR activation, and sustain neurogenic inflammation. In parallel, retrograde nerve growth factor (NGF) signalling activates p38 MAPK, upregulates TRPA1 and TRPV1, and increases SP and CGRP synthesis, promoting nerve sprouting, chronic pain hypersensitivity, and persistent neurogenic inflammation [21, 51, 63-66].

Neuropeptide release contributes to both acute and chronic pulp inflammation. SP upregulates intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) on endothelial cells [21, 67], while SP and CGRP stimulate pulp and endothelial cells to secrete chemokines, including MCP-1/CCL2 and CXCL8/IL-8, sustaining leukocyte recruitment. Concurrently, IL-1β and IL-18, generated via NF-κB and inflammasome activation, sensitise nociceptors and amplify neurogenic inflammation [68]. SP and CGRP orchestrate the release of pro-inflammatory mediators, including IL-1, IL-2, IL-6, IL-8, TNF-α, and PGE2, from immunocompetent cells [21, 69-71]. SP induces cytokine release in T lymphocytes, while SP and CGRP trigger histamine release from mast cells [21, 71], amplifying local immunity. Chronic neuroimmune activation sustains low-grade inflammation, establishing a self-perpetuating loop that underlies persistent pulpal inflammation [21, 66].

Chronic pulp inflammation is characterised by persistent innate and adaptive immune activation, with macrophage, lymphocyte, and plasma cell infiltration [20, 55, 72]. Sustained inflammation expands this infiltrate while promoting angiogenesis and fibrosis [20]. B-cell expansion, plasma cell accumulation, and Th1/Th17 cytokines, including IFN-γ, IL-17, IL-21, and IL-22, perpetuate inflammation through reciprocal activation of T cells



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

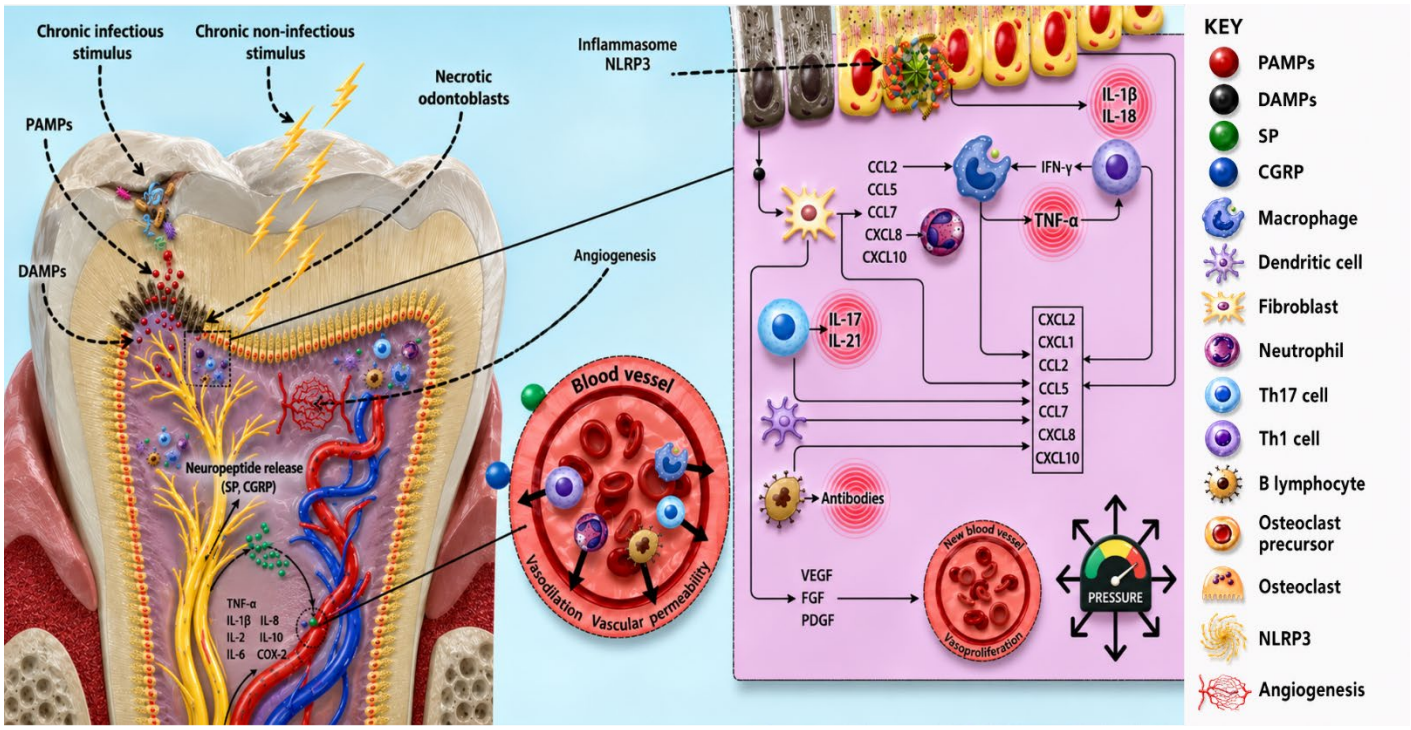



***Figure 1.*** DAMP-mediated and neurogenic pathways in pulp inflammation. Cellular stress and death release DAMPs that activate PRRs (TLRs, NLRs) on odontoblasts, fibroblasts, and immune cells, driving cytokine/chemokine secretion and NLRP3 inflammasome activation. In parallel, neuropeptides such as SP and CGRP released by nociceptors amplify vasodilation, leukocyte recruitment, and immune activation. These self-sustaining loops promote chronic pulp inflammation, fibrosis, angiogenesis, and apical spread toward periapical tissues even in the absence of infection.

and macrophages [55, 73-76]. Persistent IL-1β, TNF-α, IL-18, TGF-β1, VEGF, fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) drive fibrosis, angiogenesis, neovascularisation, vascular permeability, and tissue remodelling, maintaining a chronically inflamed but metabolically active pulp [77-79]. Collectively, DAMP-mediated signalling and neurogenic inflammation converge to establish self-amplifying innate immune and neuroimmune networks that perpetuate host-derived inflammatory signalling within the dental pulp. Through continuous release of cytokines, chemokines, neuropeptides, and endogenous danger signals, these interconnected pathways progressively amplify and propagate inflammation from the coronal towards the apical pulp, generating chemotactic gradients, increasing intrapulpal pressure, and providing a mechanistic basis by which persistent vital pulpitis may contribute to inflammation-mediated AP [6, 7, 18-20, 50, 55] (Fig. 1).

## Apical Migration of Pulpal Inflammation: Mechanistic Insights

Pulp inflammation propagates apically, activating immune responses in the periapical tissues. This process is the result of a sequence of neurogenic, hydrostatic, chemotactic, and structural mechanisms that together cause the inflammation to migrate from the coronal pulp to the apical region.

### *Neurogenic propagation of pulpal inflammation: the axon reflex mechanism*

The axon reflex is a neurophysiological mechanism whereby peripheral nociceptive C- and Aδ-fibres transmit antidromic impulses, releasing neuropeptides from branching terminals without central synaptic transmission [21, 23, 80]. As inflammation progresses, these mediators diffuse through the pulp, sequentially activating progressively more apical regions along the course of nociceptive fibres [6, 7, 20, 57]. Endothelial cells, fibroblasts, and resident immune cells respond to this increasing local neuropeptide concentration, with the subsequent release of additional inflammatory mediators and DAMPs in response to cellular stress, further amplifying host-derived inflammatory signalling [21]. Consequently, neuroimmune activation and endogenous danger signalling reinforce one another, propagating pulpal inflammation towards the periapical tissues. Accordingly, early periapical inflammation is considered predominantly neurogenic [18, 81, 82].



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

***Intrapulpal pressure as a hydrostatic driver of pulp-to-periapical inflammatory progression***

Tissue pressure refers to the hydrostatic pressure exerted by interstitial fluid surrounding the cells of the dental pulp. Under physiological conditions, intrapulpal (interstitial) pressure remains considerably lower than intravascular blood pressure, enabling efficient microcirculatory exchange [83, 84]. Nevertheless, the pulp's anatomical restriction encased within rigid dentinal walls makes it a low-compliance environment in which changes in capillary filtration and vascular permeability can translate into measurable increases in interstitial pressure [57, 84]. During inflammation, pulpal interstitial fluid pressure has been reported to rise approximately threefold [85].

However, as emphasised by Donaldson's physiological interpretation of the findings of Bletsa *et al*., [85] acute pulpal inflammation may reduce blood flow without increasing interstitial fluid volume; thus, inflamed vessels are not necessarily compressed to the point of closure. Instead, reduced perfusion reflects increased postcapillary resistance, enhanced microvascular permeability, and altered hydrostatic and colloid osmotic gradients, making tissue fluid homeostasis largely dependent on lymphatic drainage [85]. When filtration exceeds lymphatic clearance, the resulting pressure gradient may promote the apical movement of extracellular fluid carrying cytokines, chemokines, DAMPs, and neuropeptides through the apical foramen into the periodontal ligament (PDL) and periapical tissues [57, 84]. This pressure-facilitated (hydraulic) translocation may propagate inflammatory signals corono-apically and contribute to AP without uniform or immediate pulpal necrosis [57, 84].

***Chemokine signalling in persistent pulpal inflammation: apical gradients guiding immune cell migration***

Inflammasome activation is an upstream regulatory node linking danger sensing to chemokine-driven immune cell recruitment in pulpal inflammation. Redistribution of NLRP3 from the odontoblast layer in healthy pulp to a diffuse pattern in pulpitis reflects the transition from localised barrier signalling to widespread inflammatory amplification. Inflammasome assembly may also mark the transition from reversible to irreversible pulpal inflammation, facilitating corono-apical propagation of host-derived immune responses through chemokine-mediated recruitment and activation of inflammatory cells towards the periapical tissues [38]. This sustained inflammatory activity provides a mechanistic basis for the limited regenerative capacity of advanced pulpitis and supports vital pulp therapy (VPT) before irreversible inflammatory reprogramming is established [38].

Furthermore, the production of chemokines by pulpal cells is a key mechanism for guiding the recruitment of immune cells during pulpal inflammation. When activated by DAMPs, PAMPs, pro-inflammatory cytokines, oxidative stress, or neurogenic mediators, various resident and immune cells within the pulp including odontoblasts, fibroblasts, endothelial cells, macrophages, mast cells, and lymphocytes upregulate the expression of a broad range of chemokines [19, 23]. These include CCL2 (MCP-1), CCL3 (MIP-1α), CCL5 (RANTES), CXCL8 (IL-8), CXCL10 (IP-10), and CCL20 (MIP-3α), which collectively coordinate leukocyte migration within inflamed tissues [19, 23, 38, 55, 86]. CXCL8, a potent attractant for neutrophils, is secreted in large amounts by activated odontoblasts and pulpal fibroblasts. CCL2 plays a crucial role in recruiting circulating monocytes and promoting their differentiation into pro-inflammatory macrophages. CCL3 and CCL5 are vital mediators in recruiting activated T lymphocytes to sites of chronic inflammation [19, 23, 55, 86].

Inflammatory mediators in the pulp extracellular matrix establish chemotactic gradients that guide immune cell migration [23, 87]. As inflammation advances apically, mediator concentration peaks near the apical foramen, and intrapulpal pressure-driven flow enhances apical diffusion, directing circulating immune cells into the apical pulp and periapical tissues [57]. Neuropeptides such as CGRP and SP amplify chemokine production by pulpal and endothelial cells [21, 82]. The resulting apical chemokine gradient, together with tissue degradation, neuropeptide signalling, and hydrostatic forces, coordinates the apical propagation of host-driven inflammatory responses along the pulp–periapical axis (Fig. 2).

## Immune and Cellular Responses in Inflammation-Mediated AP

Sublethal stimuli activate sensory nociceptors and immune pathways, extending inflammation beyond the pulp. Aδ and C fibres detect PGE2, IL-1β, TNF-α, DAMPs, and PAMPs, releasing neuropeptides via axon reflexes [21, 35, 51]. These mediators induce endothelial activation, vasodilation, plasma extravasation, oedema, and hypoxia, promoting further cellular damage and DAMP release [51, 57]. The resulting inflammatory signals diffuse apically, establishing a host-derived inflammatory gradient that sustains chronic neuroimmune activation in the apical pulp and periapical tissues [7, 18-20, 57].

As pulp inflammation reaches the periapex, neuropeptides such as SP and CGRP are released by peripheral nerve terminals in the apical PDL, propagating neurogenic inflammation [21, 23, 81].



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

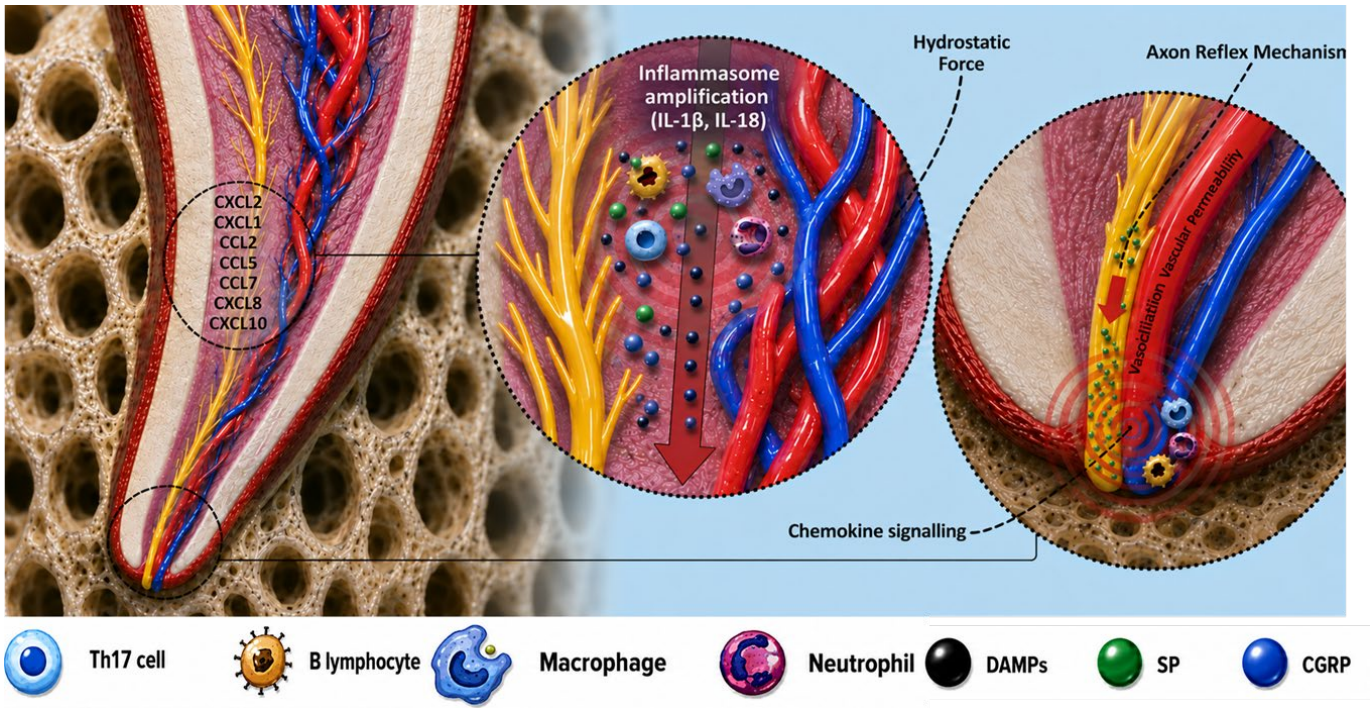



***Figure 2.*** Mechanistic pathways of apical migration in pulpal inflammation**.** Neurogenic propagation via the axon reflex releases neuropeptides along nociceptive fibres, amplifying local immune activation. Concurrently, rising intrapulpal pressure forces cytokines, DAMPs, and chemokines apically, while resident pulp and endothelial cells establish chemotactic gradients that recruit leukocytes toward the apical foramen. Together, these mechanisms may contribute to the transition from pulpitis to inflammation-mediated AP.

This signalling activates endothelial cells to express ICAM-1 and VCAM-1, promoting leukocyte transmigration. Local fibroblasts, mast cells, macrophages, and immune cells expressing neuropeptide receptors are activated to secrete pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-8, TNF, PGE2) and chemokines (CCL2, CXCL8) [21, 23]. This early periapcal activation marks the onset of inflammation-mediated AP.

DAMPs from inflamed pulp diffuse through the apical foramen or are locally produced, engaging PRRs on PDL and periapical bone cells. They activate TLR2 and TLR4, promoting periapical lesion progression via nitric oxide (NO) and reactive oxygen species (ROS) by macrophages [38, 88]. TLRs/NLRs stimulation in gingival fibroblasts induces IL-6 and IL-8, confirming PRR activity in periodontal tissue [38]. PRR detection of DAMPs triggers canonical signalling cascades converging on NF-κB, activator protein-1 (AP-1), and MAPK [38, 89-92], driving transcription of pro-inflammatory cytokines and chemokines (IL-1, TNF-α, IL-6). These mediators regulate osteoclast differentiation, bone resorption, enhance vascular permeability, and recruit neutrophils, monocytes, and lymphocytes [38, 89-92]. TNF-α directly promotes osteoclast precursors, enhancing RANKL-induced osteoclastogenesis [93], while TLR-driven TNF-α and IL-6 further support osteoclast differentiation alongside RANKL [94]. This host-mediated inflammatory milieu recapitulates molecular signatures typically associated with infection-driven responses.

NLRP3 and AIM2 inflammasomes are expressed in inflammatory periapical tissues [94, 95]. Upon DAMP recognition, ASC and procaspase-1 are recruited via pyrin and caspase recruitment domains, activating caspase-1 to mature and secrete IL-1β and IL-18 [94-97]. Inflammasomes are present in fibroblasts, monocytes, neutrophils, macrophages, and endothelial cells, with NLRP3-positive cell counts correlating with inflammatory infiltration and IL-1β/IL-18 expression [95].

Activation of inflammasomes plays a pivotal role in regulating osteoclast activity and periapical bone resorption [94]. Both PAMPs and DAMPs can stimulate inflammasome complexes in osteoclasts and their precursors, leading to hypermultinucleation and the secretion of IL-1β [94, 98]. This cytokine, primarily produced through inflammasome activation, exerts both direct and indirect effects on osteoclastogenesis [99, 100]. IL-1β promotes osteoclast differentiation from early blasts, myeloid progenitors, and monocytes in the presence of macrophage colony-stimulating factor (M-CSF) and RANKL, and also acts synergistically with TNF-α to enhance osteoclastogenesis [101, 102]. IL-1β stimulates RANKL expression in osteoblasts and osteocytes while increasing M-CSF levels and reducing OPG



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

production, tipping the balance toward enhanced bone resorption [103, 104]. IL-1β-induced chemokines, such as CX3CL1, also facilitate the migration and differentiation of osteoclast precursors [105]. Beyond differentiation, IL-1β upregulates proteolytic enzymes, such as cathepsin K and matrix metalloproteinases (MMPs), thereby augmenting the degradative capacity of osteoclasts on the extracellular matrix, particularly in periodontal tissues [94, 106, 107][95,107,108]. IL-18 has been reported to mediate inflammation in AP [108]. IL-18-induced IFN-γ from Th1 and NK cells exerts complex effects, being both anti-osteoclastogenic in direct settings and pro-resorptive in inflammatory environments [109]. IL-1β and IL-18 also modulate adaptive immune responses that indirectly amplify osteoclastogenesis by enhancing B cell activation and T cell differentiation, stimulating further RANKL production [94, 110][95,111]. IL-1β is crucial for the differentiation of Th17 cells, whose IL-17 secretion drives RANKL and RANK expression in osteoclastogenesis-supporting cells [94, 111-114]. Additionally, dendritic cells especially under inflammatory stimuli can transdifferentiate into osteoclast-like cells, a process further potentiated by IL-1β [115, 116]. Inflammatory osteoclasts derived from dendritic cells produce higher levels of IL-1β compared to homeostatic monocyte-derived osteoclasts, contributing to the activation of TNF-α-producing CD4+ T cells and exacerbating bone loss [117].

Inflammasome activation enhances osteoclast maturation by promoting NF-κB signalling via ADP-ribosyltransferase diphtheria toxin-like 1 degradation and facilitates actin cytoskeleton remodelling, increasing resorptive capacity [95]. It modulates osteoclasts, osteoblasts, and immune/stromal cells, including PDL cells, macrophages, monocytes, neutrophils, and Th17 cells [94], contributing broadly to inflammatory bone lysis. Notably, DAMPs released from the bone matrix during osteolysis can activate inflammasome pathways, a process shown to be significantly attenuated in Nlrp3-deficient mice, which exhibit reduced bone loss compared to wild-type controls. Conversely, pharmacologic inhibition of bone resorption has been associated with diminished inflammasome activation, suggesting a reciprocal relationship between these processes [118]. Therefore, inflammasome activation appears to function not only as a driver but also as a downstream consequence of inflammatory bone degradation. This bidirectional feedback loop highlights the inflammasome as a key amplifier in the vicious cycle of bone inflammation and destruction. Collectively, inflammasome signalling emerges as a central regulator of osteoclast function and inflammatory bone loss in non-infectious inflammatory contexts.

In inflammation-mediated AP, the RANK/RANKL/OPG axis is dysregulated: PRR activation in fibroblasts, osteoblasts, and activated lymphocytes upregulates RANKL, while inflammatory cytokines suppress OPG [81, 94]. RANKL binds RANK on monocyte-derived precursors, driving multinucleated osteoclast formation and enhancing resorptive function, resulting in progressive periapical osteolysis [119, 120]. Experimental models confirm that IL-17, IL-1β, TNF-α, or DAMPs alone suffice to induce bone resorption via neurogenic and PRR-mediated mechanisms, independent of microbial infection [118, 121] (Fig. 3). Fig 4 presents a schematic representation of the biological model of inflammation-mediated AP.

## Clinical Evidence

Multiple clinical studies have systematically demonstrated that teeth diagnosed with inflamed but vital pulps can present with periapical osteolytic lesions of endodontic origin [9-17, 122-132]. In cases when pulpal inflammation is produced by infectious stimuli, such as deep caries or microbial penetration, the current literature firmly supports the use of VPT as an effective biological method to stop disease progression and promote periapical healing. Different VPTs (including direct and indirect pulp capping, as well as partial and full pulpotomies) achieved high clinical and radiographic success rates in permanent teeth diagnosed with irreversible pulpitis even in cases with radiographic signs of osteolytic periapical lesions [9-17, 122-132]. Importantly, baseline periapical status is a clinically relevant prognostic modifier. In a large retrospective cohort study of 1257 VPT-treated mature permanent teeth with carious pulp exposures, radiographic signs of AP at baseline were associated with a significantly higher risk of failure (adjusted hazard ratio=2.983), and among cases with concurrent symptomatic irreversible pulpitis and AP with PAI=3, the reported success rate was 78.5% (*i.e.*, lower than the overall success rate of 91.6%). Therefore, while VPT can be effective even in vital teeth presenting with AP, expected outcomes should be presented stratified by the presence/absence and severity of AP [125].

Histopathological and histobacteriological studies show that pulpal necrosis is closely associated with bacterial infiltration and sustained microbial colonisation. In the absence of bacterial invasion, preservation of pulpal blood flow and controlled bleeding during VPT indicate that the remaining apical pulp is viable and uncontaminated. Under these conditions, periapical osteolytic lesions are more plausibly explained by the apical propagation of inflammatory mediators from the inflamed pulp than by infectious signalling from the apical pulp [27].



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

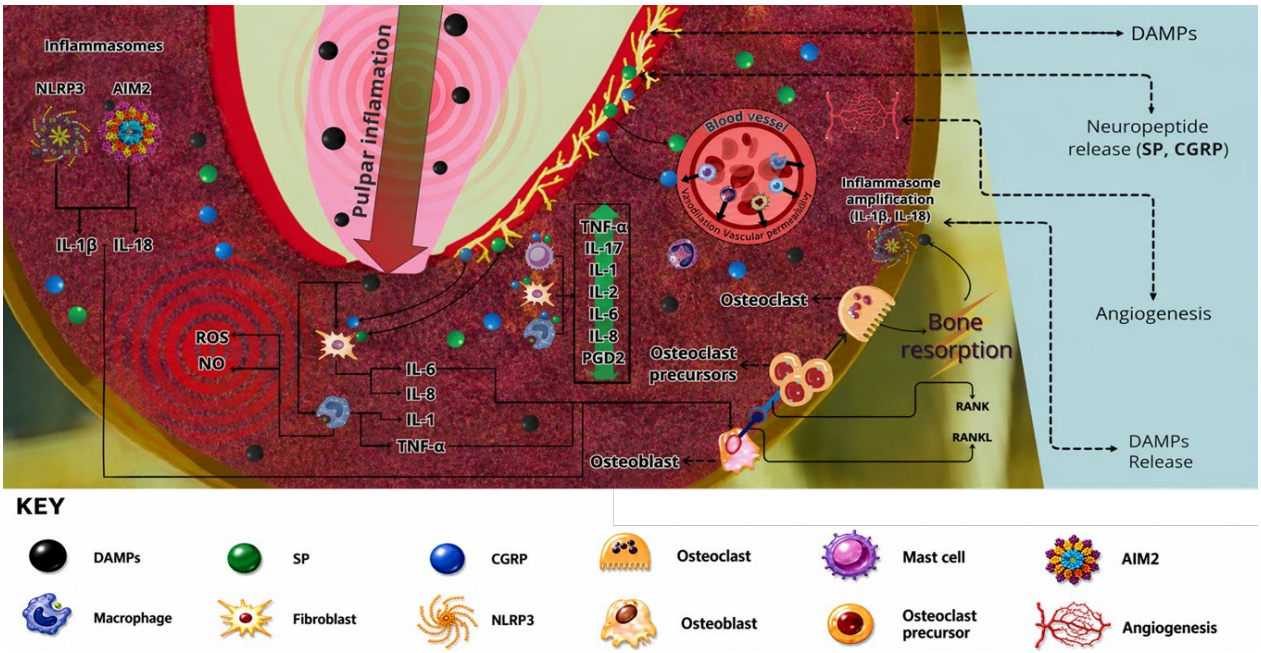



***Figure 3.*** Immune and cellular responses/inflammation-mediated AP. Neurogenic signalling from nociceptors (SP, CGRP) and the release of DAMPs initiate endothelial activation, oedema, and apical diffusion of inflammatory mediators. In the periapical tissues, neuropeptides and DAMP–PRR interactions trigger cytokine and chemokine production, inflammasome activation (NLRP3, AIM2), and NF-κB/MAPK pathways. These cascades amplify leukocyte recruitment, osteoclastogenesis via the RANK/RANKL/OPG axis, and progressive bone resorption in the absence of microbial infection.

Conversely, when inflammation is initiated by non-infectious stimuli, resolution often depends on eliminating the underlying insult, highlighting that biological rationale and treatment should be tailored to the initiating aetiology [21, 82, 126, 127]. Table 1 summarises clinical studies reporting teeth with pulpal inflammation of infectious or non-infectious origin associated with apical osteolytic lesions and their proposed treatment approaches.

Collectively, these clinical observations support the concept that pulp vitality and apical inflammatory responses are not mutually exclusive biological states. Further, these findings provide a biological rationale for VPT in carefully selected teeth with vital inflamed pulps and AP. By interrupting the inflammatory cascade while preserving healthy apical pulp tissue, VPT may not only maintain pulp vitality but also prevent further propagation of host-derived inflammatory signalling towards the periapical tissues, thereby creating conditions conducive to periapical healing.

***Limitations***

Although well-designed clinical and observational studies, including large cohorts of teeth with irreversible pulpitis, have reported periapical radiolucencies in vital teeth, they were not designed to assess microbial colonisation or the underlying inflammatory mechanisms [9, 17, 125]. Furthermore, much of the clinical evidence consists of case reports and case series, which are inherently hypothesis-generating. Mechanistic support for non-infectious pulpal inflammation, including DAMP–PRR signalling in odontoblast-lineage cells, is derived largely from preclinical studies rather than direct human validation [18-20]. Likewise, although mechanical stimuli such as occlusal interference and orthodontic forces increase pulpal neuropeptides (SP and CGRP) and VEGF, they have not been shown to cause AP or establish a temporal link with periapical lesion development. Collectively, these limitations highlight the need for robust translational and mechanistic human studies and warrant cautious interpretation of the proposed integrative model.

## Validation and Falsification of the Proposed Framework

The proposed inflammation-mediated framework should be regarded as a biologically plausible and experimentally testable model rather than an established mechanism of AP pathogenesis. Its central premise is that chronic pulpal inflammation may generate sufficient host-derived signalling to initiate periapical osteoimmune responses while the apical pulp remains vital and before established bacterial colonisation reaches the apical third. Consequently, the framework should be evaluated not by its consistency with the classical infection–necrosis paradigm, but by its ability to generate explicit, falsifiable predictions that can be rigorously tested through appropriately designed experimental and clinical studies.



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

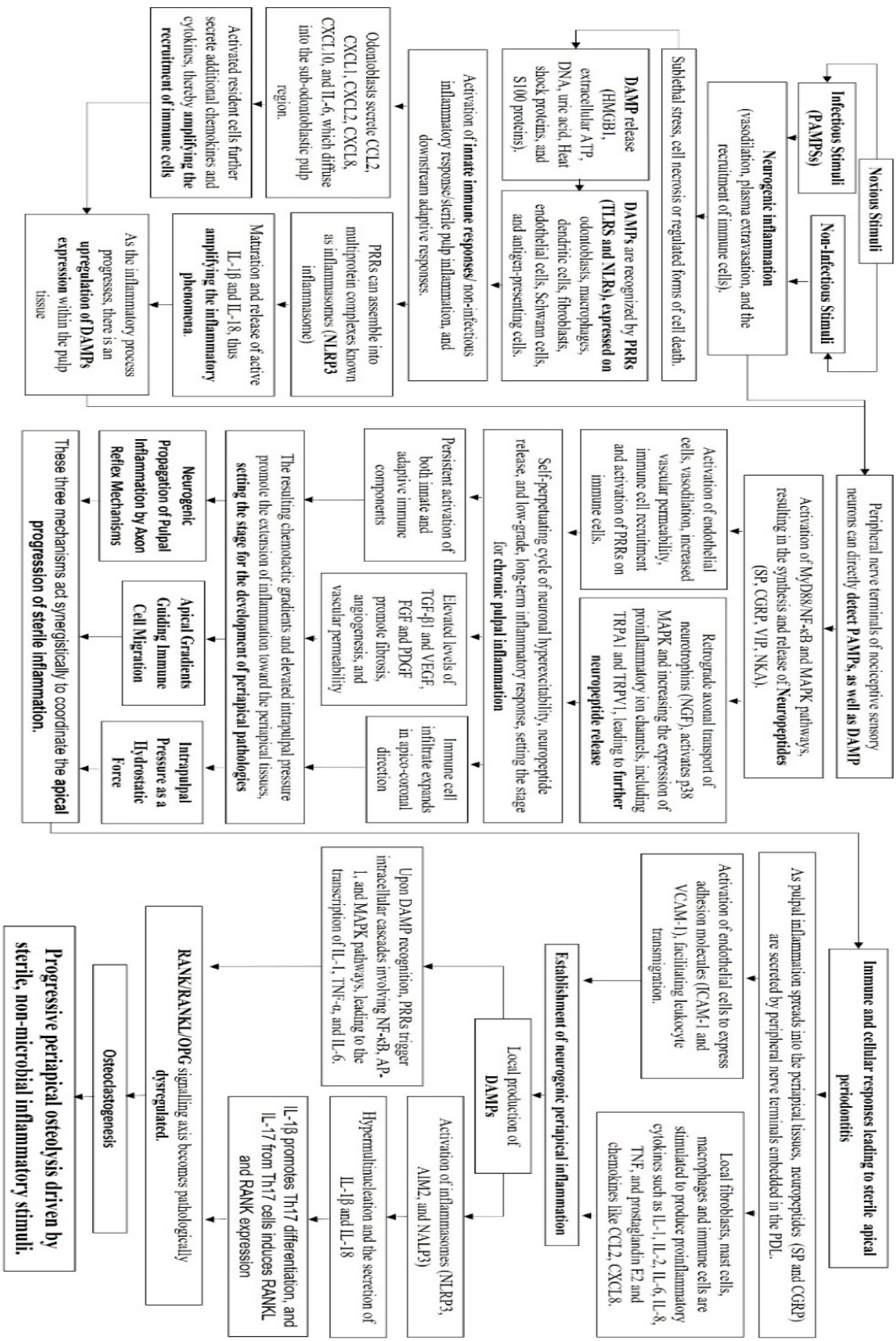



***Figure 4.*** Representation of the biological model Linking Pulpal Inflammation to inflammation-mediated AP.



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

***Table 1.*** Evidence-Based Summary of Therapeutic Approaches in Pulpitis with inflammation-mediated AP

| Authors | Study type | Therapeutic approach | Key outcomes | Relevance to inflammation-mediated AP |
|---|---|---|---|---|
| Alsharif *et al.* [128] | Case report | Partial pulpotomy with Biodentine | Complete periapical healing at 6 months. | A periapical lesion does not invariably necessitate root canal treatment. |
| Asgary *et al.* [12] | Case report | Cervical pulpotomy with calcium-enriched mixture (CEM) cement | Complete lesion healing at 2 years. | Vital pulp therapy may support recovery of periapical tissues. |
| Asgary *et al.* [14] | Case report | Direct pulp capping with CEM cement | Lesion resolution and normalization of the periodontal ligament space at 15 months. | Pulpal inflammation may coexist with apical lesions without complete pulp necrosis. |
| Abella *et al.* [9] | Cross-sectional imaging study | Comparison of periapical radiography and CBCT | Lesions were detected in 3.3% of roots by periapical radiography and 13.7% by CBCT. | Apical lesions in teeth diagnosed with irreversible pulpitis may be underdetected by periapical radiography. |
| Kim *et al.* [127] | Case report | Conservative restoration and monitoring | Complete resolution of the lesion by 14 months, with pulp vitality maintained. | Neurogenic inflammation may contribute to periapical lesion development, although causality remains unproven. |
| Bainbridge *et al.* [126] | Case report | Monitoring without root canal treatment | Complete bone fill of the lesion at approximately 15 months. | Trauma, occlusal factors, and periodontal disease may contribute to low-grade periapical inflammation. |
| Tsukiboshi *et al.* [131] | Case series | Full pulpotomy with calcium hydroxide | Pulp vitality was preserved and periapical lesions healed in all three cases. | Residual vital pulp tissue may coexist with an inflammatory periapical response. |
| Grabliauskiene *et al.* [135] | Two case reports | Pulpotomy using hydraulic calcium silicate cement | Lesions decreased and resolved during follow-up. | Periapical lesions may occur in teeth with vital pulp tissue. |
| Tran *et al.* [130] | Two case reports | Full pulpotomy with tricalcium silicate-based cement | Clinical improvement and periapical healing at 2 years. | Controlling pulpal inflammation may facilitate periapical tissue repair. |
| Asgary *et al.* [17] | Multicentre randomized clinical trial | Vital pulp therapy versus conventional root canal treatment | Among cases with preoperative periapical lesions, the root canal treatment group had a significantly higher failure rate for periapical healing at 6 and 12 months. | Comparative clinical evidence supports VPT as a potential option in selected cases. |
| Moore [122] | Case series | Conservative treatment using calcium hydroxide | Pulp vitality was maintained and lesions resolved by 6 months. | A periapical radiolucency does not necessarily indicate pulp necrosis. |
| Xiao *et al.* [129] | Randomized controlled trial | Pulpotomy versus apexification | Tooth survival was 100%; pulpotomy promoted greater root lengthening and apical narrowing. | VPT may support periapical healing and continued root development in immature teeth. |
| Asgary *et al.* [123] | Two case reports | Miniature pulpotomy with CEM cement | Pain resolved and apical lesions healed by 18 months. | Conservative VPT may be effective in selected mature teeth with pulpitis and apical periodontitis. |
| Asgary *et al.* [125] | Large retrospective cohort study | Direct pulp capping, partial pulpotomy, and full pulpotomy | Overall VPT survival was 99.1% and success was 91.6%; apical healing rates ranged from 85% to 88%. | VPT can be successful in selected vital teeth presenting with periapical lesions. |
| Asgary *et al.* [10] | Case report | Pulpotomy with CEM cement | Periapical healing and preserved function at 6 months. | Control of pulpal inflammation may contribute to resolution of periapical inflammation. |
| Torabzadeh *et al.* [13] | Case report | Selective caries removal and pulp capping with CEM cement | Pulp vitality was maintained and periapical healing was observed at 1 year. | Inflammation in a vital pulp may be associated with a periapical lesion. |
| Asgary [132] | Case report | Full pulpotomy with CEM cement | The tooth remained functional and the lesion resolved over 4 years. | Healing after removal of coronal pulp tissue, with vital radicular pulp retained, is consistent with but does not prove an inflammation-mediated mechanism. |



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

***Evidence supporting the framework: the temporal dissociation between periapical response and pulp necrosis***

The most consistent line of support across the following supporting animal studies is the demonstration that periapical tissue activation begins while the pulp is still vital, or before pulpal necrosis is complete. Using tritiated-thymidine autoradiographic analysis, Stahl *et al.* [133] reported a significant rise in labelled periapical fibroblasts, osteoblasts and cementoblasts within one h of pulpal injury while the underlying pulp remained histologically vital, suggesting that biological signals generated within the injured pulp may rapidly influence the periapical environment. The authors themselves inferred that a "proliferation-stimulation factor" released from the traumatically altered pulpal environment reached and activated distant cells, a mechanistic interpretation that anticipates, in observational terms, the mediator-propagation mechanism this framework proposes. Likewise, Yamasaki *et al.* [7] in a histological and histometrical study, documented periapical inflammatory infiltration at day 3 and alveolar bone resorption at day 7, while pulpal necrosis was still confined coronally and had not reached the apex; complete necrosis occurred only around day 28, leading the authors to conclude that periapical inflammation began before complete pulpal necrosis.

Additional observations reinforce this temporal relationship. Tagger and Massler [134], in a large longitudinal study, found that the severity of periapical lesions correlated with the amount of vital pulp remaining rather than with the time elapsed since exposure, and described the vital pulp as acting as a "buffer against periapical irritation" whose efficiency was proportional to the length of the vital stump, suggesting that the biological status of the remaining pulp modulates and impacts the periapical response. Similarly, Kovačević *et al.* [8] supply a direct histopathological test of the framework's core temporal prediction in a large-animal model. All roots histologically diagnosed as pulpitis simultaneously exhibited acute AP, with active osteoclasts at the alveolar bone surface interposed between palisade-forming osteoblasts, despite preservation of the PDL at the root surface. Because the histological pulp diagnosis correlated with the stage of disease reached rather than with experimental duration, the study establishes that osteoclastic periapical bone resorption can begin during the pulpitis phase, before complete necrosis.

Complementing these histopathological observations, Tani-Ishii et al. detected early expression of IL-1α and TNF-α in the periapical region while bacterial colonisation remained restricted to the coronal pulp, supporting the concept that host-derived inflammatory signalling may precede bacterial extension into the apical region. Although these studies do not establish causality, they consistently suggest that the transition from pulpitis to apical periodontitis is biologically dynamic and that osteoimmune activation may begin before complete pulpal necrosis [136].

Mechanistically, these observations are compatible with the concept that an inflamed but metabolically active pulp constitutes a source of cytokines, lipid mediators, neuropeptides and danger-associated molecular patterns capable of diffusing towards the periapical tissues and promoting osteoclast recruitment. However, none of the reviewed studies was specifically designed to distinguish host-derived inflammatory mediators from diffusible bacterial products. Consequently, the current evidence supports the temporal plausibility of the proposed framework but does not establish its underlying mechanism.

***Evidence challenging or limiting the proposed framework***

The principal challenge to the proposed framework derives from classic animal experimental studies which collectively demonstrated that sterile necrotic pulps fail to produce persistent apical periodontitis, whereas bacterial colonisation consistently results in periapical lesion development. Möller *et al.* inoculated defined bacterial strains into mechanically devitalised monkey root canals and assessed them radiographically over 8–12 months. Apical periodontitis developed in 97–100% of canals from which viable bacteria were reisolated, whereas the four canals that became bacterium-free while still containing retained necrotic pulp tissue showed no radiographically detectable periapical reaction [137].

Fabricius *et al.* [138]reported a concordant internal negative control in the same experimental model: all teeth from which no inoculated bacteria were reisolated showed no radiographic periapical destruction, despite sealed necrotic tissue retained for six months, while polymicrobial combinations produced the greatest periapical destruction. Kakehashi *et al.* [139] supplied the foundational version of this negative control: in germ-free rats, surgically exposed pulps did not undergo complete necrosis and produced no apical abscess or granuloma, whereas conventional animals developed necrosis and periapical disease once bacterial colonisation was established. These studies firmly establish microorganisms as the principal causal factor in the conventional infection–necrosis model and demonstrate that passive necrotic tissue alone is insufficient to sustain periapical inflammation.

Importantly, these findings should not be interpreted as direct evidence against the proposed framework, as they address a fundamentally indirect biological condition. Whereas the present model concerns persistent vital pulpitis with ongoing inflammatory activity and sustained production of host-derived mediators, these investigations examined mechanically devitalised or germ-free necrotic pulps, in which metabolic activity and active inflammatory signalling were largely absent.



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

Consequently, they demonstrate that sterile necrosis alone is insufficient to induce apical periodontitis, but do not address whether chronic inflammation within a vital pulp can initiate periapical osteoimmune responses before established bacterial colonisation reaches the apical pulp. Overall, the available evidence supports several temporal predictions of the proposed framework but leaves its central biological mechanism unresolved, as no experimental study has specifically examined the combination of persistent vital pulpitis, bacterial confinement to the coronal pulp, preservation of apical pulp vitality, and simultaneous assessment of the resulting periapical osteoimmune response.

## Future Research Directions

The proposed inflammation-mediated framework is inherently falsifiable and provides a clear roadmap for future investigation. Its validation or refutation will require coordinated evidence across four complementary domains. First, human histopathological–microbiological studies should determine whether teeth with irreversible pulpitis and periapical radiolucencies retain a vital, non-colonised apical pulp at the time of earliest periapical activation, combining serial histological sectioning with contamination-controlled molecular microbiology.

Second, spatial molecular profiling using single-cell and spatial transcriptomics, together with proteomics, should characterise the corono-apical inflammatory gradient by quantifying DAMPs, PRRs, inflammasome components, and key osteoimmune mediators including IL-1β, TNF-α, NLRP3, caspase-1, and the RANK/RANKL/OPG axis while distinguishing DAMP- from PAMP-driven signalling across disease stages.

Third, prospective longitudinal cohorts of teeth with irreversible pulpitis and baseline apical periodontitis treated by VPT should determine whether periapical healing is associated with resolution of pulpal inflammation despite preservation of pulp vitality and the absence of canal disinfection, while simultaneously assessing whether changes in diffusible bacterial products or other PAMP-mediated signals contribute to the periapical response.

Finally, translational mechanistic studies including sterile animal models of chronic pulpitis induced without bacterial exposure, pathogen-free ex vivo human pulp–periapical systems, and targeted gain- and loss-of-function experiments involving NLRP3, caspase-1 and RANKL should establish whether host-derived inflammatory signalling alone is sufficient to initiate osteoimmune activation and periapical bone resorption.

The framework would be supported if these complementary approaches demonstrate that periapical inflammatory infiltration, osteoclastogenesis and bone resorption develop while the apical pulp remains histologically vital and free of established bacterial colonisation, together with early activation of IL-1β, TNF-α, NLRP3 inflammasome signalling, caspase-1, and RANKL upregulation with OPG suppression in the periapical microenvironment. Conversely, the framework would be refuted if early periapical activation is consistently associated with established apical bacterial colonisation or diffusible bacterial products, if the inflammatory and osteoimmune signatures described above are absent before bacterial invasion of the apical pulp, or if sterile chronic pulpitis fails to induce periapical osteoimmune activation and bone resorption despite persistent pulpal inflammation.

## Conclusion

This review proposes a biological framework whereby AP may arise from an inflamed but vital pulp through interconnected molecular and cellular pathways. The pulp and periapical tissues function as a continuous immunological unit linked by neural pathways, inflammatory mediators, and conserved receptor systems. Within this framework, chronic pulpal inflammation may generate sufficient host-derived signals to induce periapical bone resorption, immune cell infiltration, and tissue remodeling without requiring uniform bacterial colonisation or complete pulpal necrosis. Rather than replacing the established infection-based paradigm, the present framework complements current concepts by providing a biologically plausible explanation for selected cases in which persistent pulpal inflammation may contribute to periapical bone resorption despite preservation of pulpal vitality.

The proposed model is supported by converging mechanistic, experimental, and clinical evidence but awaits confirmation through well-designed human studies integrating histopathological, microbiological, and molecular analyses of the apical pulp and periapical tissues. Until then, it should be regarded as an evidence-informed framework that generates testable hypotheses and provides a biologically plausible explanation for inflammation-mediated AP.

***Acknowledgements***
None

***Conflict of interest***
None.

***Funding support***
None.

***Authors' contributions***
NRO is the sole author and is solely responsible for all aspects of the study, including conception, data collection, analysis, and manuscript preparation.



This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

## References


1. Nair PN. Apical periodontitis: a dynamic encounter between root canal infection and host response. Periodontol 2000. 1997;13:121-48.
2. Arias Z, Nizami MZI, Chen X, Chai X, Xu B, Kuang C, et al. Recent Advances in Apical Periodontitis Treatment: A Narrative Review. Bioengineering (Basel). 2023;10(4).
3. Rios Osorio N, Caviedes-Bucheli J, Mosquera-Guevara L, Adames-Martinez JS, Gomez-Pinto D, Jimenez-Jimenez K, et al. The Paradigm of the Inflammatory Radicular Cyst: Biological Aspects to be Considered. Eur Endod J. 2023;8(1):20-36.
4. Lin LM, Ricucci D, Lin J, Rosenberg PA. Nonsurgical root canal therapy of large cyst-like inflammatory periapical lesions and inflammatory apical cysts. J Endod. 2009;35(5):607-15.
5. Asgary S, Parhizkar A. The Role of Vital Pulp Therapy in the Management of Periapical Lesions - Letter to the Editor. Eur Endod J. 2021;6(1):130-1.
6. Asgary S, Aminoshariae A, Wesselink PR. Apical Periodontitis in Vital and Nonvital Teeth: Clinical and Radiographic Features. Iran Endod J. 2024;19(3):148-57.
7. Yamasaki M, Kumazawa M, Kohsaka T, Nakamura H, Kameyama Y. Pulpal and periapical tissue reactions after experimental pulpal exposure in rats. J Endod. 1994;20(1):13-7.
8. Kovacević M, Tamarut T, Jonjić N, Braut A, Kovacević M. The transition from pulpitis to periapical periodontitis in dogs' teeth. Aust Endod J. 2008;34(1):12-8.
9. Abella F, Patel S, Duran-Sindreu F, Mercadé M, Bueno R, Roig M. Evaluating the periapical status of teeth with irreversible pulpitis by using cone-beam computed tomography scanning and periapical radiographs. J Endod. 2012;38(12):1588-91.
10. Asgary S, Kemal Çalışkan M. Vital Pulp Therapy of a Mature Molar with Concurrent Hyperplastic Pulpitis, Internal Root Resorption and Periradicular Periodontitis: A Case Report. Iran Endod J. 2015;10(4):284-6.
11. Asgary S, Fazlyab M, Sabbagh S, Eghbal MJ. Outcomes of different vital pulp therapy techniques on symptomatic permanent teeth: a case series. Iran Endod J. 2014;9(4):295-300.
12. Asgary S. Calcium-enriched mixture pulpotomy of a human permanent molar with irreversible pulpitis and condensing apical periodontitis. J Conserv Dent. 2011;14(1):90-3.
13. Torabzadeh H, Asgary S. Indirect pulp therapy in a symptomatic mature molar using calcium enriched mixture cement. J Conserv Dent. 2013;16(1):83-6.
14. Asgary S, Nosrat A, Homayounfar N. Periapical healing after direct pulp capping with calcium-enriched mixture cement: a case report. Oper Dent. 2012;37(6):571-5.
15. Kahler B, Taha NA, Lu J, Saoud TM. Vital pulp therapy for permanent teeth with diagnosis of irreversible pulpitis: biological basis and outcome. Aust Dent J. 2023;68 Suppl 1:S110-s22.
16. Lin L, Langeland K. Light and electron microscopic study of teeth with carious pulp exposures. Oral Surg Oral Med Oral Pathol. 1981;51(3):292-316.
17. Asgary S, Eghbal MJ, Ghoddusi J, Yazdani S. One-year results of vital pulp therapy in permanent molars with irreversible pulpitis: an ongoing multicenter, randomized, non-inferiority clinical trial. Clin Oral Investig. 2013;17(2):431-9.
18. Al Natour B, Lundy FT, Moynah PN, About I, Jeanneau C, Irwin CR, et al. Odontoblast cell death induces NLRP3 inflammasome-dependent sterile inflammation and regulates dental pulp cell migration, proliferation and differentiation. Int Endod J. 2021;54(6):941-50.
19. Yumoto H, Hirao K, Hosokawa Y, Kuramoto H, Takegawa D, Nakanishi T, et al. The roles of odontoblasts in dental pulp innate immunity. Jpn Dent Sci Rev. 2018;54(3):105-17.
20. Pohl S, Akamp T, Smeda M, Uderhardt S, Besold D, Krastl G, et al. Understanding dental pulp inflammation: from signaling to structure. Front Immunol. 2024;15:1474466.
21. Caviedes-Bucheli J, Muñoz HR, Azuero-Holguín MM, Ulate E. Neuropeptides in dental pulp: the silent protagonists. J Endod. 2008;34(7):773-88.
22. Ríos-Osorio N, Muñoz-Alvear HD, Montoya Cañón S, Restrepo-Mendez S, Aguilera-Rojas SE, Jiménez-Peña O, et al. Association between type 2 diabetes mellitus and the evolution of endodontic pathology. Quintessence Int. 2020;51(2):100-7.
23. Silva TA, Garlet GP, Fukada SY, Silva JS, Cunha FQ. Chemokines in oral inflammatory diseases: apical periodontitis and periodontal disease. J Dent Res. 2007;86(4):306-19.
24. Nair PN. Pathogenesis of apical periodontitis and the causes of endodontic failures. Crit Rev Oral Biol Med. 2004;15(6):348-81.
25. Widmer C, Skutas J, Easson C, Lopez JV, Torneck C, Flax M, et al. Culture-independent Characterization of the Microbiome of Healthy Pulp. J Endod. 2018;44(7):1132-9.e2.
26. Bérard A, Mauffrey F, Gaïa N, Perez A, Chaabane C, Schrenzel J, et al. Microbiota of Healthy Dental Pulp Under the Omics Loupe. Int J Mol Sci. 2025;26(7).
27. Ricucci D, Siqueira JF, Jr., Li Y, Tay FR. Vital pulp therapy: histopathology and histobacteriology-based guidelines to treat teeth with deep caries and pulp exposure. J Dent. 2019;86:41-52.
28. Ricucci D, Siqueira JF, Jr., Abdelsayed RA, Lio SG, Rôças IN. Bacterial Invasion of Pulp Blood Vessels in Teeth with Symptomatic Irreversible Pulpitis. J Endod. 2021;47(12):1854-64.
29. Yu C, Abbott PV. An overview of the dental pulp: its functions and responses to injury. Aust Dent J. 2007;52(1 Suppl):S4-16.
30. Caviedes-Bucheli J, Azuero-Holguin MM, Correa-Ortiz JA, Aguilar-Mora MV, Pedroza-Flores JD, Ulate E, et al. Effect of experimentally induced occlusal trauma on substance p expression in human dental pulp and periodontal ligament. J Endod. 2011;37(5):627-30.
31. Caviedes-Bucheli J, Moreno JO, Ardila-Pinto J, Del Toro-Carreño HR, Saltarín-Quintero H, Sierra-Tapias CL, et al. The effect of orthodontic forces on calcitonin gene-related peptide expression in human dental pulp. J Endod. 2011;37(7):934-7.
32. Caviedes-Bucheli J, Lopez-Moncayo LF, Muñoz-Alvear HD, Gomez-Sosa JF, Diaz-Barrera LE, Curtidor H, et al. Expression of substance P, calcitonin gene-related peptide and vascular endothelial growth factor in human dental pulp under different clinical stimuli. BMC Oral Health. 2021;21(1):152.
33. Caviedes-Bucheli J, Ariza-García G, Restrepo-Méndez S, Ríos-Osorio N, Lombana N, Muñoz HR. The effect of tooth bleaching on substance P expression in human dental pulp. J Endod. 2008;34(12):1462-5.
34. Murao A, Aziz M, Wang H, Brenner M, Wang P. Release mechanisms of major DAMPs. Apoptosis. 2021;26(3-4):152-62.
35. Bianchi ME. DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukoc Biol. 2007;81(1):1-5.
36. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018;9(6):7204-18.




This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

37. Jiang HW, Zhang W, Ren BP, Zeng JF, Ling JQ. Expression of toll like receptor 4 in normal human odontoblasts and dental pulp tissue. J Endod. 2006;32(8):747-51.
38. Jiang W, Lv H, Wang H, Wang D, Sun S, Jia Q, et al. Activation of the NLRP3/caspase-1 inflammasome in human dental pulp tissue and human dental pulp fibroblasts. Cell Tissue Res. 2015;361(2):541-55.
39. Lin ZM, Song Z, Qin W, Li J, Li WJ, Zhu HY, et al. Expression of nucleotide-binding oligomerization domain 2 in normal human dental pulp cells and dental pulp tissues. J Endod. 2009;35(6):838-42.
40. Keller JF, Carrouel F, Colomb E, Durand SH, Baudouin C, Msika P, et al. Toll-like receptor 2 activation by lipoteichoic acid induces differential production of pro-inflammatory cytokines in human odontoblasts, dental pulp fibroblasts and immature dendritic cells. Immunobiology. 2010;215(1):53-9.
41. Park C, Lee SY, Kim HJ, Park K, Kim JS, Lee SJ. Synergy of TLR2 and H1R on Cox-2 Activation in Pulpal Cells. J Dent Res. 2010;89(2):180-5.
42. Mutoh N, Tani-Ishii N, Tsukinoki K, Chieda K, Watanabe K. Expression of toll-like receptor 2 and 4 in dental pulp. J Endod. 2007;33(10):1183-6.
43. Ziegler-Heitbrock HW, Ulevitch RJ. CD14: cell surface receptor and differentiation marker. Immunol Today. 1993;14(3):121-5.
44. Desai SV, Love RM, Rich AM, Seymour GJ. Antigen recognition and presentation in periapical tissues: a role for TLR expressing cells? Int Endod J. 2011;44(2):87-99.
45. Staquet MJ, Durand SH, Colomb E, Roméas A, Vincent C, Bleicher F, et al. Different roles of odontoblasts and fibroblasts in immunity. J Dent Res. 2008;87(3):256-61.
46. Gong T, Liu L, Jiang W, Zhou R. DAMP-sensing receptors in sterile inflammation and inflammatory diseases. Nat Rev Immunol. 2020;20(2):95-112.
47. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010;140(6):805-20.
48. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta. Mol Cell. 2002;10(2):417-26.
49. Wang W, Wang X, Chun J, Vilaysane A, Clark S, French G, et al. Inflammasome-independent NLRP3 augments TGF-β signaling in kidney epithelium. J Immunol. 2013;190(3):1239-49.
50. Anders HJ, Schaefer L. Beyond tissue injury-damage-associated molecular patterns, toll-like receptors, and inflammasomes also drive regeneration and fibrosis. J Am Soc Nephrol. 2014;25(7):1387-400.
51. Donnelly CR, Chen O, Ji RR. How Do Sensory Neurons Sense Danger Signals? Trends Neurosci. 2020;43(10):822-38.
52. Al Natour B, Lundy FT, About I, Jeanneau C, Dombrowski Y, El Karim IA. Regulation of caries-induced pulp inflammation by NLRP3 inflammasome: A laboratory-based investigation. Int Endod J. 2023;56(2):193-202.
53. Bleicher F. Odontoblast physiology. Exp Cell Res. 2014;325(2):65-71.
54. Ríos-Osorio N, Gutmann JL, Botero TM, Taha N, Fernández-Grisales R, Guerrero-Torres M, et al. Redefining the Evolution of Pulpal Pathology: Inflammasomes as Central Integrative Hubs and Biological Switches Governing the Transition From Reversible to Irreversible Pulpal Inflammation Beyond Symptom-Based Classification. Int Endod J. 2026;59(10):1986-2027.
55. Farges JC, Alliot-Licht B, Renard E, Ducret M, Gaudin A, Smith AJ, et al. Dental Pulp Defence and Repair Mechanisms in Dental Caries. Mediators Inflamm. 2015;2015:230251.
56. Turner MD, Nedjai B, Hurst T, Pennington DJ. Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. Biochim Biophys Acta. 2014;1843(11):2563-82.
57. Samir PV, Mahapatra N, Dutta B, Bagchi A, Dhull KS, Verma RK. A Correlation between Clinical Classification of Dental Pulp and Periapical Diseases with its Patho Physiology and Pain Pathway. Int J Clin Pediatr Dent. 2023;16(4):639-44.
58. Caviedes-Bucheli J, Correa-Ortiz JA, Ballestero AC, Jimenez M, Munoz A, Rivero C, et al. The effect of dentine-bonding agents on substance P release in human dental pulp. Int Endod J. 2010;43(2):95-101.
59. Wang L, Manji GA, Grenier JM, Al-Garawi A, Merriam S, Lora JM, et al. PYPAF7, a novel PYRIN-containing Apaf1-like protein that regulates activation of NF-kappa B and caspase-1-dependent cytokine processing. J Biol Chem. 2002;277(33):29874-80.
60. Zhang ZJ, Guo JS, Li SS, Wu XB, Cao DL, Jiang BC, et al. TLR8 and its endogenous ligand miR-21 contribute to neuropathic pain in murine DRG. J Exp Med. 2018;215(12):3019-37.
61. He L, Han G, Wu S, Du S, Zhang Y, Liu W, et al. Toll-like receptor 7 contributes to neuropathic pain by activating NF-κB in primary sensory neurons. Brain Behav Immun. 2020;87:840-51.
62. Li Y, Zhang H, Zhang H, Kosturakis AK, Jawad AB, Dougherty PM. Toll-like receptor 4 signaling contributes to Paclitaxel-induced peripheral neuropathy. J Pain. 2014;15(7):712-25.
63. Ji RR, Samad TA, Jin SX, Schmoll R, Woolf CJ. p38 MAPK activation by NGF in primary sensory neurons after inflammation increases TRPV1 levels and maintains heat hyperalgesia. Neuron. 2002;36(1):57-68.
64. Obata K, Katsura H, Mizushima T, Yamanaka H, Kobayashi K, Dai Y, et al. TRPA1 induced in sensory neurons contributes to cold hyperalgesia after inflammation and nerve injury. J Clin Invest. 2005;115(9):2393-401.
65. Liu XJ, Zhang Y, Liu T, Xu ZZ, Park CK, Berta T, et al. Nociceptive neurons regulate innate and adaptive immunity and neuropathic pain through MyD88 adapter. Cell Res. 2014;24(11):1374-7.
66. Byers MR, Närhi MV. Dental injury models: experimental tools for understanding neuroinflammatory interactions and polymodal nociceptor functions. Crit Rev Oral Biol Med. 1999;10(1):4-39.
67. Smith CH, Barker JN, Morris RW, MacDonald DM, Lee TH. Neuropeptides induce rapid expression of endothelial cell adhesion molecules and elicit granulocytic infiltration in human skin. J Immunol. 1993;151(6):3274-82.
68. Cao B, Xu Q, Shi Y, Zhao R, Li H, Zheng J, et al. Pathology of pain and its implications for therapeutic interventions. Signal Transduct Target Ther. 2024;9(1):155.
69. Park SH, Hsiao GY, Huang GT. Role of substance P and calcitonin gene-related peptide in the regulation of interleukin-8 and monocyte chemotactic protein-1 expression in human dental pulp. Int Endod J. 2004;37(3):185-92.
70. Patel T, Park SH, Lin LM, Chiappelli F, Huang GT. Substance P induces interleukin-8 secretion from human dental pulp cells. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96(4):478-85.
71. Hargreaves KM, Swift JQ, Roszkowski MT, Bowles W, Garry MG, Jackson DL. Pharmacology of peripheral neuropeptide and inflammatory mediator release. Oral Surg Oral Med Oral Pathol. 1994;78(4):503-10.
72. Wang R, Lan C, Benlagha K, Camara NOS, Miller H, Kubo M, et al. The interaction of innate immune and adaptive immune system. MedComm (2020). 2024;5(10):e714.




This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

73. Osaki J, Yamazaki S, Hikita A, Hoshi K. Hematopoietic progenitor cells specifically induce a unique immune response in dental pulp under conditions of systemic inflammation. Heliyon. 2022;8(2):e08904.
74. Kawashima N, Okiji T. Characteristics of inflammatory mediators in dental pulp inflammation and the potential for their control. Front Dent Med. 2024;5:1426887.
75. Eisenstein EM, Williams CB. The T(reg)/Th17 cell balance: a new paradigm for autoimmunity. Pediatr Res. 2009;65(5 Pt 2):26r-31r.
76. Liu M, Zhao Y, Wang C, Luo H, A P, Ye L. Interleukin-17 plays a role in pulp inflammation partly by WNT5A protein induction. Arch Oral Biol. 2019;103:33-9.
77. Balic A, Perver D, Pagella P, Rehrauer H, Stadlinger B, Moor AE, et al. Extracellular matrix remodelling in dental pulp tissue of carious human teeth through the prism of single-cell RNA sequencing. Int J Oral Sci. 2023;15(1):30.
78. Álvarez-Vásquez JL, Castañeda-Alvarado CP. Dental Pulp Fibroblast: A Star Cell. J Endod. 2022;48(8):1005-19.
79. Boyle M, Chun C, Strojny C, Narayanan R, Bartholomew A, Sundivakkam P, et al. Chronic inflammation and angiogenic signaling axis impairs differentiation of dental-pulp stem cells. PLoS One. 2014;9(11):e113419.
80. Steinhoff M, Bienenstock J, Schmelz M, Maurer M, Wei E, Bíró T. Neurophysiological, neuroimmunological, and neuroendocrine basis of pruritus. J Invest Dermatol. 2006;126(8):1705-18.
81. Braz-Silva PH, Bergamini ML, Mardegan AP, De Rosa CS, Hasseus B, Jonasson P. Inflammatory profile of chronic apical periodontitis: a literature review. Acta Odontol Scand. 2019;77(3):173-80.
82. Caviedes-Bucheli J, Moreno JO, Aranguren-Carrero M, Buitrago-Rojas S, Lopez-Matheus R, Martinez-Corredor G, et al. The effect of orthodontic forces on calcitonin gene-related peptide (CGRP) expression in the human periodontal ligament and its relationship with the human dental pulp. J Clin Exp Dent. 2022;14(11):e932-e7.
83. Berggreen E, Wiig H, Virtej A. Fluid transport from the dental pulp revisited. Eur J Oral Sci. 2020;128(5):365-8.
84. Heyeraas KJ, Berggreen E. Interstitial fluid pressure in normal and inflamed pulp. Crit Rev Oral Biol Med. 1999;10(3):328-36.
85. Donaldson LF. Understanding pulpitis. J Physiol. 2006;573(Pt 1):2-3.
86. Kawka E, Witowski J, Fouqet N, Tayama H, Bender TO, Catar R, et al. Regulation of chemokine CCL5 synthesis in human peritoneal fibroblasts: a key role of IFN-γ. Mediators Inflamm. 2014;2014:590654.
87. Terricabras E, Benjamim C, Godessart N. Drug discovery and chemokine receptor antagonists: eppur si muove! Autoimmun Rev. 2004;3(7-8):550-6.
88. Marcato LG, Ferlini AP, Bonfim RC, Ramos-Jorge ML, Ropert C, Afonso LF, et al. The role of Toll-like receptors 2 and 4 on reactive oxygen species and nitric oxide production by macrophage cells stimulated with root canal pathogens. Oral Microbiol Immunol. 2008;23(5):353-9.
89. He W, Qu T, Yu Q, Wang Z, Lv H, Zhang J, et al. LPS induces IL-8 expression through TLR4, MyD88, NF-kappaB and MAPK pathways in human dental pulp stem cells. Int Endod J. 2013;46(2):128-36.
90. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell. 2006;124(4):783-801.
91. Kawai T, Akira S. The roles of TLRs, RLRs and NLRs in pathogen recognition. Int Immunol. 2009;21(4):317-37.
92. Lee SI, Kim GT, Kim HJ, Park SH, Kim EC. NOD2 Mediates Odontoblast Differentiation and RANKL Expression. J Dent Res. 2014;93(7):678-84.
93. Lam J, Takeshita S, Barker JE, Kanagawa O, Ross FP, Teitelbaum SL. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. J Clin Invest. 2000;106(12):1481-8.
94. Li Y, Ling J, Jiang Q. Inflammasomes in Alveolar Bone Loss. Front Immunol. 2021;12:691013.
95. Liu S, Li Q, Liu Y. Immunohistochemical localization of NALP3 inflammasome in experimental periapical lesions. Int Endod J. 2014;47(10):949-57.
96. Anand PK, Malireddi RK, Kanneganti TD. Role of the nlrp3 inflammasome in microbial infection. Front Microbiol. 2011;2:12.
97. Song Z, Lin Z, He F, Jiang L, Qin W, Tian Y, et al. NLRP3 is expressed in human dental pulp cells and tissues. J Endod. 2012;38(12):1592-7.
98. Qu C, Bonar SL, Hickman-Brecks CL, Abu-Amer S, McGeough MD, Peña CA, et al. NLRP3 mediates osteolysis through inflammation-dependent and -independent mechanisms. Faseb j. 2015;29(4):1269-79.
99. Monteleone M, Stow JL, Schroder K. Mechanisms of unconventional secretion of IL-1 family cytokines. Cytokine. 2015;74(2):213-8.
100. Pyrillou K, Burzynski LC, Clarke MCH. Alternative Pathways of IL-1 Activation, and Its Role in Health and Disease. Front Immunol. 2020;11:613170.
101. Kim JH, Jin HM, Kim K, Song I, Youn BU, Matsuo K, et al. The mechanism of osteoclast differentiation induced by IL-1. J Immunol. 2009;183(3):1862-70.
102. Wei S, Kitaura H, Zhou P, Ross FP, Teitelbaum SL. IL-1 mediates TNF-induced osteoclastogenesis. J Clin Invest. 2005;115(2):282-90.
103. Tao Z, Wang J, Wen K, Yao R, Da W, Zhou S, et al. Pyroptosis in Osteoblasts: A Novel Hypothesis Underlying the Pathogenesis of Osteoporosis. Front Endocrinol (Lausanne). 2020;11:548812.
104. Roper PM, Shao C, Veis DJ. Multitasking by the OC Lineage during Bone Infection: Bone Resorption, Immune Modulation, and Microbial Niche. Cells. 2020;9(10).
105. Matsuura T, Ichinose S, Akiyama M, Kasahara Y, Tachikawa N, Nakahama KI. Involvement of CX3CL1 in the Migration of Osteoclast Precursors Across Osteoblast Layer Stimulated by Interleukin-1ß. J Cell Physiol. 2017;232(7):1739-45.
106. Heo SC, Kim YN, Choi Y, Joo JY, Hwang JJ, Bae MK, et al. Elevated Expression of Cathepsin K in Periodontal Ligament Fibroblast by Inflammatory Cytokines Accelerates Osteoclastogenesis via Paracrine Mechanism in Periodontal Disease. Int J Mol Sci. 2021;22(2).
107. Behm C, Nemec M, Blufstein A, Schubert M, Rausch-Fan X, Andrukhov O, et al. Interleukin-1β Induced Matrix Metalloproteinase Expression in Human Periodontal Ligament-Derived Mesenchymal Stromal Cells under In Vitro Simulated Static Orthodontic Forces. Int J Mol Sci. 2021;22(3).
108. Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. Interleukin-18 regulates both Th1 and Th2 responses. Annu Rev Immunol. 2001;19:423-74.
109. Gao Y, Grassi F, Ryan MR, Terauchi M, Page K, Yang X, et al. IFN-gamma stimulates osteoclast formation and bone loss in vivo via antigen-driven T cell activation. J Clin Invest. 2007;117(1):122-32.
110. Evavold CL, Kagan JC. How Inflammasomes Inform Adaptive Immunity. J Mol Biol. 2018;430(2):217-37.




This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).

111. Dai SM, Nishioka K, Yudoh K. Interleukin (IL) 18 stimulates osteoclast formation through synovial T cells in rheumatoid arthritis: comparison with IL1 beta and tumour necrosis factor alpha. Ann Rheum Dis. 2004;63(11):1379-86.
112. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol. 2005;6(11):1123-32.
113. Deng J, Yu XQ, Wang PH. Inflammasome activation and Th17 responses. Mol Immunol. 2019;107:142-64.
114. Sato K, Suematsu A, Okamoto K, Yamaguchi A, Morishita Y, Kadono Y, et al. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. J Exp Med. 2006;203(12):2673-82.
115. Speziani C, Rivollier A, Gallois A, Coury F, Mazzorana M, Azocar O, et al. Murine dendritic cell transdifferentiation into osteoclasts is differentially regulated by innate and adaptive cytokines. Eur J Immunol. 2007;37(3):747-57.
116. Alnaeeli M, Penninger JM, Teng YT. Immune interactions with CD4+ T cells promote the development of functional osteoclasts from murine CD11c+ dendritic cells. J Immunol. 2006;177(5):3314-26.
117. Ibáñez L, Abou-Ezzi G, Ciucci T, Amiot V, Belaïd N, Obino D, et al. Inflammatory Osteoclasts Prime TNFα-Producing CD4(+) T Cells and Express CX(3) CR1. J Bone Miner Res. 2016;31(10):1899-908.
118. Alippe Y, Wang C, Ricci B, Xiao J, Qu C, Zou W, et al. Bone matrix components activate the NLRP3 inflammasome and promote osteoclast differentiation. Sci Rep. 2017;7(1):6630.
119. Oliveira TC, Gomes MS, Gomes AC. The Crossroads between Infection and Bone Loss. Microorganisms. 2020;8(11).
120. Baron R, Neff L, Louvard D, Courtoy PJ. Cell-mediated extracellular acidification and bone resorption: evidence for a low pH in resorbing lacunae and localization of a 100-kD lysosomal membrane protein at the osteoclast ruffled border. J Cell Biol. 1985;101(6):2210-22.
121. Cioffi M, Esposito K, Vietri MT, Gazzerro P, D'Auria A, Ardovino I, et al. Cytokine pattern in postmenopause. Maturitas. 2002;41(3):187-92.
122. Moore DL. Conservative treatment of teeth with vital pulps and periapical lesions: a preliminary report. J Prosthet Dent. 1967;18(5):476-81.
123. Asgary S, Nourzadeh M, Eghbal MJ. Miniature Pulpotomy of Symptomatic Mature Permanent Teeth: A Report of Two Cases. Iran Endod J. 2016;11(1):75-8.
124. Asgary S, Hassanizadeh R, Torabzadeh H, Eghbal MJ. Treatment Outcomes of 4 Vital Pulp Therapies in Mature Molars. J Endod. 2018;44(4):529-35.
125. Asgary S, Roghanizadeh L, Eghbal MJ, Akbarzadeh Baghban A, Aminoshariae A, Nosrat A. Outcomes and predictive factors of vital pulp therapy in a large-scale retrospective cohort study over 10 years. Sci Rep. 2024;14(1):2063.
126. Bainbridge M, Cousley RR. Spontaneous resolution of a periapical lesion during orthodontic treatment: a case report. Dent Update. 2013;40(2):114-6, 8-9.
127. Kim H-J, Lee S-J, Jung I-Y, Park S-H. Vital tooth with periapical lesion: spontaneous healing after conservative treatment. Restorative Dentistry & Endodontics. 2012;37(2):123-6.
128. Alsharif MB. Successful Healing of Periapical Pathology with Partial Pulpotomy in a Mature Permanent Molar: A Case Report. Am J Case Rep. 2024;25:e942937.
129. Xiao W, Chi Z, Shi W, Wang J. Modified pulpotomy procedure in immature permanent teeth with apical periodontitis: a randomised controlled trial. BMJ Open. 2022;12(12):e057714.
130. Tran XV, Ngo LTQ, Boukpessi T. Biodentine(TM) Full Pulpotomy in Mature Permanent Teeth with Irreversible Pulpitis and Apical Periodontitis. Healthcare (Basel). 2021;9(6).
131. Tsukiboshi M, Ricucci D, Siqueira JF, Jr. Mandibular Premolars with Immature Roots and Apical Periodontitis Lesions Treated with Pulpotomy: Report of 3 Cases. J Endod. 2017;43(9s):S65-s74.
132. Asgary S. Intraoperative Identification of Vital Radicular Pulp in a Tooth Diagnosed with Pulp Necrosis: Four-Year Outcome of Tampon Pulpotomy. Iran Endod J. 2026;21(1):e22.
133. Stahl SS, Weiss R, Tonna EA. Autoradiographic evaluation of periapical responses to pulpal injury. I. Young rats. Oral Surg Oral Med Oral Pathol. 1969;28(2):249-58.
134. Tagger M, Massler M. Periapical tissue reactions after pulp exposure in rat molars. Oral Surg Oral Med Oral Pathol. 1975;39(2):304-17.
135. Grabliauskiene Z, G L. Pulpotomy in young permanent teeth with signs of apical periodontitis: Case series. IPDOAJ 2003;8(4):987-90.
136. Tani-Ishii N, Wang CY, Stashenko P. Immunolocalization of bone-resorptive cytokines in rat pulp and periapical lesions following surgical pulp exposure. Oral Microbiol Immunol. 1995;10(4):213-9.
137. Möller AJ, Fabricius L, Dahlén G, Sundqvist G, Happonen RP. Apical periodontitis development and bacterial response to endodontic treatment. Experimental root canal infections in monkeys with selected bacterial strains. Eur J Oral Sci. 2004;112(3):207-15.
138. Fabricius L, Dahlén G, Holm SE, Möller AJ. Influence of combinations of oral bacteria on periapical tissues of monkeys. Scand J Dent Res. 1982;90(3):200-6.
139. Kakehashi S, Stanley HR, Fitzgerald RJ. The Effects of Surgical Exposures of Dental Pulps in Germ-Free and Conventional Laboratory Rats. Oral Surg Oral Med Oral Pathol. 1965;20:340-9.

***Please cite this paper as***: Ríos-Osorio N. Beyond the Necrosis-first Model: Towards a New Integrated Biological Framework for Inflammation-mediated Apical Periodontitis. Iran Endod J. 2026;21(1): e44. Doi: 10.22037/iej.v21i1.52669.



*This open-access article has been distributed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0).*