

The role of NF-kappaB in the inflammatory processes related to dental caries, pulpitis, apical periodontitis, and periodontitis—a narrative review

Zhonglan Chen¹, Guangping Lang², Xi Xu¹, Xinghua Liang², Yalin Han¹ and Yingying Han¹

¹Zunyi Medical University, Special Key Laboratory of Oral Diseases Research, Hospital/School of Stomatology, Zunyi, Guizhou, China

²Zunyi Medical University, Key Laboratory of Basic Pharmacology of Ministry of Education and Joint International Research Laboratory of Ethnomedicine of Ministry of Education, Zunyi, Guizhou, China

ABSTRACT

Tooth-related inflammatory disorders, including caries, pulpitis, apical periodontitis (AP), and periodontitis (PD), are primarily caused by resident oral microorganisms. Although these dental inflammatory conditions are typically not life-threatening, neglecting them can result in significant complications and greatly reduce an individual's quality of life. Nuclear factor κ B (NF- κ B), a family formed by various combinations of Rel proteins, is extensively involved in inflammatory diseases and even cancer. This study reviews recent data on NF- κ B signaling and its role in dental pulp stem cells (DPSCs), dental pulp fibroblasts (DPFs), odontoblasts, human periodontal ligament cells (hPDLCs), and various experimental animal models. The findings indicate that NF- κ B signaling is abnormally activated in caries, pulpitis, AP, and PD, leading to changes in related cellular differentiation. Under specific conditions, NF- κ B signaling occasionally interacts with other signaling pathways, affecting inflammation, bone metabolism, and tissue regeneration processes. In summary, data collected over recent years confirm the central role of NF- κ B in dental inflammatory diseases, potentially providing new insights for drug development targeting NF- κ B signaling pathways in the treatment of these conditions. **Keywords:** NF- κ B, dental caries, pulpitis, apical periodontitis, periodontitis.

Submitted 16 April 2024
Accepted 31 July 2024
Published 29 August 2024

Corresponding author
Yingying Han,
hanyingying5219@163.com

Academic editor
Xin Zhang

Additional Information and
Declarations can be found on
page 13

DOI [10.7717/peerj.17953](https://doi.org/10.7717/peerj.17953)

© Copyright
2024 Chen et al.

Distributed under
Creative Commons CC-BY 4.0

OPEN ACCESS

Subjects Cell Biology, Dentistry

Keywords NF- κ B, Caries, Pulpitis, Apical periodontitis, Periodontitis

INTRODUCTION

In a physiological state, the mouth hosts over 700 species of bacteria, existing in a biofilm to maintain ecological balance with the host. Preserving the stability of this oral microbiome balance is crucial, as its disruption can lead to various oral infectious diseases, including dental caries, periodontitis (PD), and apical periodontitis (AP) (*Anne Marie et al., 2023*). Despite the rapid economic growth and improvements in living conditions over the past few decades, the public continues to be afflicted by inflammatory dental

disorders. Dental caries, a widespread and chronic degenerative condition affecting nearly half of the world's population (Alawady et al., 2023), is particularly concerning. This bacterial infection-driven disease disproportionately affects individuals in developing nations, where prevalence rates are notably higher. If untreated, bacteria can infiltrate the pulp through damaged tooth tissue, leading to pulpitis and periapical inflammation, eventually resulting in tooth loss. A recent systematic review revealed that approximately 50% of adults worldwide have at least one tooth affected by AP (Tibúrcio-Machado et al., 2021). Meanwhile, PD is a prevalent chronic inflammatory disease, second only to cavities, affecting more than 10% of individuals (Khajavi, Radvar & Moeintaghavi, 2022), with a prevalence rate negatively correlated with the level of economic development (Zhang et al., 2022). Investigating the underlying mechanisms of these inflammatory diseases is essential. Previous research has shown that pro-inflammatory agents can stimulate the activation of NF- κ B, which plays a critical role in regulating both inflammatory responses and bone metabolism processes.

NF- κ B, a transcription factor first identified in 1986 within the nuclear extracts of B lymphocytes, has the distinctive capability to bind specifically with the enhancer B sequence found in the immunoglobulin kappa light chain gene, thereby stimulating and increasing the expression of this gene (Sen & Baltimore, 1986). NF- κ B regulates the expression of genes and proteins, influencing various biological processes such as cell proliferation, apoptosis, inflammation, oxidative stress, and angiogenesis (Govindappa et al., 2020). The NF- κ B transcription factor consists of five Rel family members: RelA (p65), RelB, c-Rel, NF- κ B1 (p105/p50), and NF- κ B2 (p100/p52) (Pai & Sukumar, 2020). Among these, NF- κ B1 and NF- κ B2 are considered repressors due to the absence of C-terminal transcriptional activation domains (TADs) (Zhang et al., 2019). Consequently, NF- κ B dimers composed solely of NF- κ B1 or NF- κ B2 are not capable of initiating transcription activity both *in vivo* and *in vitro* (Barnabei et al., 2021). Conversely, RelA, RelB, and c-Rel, which possess TADs, can form homologous and heterodimers with other family members to act as transcriptional activators. Additionally, RelB can function as both an activator (Ryseck et al., 1992) and an inhibitor (Ruben et al., 1992). Except for RelA, the transcription of genes encoding NF- κ B polypeptides is upregulated by NF- κ B, creating a positive feedback loop upon cell stimulation (Ghosh et al., 2012). The Both NF- κ B1 and NF- κ B2 subunits have the Rel homology domain (RHD) structure, a fundamental feature shared among all NF- κ B family members. The RHD region contains a nuclear localization sequence (NLS) essential for dimerization, sequence-specific DNA binding, and interaction with inhibitory I κ B proteins (Ghosh, May & Kopp, 1998). In most cell types, I κ Bs, such as I κ B α , I κ B β , I κ B γ , and I κ B ϵ , sequester NF- κ B dimers in the cytoplasm, preventing their nuclear translocation and transcriptional activation (Karin et al., 2002). The NF- κ B signaling pathway can be activated through two primary routes: the classical and non-classical pathways, as shown in Fig. 1. The classical pathway is mainly triggered by stimuli such as TNF- α , IL-1 β , LPS, and RANKL, which activate specific Rel family proteins, including c-Rel, Rel A, and NF- κ B1. The phosphorylation of I κ B α , I κ B β , or I κ B γ by IKK β results in their degradation in the proteasome (Annunziata et al., 2007). This process permits the activation of c-Rel, Rel A, and NF- κ B1, regulating the expression of

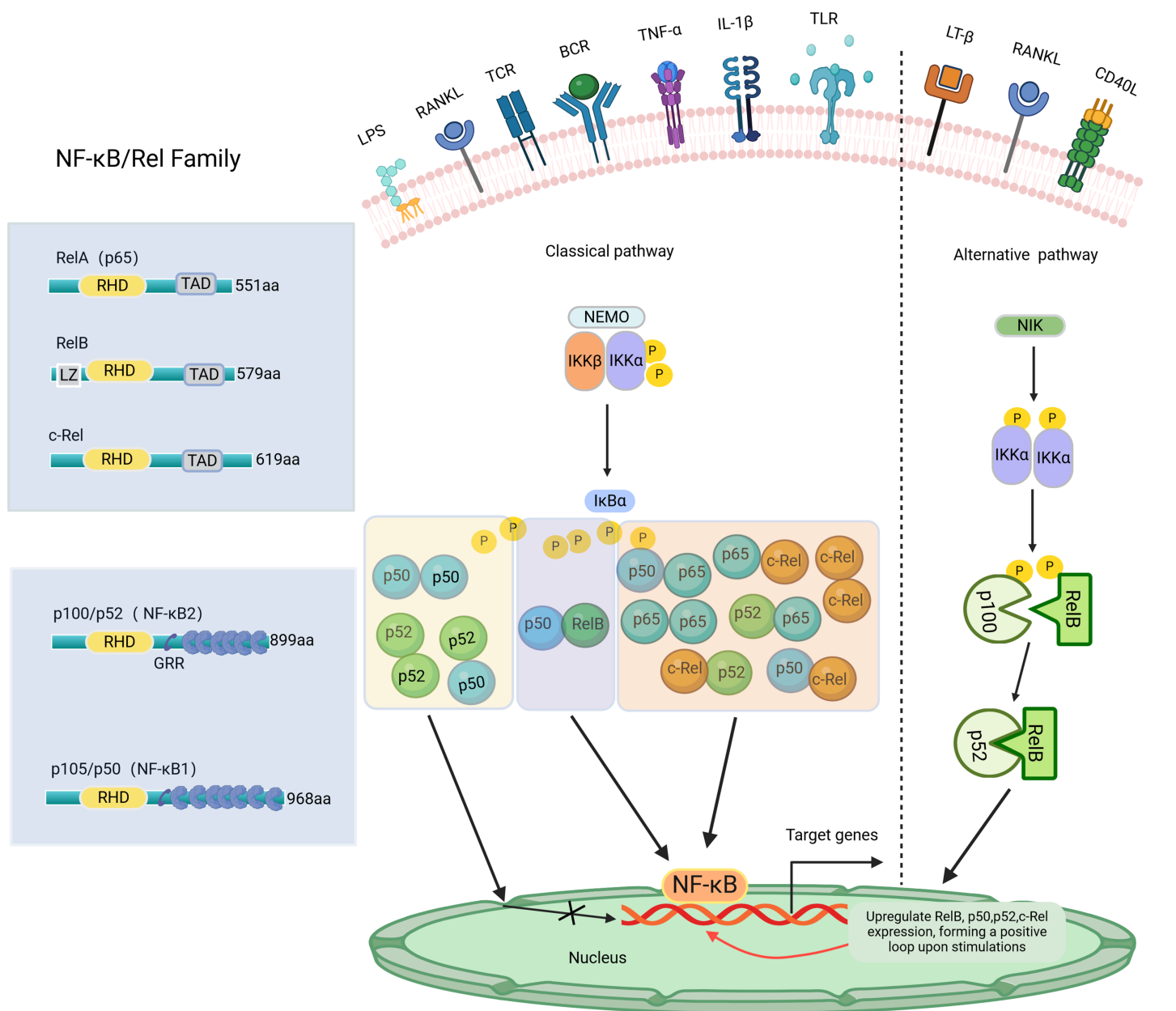


Figure 1 The NF-κB family, member characteristics and signaling pathways involved. The amino-terminal half of these proteins contains a highly conserved 300-amino-acid Rel homology domain (RHD) shared by all members. RelA, c-Rel, and RelB possess transactivation domains (TADs) involved in transcription. In contrast, p50 and p52 lack transactivation domains, thus inhibiting rather than stimulating gene transcription. The length of each protein is indicated on the right side. NF-κB signaling pathway: Classical and Alternative Arms. The classical NF-κB pathway is triggered by TNF-α, IL-1β, LPS, RANKL, *etc.* The initiation of this pathway heavily relies on the IκB kinase (IKK) complex known as IKKEMO, leading to the rapid degradation of IκBα through phosphorylation. The alternative pathways are activated by LT-β, CD40L, RANKL, *etc.* This pathway involves the activation of NIK and IKKα, resulting in the gradual processing of p100 and the formation of p52. The p52/RelB heterodimer is then activated by dimerization. P, phosphorylation; LZ, leucine zipper domain on IKK/and Rel-B, and GRR, glycine-rich region. Created with BioRender.com. [Full-size DOI: 10.7717/peerj.17953/fig-1](https://doi.org/10.7717/peerj.17953/fig-1)

targeted genes. In contrast, the non-classical pathway, mediated by Rel B and NF-κB2, is regulated by the stimulation of NEMO-independent signaling modules, such as NF-κB-inducible kinase (NIK) and IKKα. This pathway is stimulated by certain TNF

family members, including CD40 ligand (CD40L), lymphotoxin- β (LT- β), and RANKL (Ghosh & Karin, 2002). Specifically, the alternative pathway facilitates the cleavage of p100 into NF- κ B2 through the activation of IKK α , supporting the nuclear translocation of NF- κ B2 without relying on IKK β and IKK γ (Sun, 2011). The important roles of NF- κ B signaling have been reported in various diseases, such as arthritis (Wang et al., 2017), cancer (Yu et al., 2020), colitis (He et al., 2019), and mastitis (He et al., 2015; Liang et al., 2014). NF- κ B activation may aid antiviral responses by inducing interferon genes (Boehm et al., 1997; Stark et al., 1998). Recent research indicates that excessive activation of NF- κ B signaling in individuals with COVID-19 may worsen the body's inflammatory response (Amini-Farsani et al., 2021). Notably, the NF- κ B signaling pathway has significant potential in regulating dental inflammation, such as caries (Feng et al., 2021), pulpitis (Nam et al., 2024), AP (Guan et al., 2021), and PD (Tian et al., 2022). Studies have demonstrated that inhibiting the NF- κ B signaling pathway may promote tooth/bone matrix formation and exert anti-inflammatory effects (Aoki et al., 2023; He et al., 2017; Liu et al., 2013). However, research on NF- κ B signaling in dental-related inflammation is still limited, and its specific mechanisms remain unclear. Currently, there are no clinical drugs or materials based on this pathway. Future research should focus on the NF- κ B pathway to develop more effective drugs for preventing or treating dental-related inflammatory diseases, such as caries preventive agents, pulp capping agents, root canal disinfectants, or bone regeneration materials.

METHODS

This study conducted comprehensive literature searches in the PubMed and Web of Science databases, focusing on studies published before 2024. Searches were performed using the terms “NF- κ B (Title)”, “caries (Title)”, “pulpitis (Title)”, and “periodontitis (Title)”. Duplicate articles and those not indexed in SCI were excluded, as well as those without full text availability. The articles were then ranked based on relevance, prioritizing timeliness, explanatory value, and comprehensiveness when reading the full texts, with a focus on citing 42 articles for professional background. The key search terms “NF- κ B and dental caries” ($n = 45$), “NF- κ B and pulpitis” ($n = 73$), “NF- κ B and apical periodontitis” ($n = 69$), and “NF- κ B and periodontitis” ($n = 1,531$) guided the search process. Articles were further excluded based on duplication, non-SCI indexing, lack of relevance to the target diseases and/or NF- κ B, unavailability of full-text, articles with comorbidities, and less common etiologies. Titles and abstracts were reviewed, and original articles were selected for full-text reading, adhering to the SANRA quality criteria, resulting in the selection of 74 articles. A total of 116 references were cited, as shown in Fig. 2.

NF- κ B in dental caries

Dental caries results from the complex interaction between the resident commensal microbiota in dental biofilms, host susceptibility traits, and environmental factors, with diet being particularly significant (Keller et al., 2017). The pathological changes typically involve the demineralization and destruction of hard tissues in teeth, primarily affecting the enamel, dentin, and cementum (Kang, Njimbouom & Kim, 2023). The onset of dental

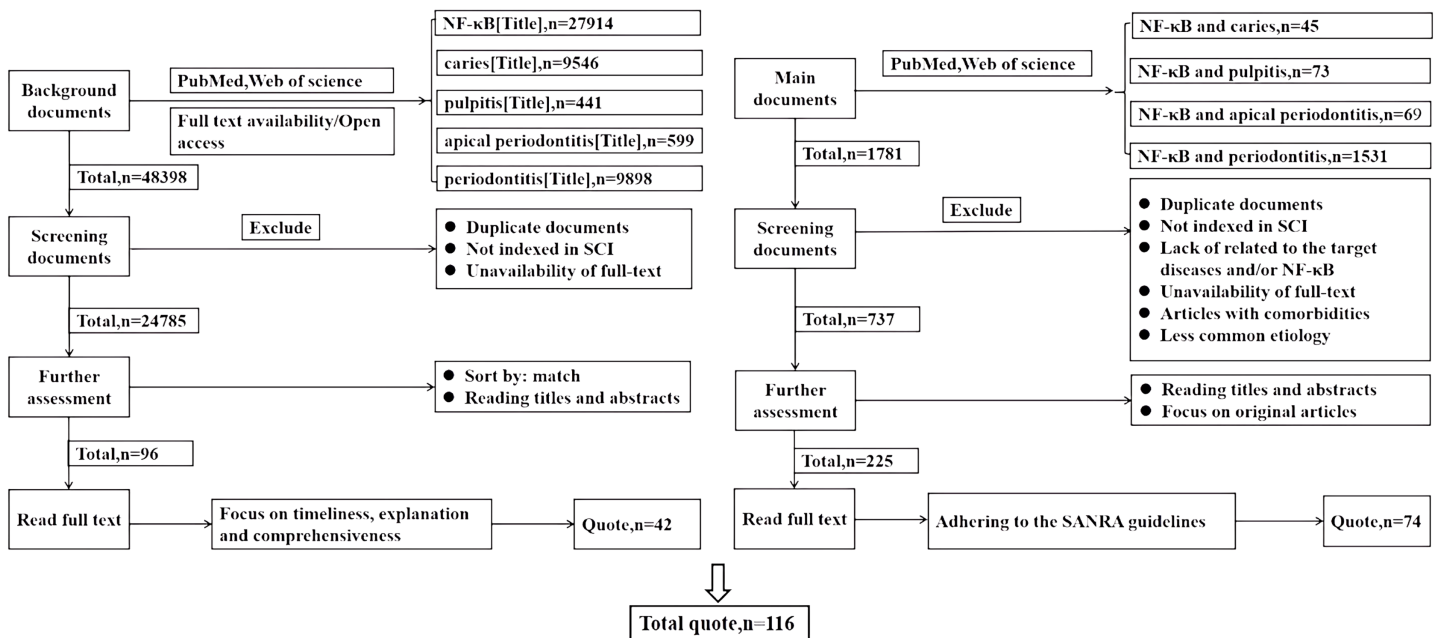


Figure 2 This review literature search flowchart. How the literature cited in this review is selected. Left: the screening of literature cited for professional background. Right: the screening of literature cited in the main text. Full-size [DOI: 10.7717/peerj.17953/fig-2](https://doi.org/10.7717/peerj.17953/fig-2)

caries begins with the formation of a dental plaque biofilm on the tooth's surface, as oral microorganisms adhere to the enamel or cementum. These bacteria metabolize nutrients, producing acids that lead to the demineralization of tooth structures. Over time, this process results in cavities, causing dental caries (Gao *et al.*, 2016). The presence of *Streptococcus mutans* (*S. mutans*) in the oral cavity is widely acknowledged as a key factor in the formation of dental plaque biofilm and the onset of dental caries (Li *et al.*, 2015; Zhang *et al.*, 2021b). It has been recognized that inhibiting or breaking down oral biofilms could serve as an effective approach to halt the development of dental caries (Kawada-Matsuo & Komatsuzawa, 2017). This concept has gained traction in recent research and is increasingly considered a potential strategy for preventing oral health issues. Previous studies found that *S. mutans* can activate NF-κB in a mouse macrophage cell line (Kim *et al.*, 2012). One study demonstrated that the antimicrobial peptide LL-37 derivatives IG-13-1 and IG-13-2 not only inhibit *S. mutans* but also reduce the levels of the transcription factor NF-κB, suggesting a potential role of NF-κB in their antimicrobial activity (Chen *et al.*, 2019b). Currently, the main focus of NF-κB in dental caries is on regulating the differentiation of odontoblasts and dental pulp stem cells (DPSCs) in an inflammatory environment. In the tooth, odontoblasts are considered the initial defense for the host and are involved in initiating, developing, and maintaining the pulp's immune and inflammatory responses to dentine invaders (Farges *et al.*, 2015; Goldberg & Lasfargues, 1995). Studies have shown a link between the formation of reactive dentine and the NF-κB pathway. Specifically, when NF-κB signaling is blocked by NF-κB inhibitors MG132 or p65 siRNA in DPSC, odontoblastic differentiation and collagen matrix formation significantly improve, suggesting that inhibiting the NF-κB signaling pathway promotes dentin

formation (Hozhabri et al., 2015). Other research indicates that blocking NF- κ B promotes odontoblast differentiation by promoting lipopolysaccharide (LPS)-induced autophagy (Pei et al., 2016). Additionally, the phosphorylation of NF- κ B signaling proteins such as IKK α / β , I κ B α , and p65 increased with the deletion of DNA methyltransferase (DNMT)-1 in the lipoteichoic acid (LTA)-induced inflammatory environment of human odontoblasts (Meng et al., 2019). Another study showed that NF- κ B signaling might play a role in upregulating adhesion molecules and chemotactic factors in the LPS-induced inflammatory environment of hDPSCs (Li & Wang, 2014). In the LPS-induced DPCs model, inhibiting the NF- κ B signaling pathway can reduce inflammation (Long et al., 2023) and increase the odontogenic differentiation potential of DPCs (Zhu et al., 2019). NF- κ B not only regulates odontoblasts but also controls DPSCs during dental caries development. DPSCs are known for their ability to self-renew and differentiate into multiple lineages. Research has shown that increased nuclear translocation of phosphorylated NF- κ B p-p65 negatively impacts the differentiation of DPSCs into odontoblasts. This hindrance occurs when muramyl dipeptide (MDP), a component influencing DPSC differentiation under inflammatory conditions, is present. MDP exposure leads to a substantial upregulation of nucleotide-binding oligomerisation domain 2 (NOD2), a protein that regulates inflammatory homeostasis (Xiao et al., 2022). Existing studies show that activating the NF- κ B signaling pathway can exacerbate the inflammatory response and inhibit the differentiation of DPSCs into odontoblasts (Song et al., 2018). In conclusion, NF- κ B signaling is involved in the anti-caries process by reducing inflammation and promoting the differentiation of odontoblasts and DPSC/DPCs in inflammatory conditions.

NF- κ B in pulpitis

Pulp infection and necrosis can occur due to microbial invasion of teeth through dentinal tubules, deep cavities, dental trauma, or tooth fractures (Chang et al., 2022). In cases of pulpitis, there is typically activation and infiltration of inflammatory cells, including T lymphocytes, monocytes, macrophages, and eosinophils. Previous reports have indicated that reducing the nuclear translocation of NF- κ B is beneficial for maintaining dental pulp health (Galler et al., 2021). Blocking NF- κ B signaling can decrease inflammation and cytokine release while promoting the differentiation of DPSC and collagen matrix formation (Hozhabri et al., 2015). Wang et al. (2024) found that inhibiting NF- κ B may partially restore the mineralization function of DPSCs in an inflammatory environment. Conversely, activation of the NF- κ B signaling pathway can lead to inflammatory cell infiltration and exacerbate pulpitis (Liu et al., 2020b). The LPS of Gram-negative bacteria is a major pathogenic factor known to cause severe inflammation in dental pulp tissues (Qiao et al., 2019). LPS stimulation leads to the translocation of NF- κ B p65 from the cytoplasm to the nucleus (Pei et al., 2016). When LPS binds to its specific receptor toll-like receptor 4 (TLR4), it activates the MyD88-dependent signaling cascade, triggering a transcriptional response involving NF- κ B p65 and inducing the secretion of proinflammatory cytokines by epithelial cells, macrophages, and dendritic cells (Ciesielska, Matyjek & Kwiatkowska, 2021) in dental pulp inflammation (Wang et al., 2019). In a rat model of acute pulpitis, the

addition of TLR4 antagonists significantly down-regulated MyD88 and NF- κ B to combat pulp inflammation (Lin *et al.*, 2015). However, an *in vitro* study found that LPS stimulation of human dental pulp cells (hDPCs) caused a protective inflammatory response. Concretely speaking, immunofluorescence revealed that nuclear translocation of NF- κ B promotes the differentiation of hDPCs (Huang *et al.*, 2015). This may be because LPS from different bacteria cannot mimic the same receptor, resulting in varying effects on other receptors. Subsequent cellular trials showed that downregulation of nuclear translocation of NF- κ B p65 can maintain pulp viability by knockdown of astrocyte elevated gene-1 (AEG-1) (Wu *et al.*, 2018). Current research in pulpitis is heavily focused on pulp tissue regeneration, a complex and challenging area that represents both a persistent challenge and a promising trend within the field. Revascularization is a crucial component for achieving successful pulp regeneration (Siddiqui *et al.*, 2022). Inhibition of NF- κ B p65 has been shown to have anti-inflammatory and pro-angiogenic effects when the angiogenic factor G-patch and FHA domain 1 (AGGF1) is regulated (Shen *et al.*, 2021). Rescue experiments have demonstrated that breaking the low AGGF1 levels promotes p65 nuclear transfer and suppresses DPCs angiogenesis. Furthermore, overexpression of Pannexin3 in hDPCs suppresses TNF- α -induced NF- κ B transcriptional activity by attenuating I κ B α degradation and inhibiting p65 nuclear translocation, which significantly reduces the expression of inflammatory cytokines IL-6 and IL-1 β (Song *et al.*, 2017). Additionally, targeting regulation in human dental pulp fibroblasts (HDPF) shows potential as an effective anti-inflammatory approach in pulpitis treatment. In the HDPF inflammation model, p65 and IKK expression significantly decreased, and the inflammatory response in LPS-stimulated HDPF was suppressed with the addition of berberine (BBR), leading to a significant reduction in RelA mRNA expression and the ratio of n/c-p65 (Song *et al.*, 2020). NF- κ B activation was effectively suppressed by oxidoreductase E1 (RvE1) and lipoxygenase A4 (LXA4), which decreased the production of pro-inflammatory molecules and promoted the resolution of pulpitis inflammation (Liu *et al.*, 2022). In summary, NF- κ B signaling regulates the expression of pro-inflammatory molecules and influences the differentiation of DPCs and HDPFs, helping to counteract inflammation in the tooth pulp. This regulation contributes to preventing excessive dental pulp inflammation and preserving the viability of dental pulp tissues, especially in the early stages of inflammation.

NF- κ B in apical periodontitis

Apical periodontitis (AP) is an inflammatory and immune response caused by anaerobic polymicrobial infection of the dental pulp and root canals (Siqueira & Rôças, 2009; Sjögren *et al.*, 1997). It is characterized by the formation of granulation tissue and the destruction of the alveolar bone around the root apex of the tooth, eventually leading to bone resorption or tooth loss (Luo *et al.*, 2022). In immunology, NF- κ B signaling pathways are increasingly recognized for their crucial role in regulating immune responses in AP (Silva-García, Valdez-Alarcón & Baizabal-Aguirre, 2019). Immunohistochemical staining and Western blotting have shown that NF- κ B (p65) expression is relatively low in healthy individuals but significantly upregulated in the thyroid tissues of human AP patients. A rat model of AP confirmed the positive correlation between the NF- κ B signaling pathway and

AP progression (Guan et al., 2021). In cell experiments, exposure to LTA led to the translocation of NF- κ B p65 into the nucleus, worsening periapical inflammation (Wang et al., 2016). Additionally, research by Dong et al. (2018) found that osteopontin, through the activation of NF- κ B (p65) signaling, contributes to bone destruction in patients with periapical inflammation at the tooth root. Further studies have shown that activation of hypoxia-inducible factor 1 (HIF-1) can reduce periapical inflammation and bone loss by down-regulating NF- κ B, pro-inflammatory cytokines, M1 macrophages, and osteoclastogenesis (Hirai et al., 2018). Other research indicates that NF- κ B activation exacerbates periapical inflammation in mice, attributed to increased TLR4 signaling due to TLR2 deficiency (Rider et al., 2016). It has been previously demonstrated that upregulation of NF- κ B exacerbates periapical bone destruction (Wei et al., 2022). This is primarily due to the significantly increased expression of NF- κ B ligand-receptor activator (RANKL) mRNA in patients with AP compared to normal subjects, which activates osteoclasts and ultimately worsens periapical bone destruction (Sabeti et al., 2005). The impact of RANKL on osteoclasts in AP was further confirmed through experiments on mice (Ikeda et al., 2022) and rats (Zhang & Peng, 2005). In one study, exposure of periodontal ligament cells (PDLC) to LPS induced activation of the NF- κ B pathway *via* translocation and phosphorylation, followed by I κ B degradation. This process resulted in an upregulation of IL-23 expression, promoting osteoclast generation and leading to apical bone destruction (Ma et al., 2017). Additionally, bacterial chaperonin 60 molecules, also known as GroEL, can overexpress and induce acetylation of NF- κ B p65 in AP. This acetylated NF- κ B p65 transcription factor binds to the promoter regions of matrix metalloproteinase 2 (MMP2) and MMP9 genes, activating their expression (Zhang et al., 2021a). Interestingly, another MMP family member, active MMP-8, has been reported to identify collagenolytic tissue destruction for early diagnosis of peri-implantitis, serving as a convenient and reliable adjunct tool for chairside assay (Guarnieri et al., 2022). Overall, NF- κ B influences the progression of periapical inflammation by regulating both the inflammatory response and bone resorption processes.

NF- κ B in periodontitis




Periodontitis (PD) is a multifactorial inflammatory disease characterized by the irreversible and progressive degradation of periodontal tissues, including the gingiva, periodontal ligament, and alveolar bone, often leading to tooth loss. The primary cause of PD is a microbial biofilm (He et al., 2022). PD is a significant global public health concern, affecting approximately 60% of the world's adult population (Wang et al., 2023). Severe PD, recognized as the sixth most common human disease, affects about 11% of the global population (Ebadi et al., 2023). The NF- κ B signaling pathway is a major mediator of inflammation and plays a crucial role in the pathogenesis of periodontal disease by activating cytokine genes (Lepetsos, Papavassiliou & Papavassiliou, 2019). *Fusobacterium nucleatum* (*F. nucleatum*) is an early pathogenic colonizer in PD, but the mechanism of the host's immune response to this pathogen remains unclear (Wang et al., 2023). *In vitro* studies have shown that NF- κ B1 and NF- κ B2 are upregulated three hours after *F. nucleatum* infection, with the expression levels of inflammatory-related genes in the NF-

κB signaling pathway increasing over time (Wang et al., 2023). Specifically, NF-κB (p65, p-p65, IKK, p-IKK) is activated following stimulation with *F. nucleatum*, as detected by Western blot analysis. Drug treatment has been shown to reduce NF-κB activity. Previous studies using Western blot analysis have shown increased expression of NF-κB transcription factors (p50/p65) and decreased levels of IκB in gingival tissues of PD patients compared to healthy individuals (Ambili et al., 2005). NF-κB activation rates were much higher (75–90%) in tissues affected by periodontal disease compared to normal tissues (5–30%). Conversely, the expression of IκB (5%) in periodontal disease tissues was significantly lower than in healthy tissue (50%), indicating the vital role of NF-κB in PD. Recent evidence on the role of NF-κB in regulating periodontal inflammation shows that inhibition of this signaling pathway reduces the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (Shi et al., 2021). Further research has shown that inhibition of the NF-κB (p-IκBα, N-p65) signaling pathway significantly downregulates the expression of IL-6 and IL-8 in hPDLs through low-intensity pulsed ultrasound (LIPUS) stimulation (Liu et al., 2020a). In a separate study, activation of the NF-κB pathway was indicated by increased phosphorylation of p65 in visfatin-overexpressing hPDLs, which subsequently upregulated the production of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) (Yao et al., 2021). Additionally, NF-κB signaling plays a role in Long non-coding RNA (lncRNA)-regulated periodontal inflammation. Mechanistically, the NF-κB p65 subunit can be directly bound by lncRNA SNHG5, which suppresses its translocation, thereby reducing pathological changes such as inflammasome formation (Han et al., 2022). Another study found that when hPDLs were exposed to LPS, the lncRNA FGD5 AS1 was overexpressed, leading to a significant decrease in p/t-p65 levels. This effectively inhibited NF-κB signaling and reduced PD severity (Chen et al., 2019a). NF-κB signaling in PD pathogenesis is regulated by both lncRNA and microRNA (miRNA). For example, the loss of microRNA-21 (miR-21) worsens PD by increasing the protein expression of phosphorylated (p)-NF-κB and reducing the total IκB levels both *in vivo* and *in vitro* (Zhou et al., 2018). NF-κB also regulates bone metabolism and affects alveolar bone loss in periodontal diseases. Previous research has shown the significant role of NF-κB in bone remodeling. Studies on mice with a double knockout of NF-κB1 and NF-κB2 genes have demonstrated that the absence of these proteins leads to osteopetrosis, a condition characterized by abnormally dense bones due to an accumulation of poorly developed osteoclasts (Franzoso et al., 1997; Iotsova et al., 1997). In an experiment using a mouse model infected with *Porphyromonas gingivalis* (*P. gingivalis*) to simulate PD, the phosphorylation rate of NF-κB p50 and p65, and TNF-α levels in the gingival epithelium were significantly elevated compared to the control group, which experienced substantial alveolar bone loss (Li et al., 2017). However, mangiferin treatment notably decreased TNF-α expression and the phosphorylation levels of p50 and p65, substantially inhibiting alveolar bone loss. Previous studies have observed that inhibiting IKK/p65/NF-κB promotes osteoblast differentiation and bone formation, with improvements such as increased trabecular numbers and enhanced bone mineral density (Alles et al., 2010; Chang et al., 2009). In addition, the mRNA and protein expression levels of the NF-κB ligand (RANKL) were significantly higher in diseased periodontal tissues compared to healthy

ones, leading to increased osteoclast activity and consequent bone damage (Crotti et al., 2003). Research has shown that the internalization of RANK, triggered by its ligand RANKL, is crucial for activating downstream signaling pathways like NF- κ B. This activation is essential for initiating and sustaining osteoclast formation and function (Wang et al., 2021). For instance, pirfenidone (PFD) suppresses the NF- κ B signaling pathway by inhibiting RANKL-induced osteoclast differentiation and LPS-induced expression of pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α), thereby slowing the progression of PD (Zhang et al., 2023). Additionally, when downstream signaling is activated by RANKL, the phosphorylation of I κ B activates NF- κ B, leading to increased expression of osteoclast-specific genes and increased osteoclast formation and function (Sakamoto et al., 2019). Recent findings suggest that the non-canonical NF- κ B signaling pathway plays a significant role in regulating PD. Experimental studies have shown that topical application of the NIK inhibitor Cpd33 suppresses osteoclast formation, reducing alveolar bone resorption and demonstrating the potential therapeutic effects of targeting this pathway in a mouse model of PD (Aoki et al., 2023). Similar results were observed in another study using a NIK inhibitor both *in vitro* and *in vivo* (Wang et al., 2020). Furthermore, several studies have shown that lncRNA interacts with proteins in the NF- κ B signaling pathway, influencing bone resorption in PD. For example, Li et al. (2022) found that lncRNA Nron accelerates the nuclear transport of the NF- κ B inhibitor, significantly reducing osteoclast formation and alveolar bone loss in PD. In another study, the activity of NF- κ B (p-p65, p-I κ B α) was partially inhibited by lncRNA Dancr expression in MC3T3-E1 cells, promoting osteogenic differentiation (Lu et al., 2020). Overall, these studies provide new insights into treating periodontal bone destruction by targeting NF- κ B signaling.

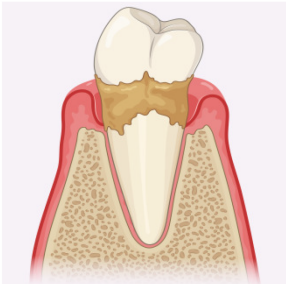
Cementum regeneration is considered the gold standard for periodontal tissue regeneration (Yang, Rossi & Putnins, 2010). Recent research has indicated that NF- κ B signaling is activated during the osteoblast differentiation of PDLs. For instance, one study showed that NF- κ B (p-p65) activation by transcription factor 7-like 2 (Tcf7l2) accelerates cementum formation and aids in guiding periodontal tissue regeneration (Zhao et al., 2019). The NF- κ B signaling pathway is triggered during the osteogenic differentiation process in PDLs (Lee et al., 2014, 2016). However, contradictory results have been observed, potentially due to differences in experimental procedures, cell types, or the source and intensity of stimuli. In the inflammation of human periodontal ligament fibroblasts (HPDLFs), significant inhibition of I κ B α and P65 phosphorylation can promote osteogenic differentiation and mineralization of HPDLFs treated with proanthocyanidins (PA) (Huang et al., 2020). Furthermore, the NF- κ B non-canonical pathway also contributes to periodontal tissue regeneration. In periodontal inflammatory conditions, inhibiting the non-classical NF- κ B2 signaling pathway significantly downregulates pro-inflammatory factors while promoting skin healing in mice *via* FGF-2-inhibited CD40 signaling (Fujihara et al., 2019). Moreover, NF- κ B interacts with other signaling pathways to encourage periodontal tissue regeneration. For example, LL37, a robust antimicrobial peptide, increases NF- κ B p65 and ERK1/2 phosphorylation levels in hPDLF, and this cascade induces the production of vascular endothelial growth factor-A

Table 1 Variation and effect of NF- κ B in caries, pulpitis, apical periodontitis and periodontitis in different experimental types. Images created with BioRender.com.

Diseases	Main factors	Experiment strategy	NF- κ B change	Effect
 Dental caries	IG-13-1 and IG-13-2 (<i>Chen et al., 2019b</i>)	Macrophages	NF- κ B↓	Anti-infla
	NF- κ B inhibitor (<i>Hozhabri et al., 2015</i>)	hDPSCs	NF- κ B gene↓, N-p6↓	
	Connexin43 (<i>Long et al., 2023</i>)	Rat, hDPCs	NF- κ B↓	
	Ag-BG/CS (<i>Zhu et al., 2019</i>)	DPCs	p-p65↓	
	DNMT1 (<i>Meng et al., 2019</i>)	hOB	p-IKK α / β ↑, p-I κ B α ↑, p-p65↑	Pro-infla
	AZA (<i>Feng et al., 2021</i>)	hOBs	p-IKK α / β ↑, p-I κ B α ↑, p-p65↑	
	Autophagy (<i>Pei et al., 2016</i>)	mDPC6T (cell line)	p-NF- κ B↓	Pro-differentiation
	MDP/NOD2 (<i>Xiao et al., 2022</i>)	hDPSC	p-p65↑, p-I κ B α ↑	Inhibition differentiation
 Pulpitis	Neuropilin-1-FYN (<i>Song et al., 2018</i>)	hDPSC	N-p65↑	Pro-infla and inhibition differentiation
	microRNA-506 (<i>Wang et al., 2019</i>)	DPSCs	p-p65↓	Anti-infla
	AEG-1 (knockout) (<i>Wu et al., 2018</i>)	Rat, hDPCs	p-p65↓	
	Pannexin3 (<i>Song et al., 2017</i>)	hDPCs	p-p65↓, I κ B α ↑	
	Berberine (<i>Song et al., 2020</i>)	hDPF	p-p65↓, p-IKK↓, I κ B α ↑	
	Resolvin and lipoxinA4 (<i>Liu et al., 2022</i>)	hDPF, rat pulpitis	RelA mRNA↓, N/C-p65↓	
	G-Rb1 (<i>Nam et al., 2024</i>)	hDPCs	p-p65↓, pI κ B α ↓	
	TLR4/MyD88 (<i>Lin et al., 2015</i>)	Rat acute pulpitis	p65↑, N-p50↑	Pro-infla
	PECAM1 and CXCR4 (<i>Liu et al., 2020b</i>)	HDPFs	p-p65↑	
	NF- κ B inhibitor (<i>Hozhabri et al., 2015</i>)	hDPSCs	NF- κ B gene↓, N-p65↓	Pro-differentiation
	Autophagy (<i>Pei et al., 2016</i>)	mDPC6T (cell line)	p-NF- κ B↓	
	 Apical periodontitis	LPS (<i>Huang et al., 2015</i>)	hDPCs	NF- κ B↑
TSG-6 (<i>Wang et al., 2024</i>)		DPSC	p-p65↓, pI κ B α ↓	
AGGF1 (knockout) (<i>Shen et al., 2021</i>)		hDPCs	p-p65↑	Pro-infla and inhibition angiogenesis
LTA/NLRP3 (<i>Wang et al., 2016</i>)		Rat, RAW 264.7 cells	N-p65↑	Pro-infla
LPS (<i>Guan et al., 2021</i>)		Subjects, hDPCs, rat	p-p65↑	Pro-infla and bone destruction
CD14 and TLR4, TLR2 (<i>Rider et al., 2016</i>)		Mice, L929 cells	NF- κ B↑	
RGS10 (inhibition) (<i>Wei et al., 2022</i>)		Mice	NF- κ B↑	
RANKL (<i>Ikedo et al., 2022</i>)		Subjects	NF- κ B↑	Bone destruction
IL-23 (<i>Ma et al., 2017</i>)		Monocyte/Macrophage cell	p-I κ B↑	
Osteopontin (<i>Dong et al., 2018</i>)		Subjects, RAW264.7 and MC3T3-E1 cells, mice	NF- κ B↑, p-p65↑	
	GroEL (<i>Zhang et al., 2021a</i>)	Subjects, MC3T3-E1 cell line, mice primary osteo-blasts	Acetyl-p65↑	
	HIF1 (<i>Hirai et al., 2018</i>)	Mice, macrophages	p-p65↓, p-IKK↓	Anti-infla and bone protection

(Continued)

Table 1 (continued)

Diseases	Main factors	Experiment strategy	NF-κB change	Effect
 Periodontitis	LIPUS (Liu et al., 2020a)	hPDLSCs	p-IκBα↓, N-p65↓	Anti-infla
	LncRNA SNHG5 (Han et al., 2022)	Mice PD, subjects	p-p65↓	
	LncRNA FGD5 AS1 (Chen et al., 2019a)	Subjects, hPDLSCs mice, PDLCS	p/t-p65↓, p/t-IκBα↑	
	FGF-2 (Fujihara et al., 2019)	Mice monocyte and fibroblast cells, mice,	P52↓	
	Resveratro liposomes (Shi et al., 2021)	Human vascular endothelial cells	p-p65↓, p-IκBα↓	
	Inflammation (Ambili et al., 2005)	Subjects	p50/p65↑	Pro-infla
	<i>F. nucleatum</i> (Wang et al., 2023)	hPDLSCs	p-IKK↑, p-p65↑	
	Visfatin (Yao et al., 2021)	hPDLCS, hGFs	p-p65↑	
	Mangiferin (Li et al., 2017)	Mice	pp50/p50↓,	Anti-infla and bone protection
	Prifenidone (Zhang et al., 2023)	Mice, macrophages, mesenchymal stem cells	pp65/p65↓ p-p65↓, p-IκBα↓	
	Non-canonical NF-κB (Aoki et al., 2023)	Mice PD, Primary osteoblasts,	non-canonical NF-κB↓	
	PA (Huang et al., 2020)	Bone marrow cells hPDLFs	p-IκBα↓, p-p65↓	
	microRNA-21 (knockout) (Zhou et al., 2018)	miR-21 deficient mice, subjects, macrophages	p-NF-κB↑, T-IκB↓	Pro-infla and, bone destruction
	NF-κB1, NF-κB2 (Franzoso et al., 1997 ; Iotsova et al., 1997)	p50 and p52 knockouted mice	NF-κB1↓, NF-κB2↓	Osteopetrosis
	IKK/NF-κB (Chang et al., 2009)	Primary calvarial cells, generation of transgenic mice	p-p65↓, NF-κB↓, p-IκBα↓	Bone protection
	NF-κB (Alles et al., 2010)	Mice, osteoblasts,	NF-κB↓ (OD p65↓, p50↓)	
	LncRNA Dancr (Lu et al., 2020)	Osteoclasts	p-p65↓, p-IκBα↓	
	LncRNA Nron (Li et al., 2022)	Osteoblastic cell line, Nron knockouted mice	NF-κB↓(NKRf↑)	
	rh-BMP-2 and rh-DSP (Lee et al., 2014)	Human cementoblasts and PDLCS	p-p65↓, p-IκBα↓	
	Tcf712 (Zhao et al., 2019)	Mice, cementoblast cell line	p-p65↑	
	Vibration (Sakamoto et al., 2019)	Osteocyte and pre-osteoclast cell line, rat	p-IκB↑, NF-κB↑	Bone destruction
	NIK (Wang et al., 2020)	Mice, osteoclasts	p-IκBα↑, p-p105↑	
	Caveolin-1 (inhibition) (Lee et al., 2016)	Mice, hPDLCS, human cementoblasts	p-IκB↑, N-p65↑	
	LL-37 (Kittaka et al., 2013)	hPL cells	p-p65↑	Pro-angiogenesis

(VEGF-A), leading to angiogenesis and promoting periodontal regeneration ([Kittaka et al., 2013](#)). In summary, NF-κB is involved not only in regulating inflammatory cytokines and bone metabolism in PD but also in periodontal tissue regeneration.

CONCLUSIONS

Despite increased awareness and a growing focus on oral health, inflammatory dental diseases remain a significant concern, with their pathogenesis still not fully understood. Research has provided substantial evidence for the role of NF-κB activation in dental inflammation, significantly affecting both the progression of inflammatory responses and

bone destruction in the oral cavity (Table 1). Traditional caries treatments, such as topical fluoride, dental sealants, and surgical procedures like fillings (He et al., 2024), often exhibit cytotoxicity to the pulp and lack long-term antimicrobial properties, leading to issues like microleakage and pulpitis. Developing NF- κ B-related materials or drugs could provide sustained antimicrobial effects and favorable biological properties. The most common treatment for pulpitis and AP is root canal therapy. For a successful canal therapy, the most critical step is the control of intracanal infection which is the main cause of periradicular lesions (Jang et al., 2024). However, current root canal disinfectants often cause significant irritation to periradicular tissues. Therefore, we aim to develop mild and long-lasting anti-infectives targeting the NF- κ B signaling pathway to achieve effective antimicrobial properties and prevent apical bone destruction. Management of PD, including initial therapy, drug therapy, and periodontal surgery, focuses on regulating inflammation and bone resorption. Inhibiting NF- κ B can provide anti-inflammatory effects (Kim et al., 2023), suppress osteoclast activity (Xie et al., 2024), and enhance angiogenesis (Yang et al., 2024), making it a promising target for clinical drug development. However, few studies focus on how NF- κ B signaling works in caries, pulpitis, and periapical inflammation. While targeting the NF- κ B signaling pathway holds great promise for treating dental inflammatory diseases, a more thorough understanding of its precise role and therapeutic potential requires further investigation through extensive cell experiments, preclinical, and clinical studies to fully reveal the underlying mechanisms.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

This work was supported by Scientific research project of colleges and universities (youth project, Education Department of Guizhou Province, Grant No. QIANJIAOJI [2022]240), the Science and Technology Department Fund Project of Zunyi City (Grant No. ZSKHHZ [2022]377), Science and technology fund project of Guizhou Provincial Health Commission (NO: gzwkj2023-201), Zunyi Oral Disease Immune Prevention and Medical Biomaterials Research and Development Innovation Talent Team (Zunyi Science Talent [2022] No.1), National Natural Science Foundation of China (Grant No. 82160181), Zunyi Medical University graduate research fund project (Grant No. ZYK258), Guizhou Provincial Science and Technology Foundation (Grant No. [2022] General 606). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosures

The following grant information was disclosed by the authors:

Scientific research project of colleges and universities (youth project, Education Department of Guizhou Province): QIANJIAOJI [2022]240.

Science and Technology Department Fund Project of Zunyi City: ZSKHHZ [2022]377.

Science and technology fund project of Guizhou Provincial Health Commission: gzwkj2023-201.

Zunyi Oral Disease Immune Prevention and Medical Biomaterials Research and Development Innovation Talent Team: Zunyi Science Talent [2022] No.1.

National Natural Science Foundation of China: 82160181.

Zunyi Medical University graduate research fund project: ZYK258.

Guizhou Provincial Science and Technology Foundation (Grant No. [2022] General 606).

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Zhonglan Chen conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Guangping Lang analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
- Xi Xu performed the experiments, prepared figures and/or tables, and approved the final draft.
- Xinghua Liang analyzed the data, prepared figures and/or tables, and approved the final draft.
- Yalin Han analyzed the data, prepared figures and/or tables, and approved the final draft.
- Yingying Han analyzed the data, authored or reviewed drafts of the article, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

This is a literature review.

REFERENCES

- Alawady A, Alharbi A, Alharbi H, Almesbah S, Alshammari N, Alkandari A, Alhazmi H, Alqaderi H. 2023. Association between sleep duration and dental caries in a nationally representative U.S. population. *BMC Oral Health* 23:497 DOI 10.1186/s12903-023-03147-z.
- Alles N, Soysa NS, Hayashi J, Khan M, Shimoda A, Shimokawa H, Ritzeler O, Akiyoshi K, Aoki K, Ohya K. 2010. Suppression of NF-kappaB increases bone formation and ameliorates osteopenia in ovariectomized mice. *Endocrinology* 151(10):4626–4634 DOI 10.1210/en.2010-0399.
- Ambili R, Santhi WS, Janam P, Nandakumar K, Pillai MR. 2005. Expression of activated transcription factor nuclear factor-kappaB in periodontally diseased tissues. *Journal of Periodontology* 76(7):1148–1153 DOI 10.1902/jop.2005.76.7.1148.
- Amini-Farsani Z, Yadollahi-Farsani M, Arab S, Forouzanfar F, Yadollahi M, Asgharzade S. 2021. Prediction and analysis of microRNAs involved in COVID-19 inflammatory processes associated with the NF-κB and JAK/STAT signaling pathways. *International Immunopharmacology* 100(2):108071 DOI 10.1016/j.intimp.2021.108071.

- Anne Marie U, Murererehe J, Rehman M, Chittilla M, Uwambaye P, Razzaque MS. 2023. Oral manifestations of iron imbalance. *Frontiers in Nutrition* 10:1272902 DOI 10.3389/fnut.2023.1272902.
- Annunziata CM, Davis RE, Demchenko Y, Bellamy W, Gabrea A, Zhan F, Lenz G, Hanamura I, Wright G, Xiao W, Dave S, Hurt EM, Tan B, Zhao H, Stephens O, Santra M, Williams DR, Dang L, Barlogie B, Shaughnessy JD Jr, Kuehl WM, Staudt LM. 2007. Frequent engagement of the classical and alternative NF-kappaB pathways by diverse genetic abnormalities in multiple myeloma. *Cancer Cell* 12(2):115–130 DOI 10.1016/j.ccr.2007.07.004.
- Aoki T, Hiura F, Li A, Yang N, Takakura-Hino N, Mukai S, Matsuda M, Nishimura F, Jimi E. 2023. Inhibition of non-canonical NF-κB signaling suppresses periodontal inflammation and bone loss. *Frontiers in Immunology* 14:1179007 DOI 10.3389/fimmu.2023.1179007.
- Barnabei L, Laplantine E, Mbongo W, Rieux-Laucat F, Weil R. 2021. NF-κB: at the borders of autoimmunity and inflammation. *Frontiers in Immunology* 12:716469 DOI 10.3389/fimmu.2021.716469.
- Boehm U, Klamp T, Groot M, Howard JC. 1997. Cellular responses to interferon-gamma. *Annual Review of Immunology* 15(1):749–795 DOI 10.1146/annurev.immunol.15.1.749.
- Chang MC, Chen NY, Chen JH, Huang WL, Chen CY, Huang CC, Pan YH, Chang HH, Jeng JH. 2022. bFGF stimulated plasminogen activation factors, but inhibited alkaline phosphatase and SPARC in stem cells from apical Papilla: Involvement of MEK/ERK, TAK1 and p38 signaling. *Journal of Advanced Research* 40(3):95–107 DOI 10.1016/j.jare.2021.12.006.
- Chang J, Wang Z, Tang E, Fan Z, McCauley L, Franceschi R, Guan K, Krebsbach PH, Wang CY. 2009. Inhibition of osteoblastic bone formation by nuclear factor-kappaB. *Nature Medicine* 15(6):682–689 DOI 10.1038/nm.1954.
- Chen H, Lan Z, Li Q, Li Y. 2019a. Abnormal expression of long noncoding RNA FGD5-AS1 affects the development of periodontitis through regulating miR-142-3p/SOCS6/ NF-κB pathway. *Artificial Cells, Nanomedicine, and Biotechnology* 47(1):2098–2106 DOI 10.1080/21691401.2019.1620256.
- Chen Z, Yang G, Lu S, Chen D, Fan S, Xu J, Wu B, He J. 2019b. Design and antimicrobial activities of LL-37 derivatives inhibiting the formation of *Streptococcus mutans* biofilm. *Chemical Biology & Drug Design* 93(6):1175–1185 DOI 10.1111/cbdd.13419.
- Ciesielska A, Matyjek M, Kwiatkowska K. 2021. TLR4 and CD14 trafficking and its influence on LPS-induced pro-inflammatory signaling. *Cellular and Molecular Life Sciences* 78(4):1233–1261 DOI 10.1007/s00018-020-03656-y.
- Crotti T, Smith MD, Hirsch R, Soukoulis S, Weedon H, Capone M, Ahern MJ, Haynes D. 2003. Receptor activator NF kappaB ligand (RANKL) and osteoprotegerin (OPG) protein expression in periodontitis. *Journal of Periodontal Research* 38(4):380–387 DOI 10.1034/j.1600-0765.2003.00615.x.
- Dong M, Yu X, Chen W, Guo Z, Sui L, Xu Y, Shang Y, Niu W, Kong Y. 2018. Osteopontin promotes bone destruction in periapical periodontitis by activating the NF-κB pathway. *Cellular Physiology and Biochemistry* 49(3):884–898 DOI 10.1159/000493219.
- Ebadi M, Miresmaeili A, Rajabi S, Shojaei S, Farhadi S. 2023. Isolation and characterization of apical papilla cells from root end of human third molar and their differentiation into cementoblast cells: an in vitro study. *Biological Procedures Online* 25(1):2 DOI 10.1186/s12575-023-00190-6.
- Farges JC, Alliot-Licht B, Renard E, Ducret M, Gaudin A, Smith AJ, Cooper PR. 2015. Dental pulp defence and repair mechanisms in dental caries. *Mediators of Inflammation* 2015(1):230251 DOI 10.1155/2015/230251.

- Feng Z, Meng R, Li Q, Li D, Xu Q. 2021. 5-aza-2'-deoxycytidine may regulate the inflammatory response of human odontoblast-like cells through the NF- κ B pathway. *International Endodontic Journal* 54(7):1105–1117 DOI 10.1111/iej.13488.
- Franzoso G, Carlson L, Xing L, Poljak L, Shores EW, Brown KD, Leonardi A, Tran T, Boyce BF, Siebenlist U. 1997. Requirement for NF- κ B in osteoclast and B-cell development. *Genes & Development* 11(24):3482–3496 DOI 10.1101/gad.11.24.3482.
- Fujihara C, Kanai Y, Masumoto R, Kitagaki J, Matsumoto M, Yamada S, Kajikawa T, Murakami S. 2019. Fibroblast growth factor-2 inhibits CD40-mediated periodontal inflammation. *Journal of Cellular Physiology* 234(5):7149–7160 DOI 10.1002/jcp.27469.
- Galler KM, Weber M, Korkmaz Y, Widbiller M, Feuerer M. 2021. Inflammatory response mechanisms of the dentine-pulp complex and the periapical tissues. *International Journal of Molecular Sciences* 22(3):1480 DOI 10.3390/ijms22031480.
- Gao X, Jiang S, Koh D, Hsu CY. 2016. Salivary biomarkers for dental caries. *Periodontology 2000* 70(1):128–141 DOI 10.1111/prd.12100.
- Ghosh S, Karin M. 2002. Missing pieces in the NF- κ B puzzle. *Cell* 109(Suppl):S81–S96 DOI 10.1016/s0092-8674(02)00703-1.
- Ghosh S, May MJ, Kopp EB. 1998. NF- κ B and Rel proteins: evolutionarily conserved mediators of immune responses. *Annual Review of Immunology* 16(1):225–260 DOI 10.1146/annurev.immunol.16.1.225.
- Ghosh G, Wang VY, Huang DB, Fusco A. 2012. NF- κ B regulation: lessons from structures. *Immunological Reviews* 246(1):36–58 DOI 10.1111/j.1600-065X.2012.01097.x.
- Goldberg M, Lasfargues JJ. 1995. Pulpo-dentinal complex revisited. *Journal of Dentistry* 23(1):15–20 DOI 10.1016/0300-5712(95)90655-2.
- Govindappa PK, Talukder MAH, Gurjar AA, Hegarty JP, Elfar JC. 2020. An effective erythropoietin dose regimen protects against severe nerve injury-induced pathophysiological changes with improved neural gene expression and enhances functional recovery. *International Immunopharmacology* 82(Suppl 1):106330 DOI 10.1016/j.intimp.2020.106330.
- Guan X, He Y, Wei Z, Shi C, Li Y, Zhao R, Pan L, Han Y, Hou T, Yang J. 2021. Crosstalk between Wnt/ β -catenin signaling and NF- κ B signaling contributes to apical periodontitis. *International Immunopharmacology* 98(12):107843 DOI 10.1016/j.intimp.2021.107843.
- Guarnieri R, Reda R, Zanza A, Miccoli G, Nardo DD, Testarelli L. 2022. Can peri-implant marginal bone loss progression and a-MMP-8 be considered indicators of the subsequent onset of peri-implantitis? A 5-year study. *Diagnostics* 12(11):2599 DOI 10.3390/diagnostics12112599.
- Han Y, Huang Y, Yang Q, Jia L, Zheng Y, Li W. 2022. Long non-coding RNA SNHG5 mediates periodontal inflammation through the NF- κ B signalling pathway. *Journal of Clinical Periodontology* 49(10):1038–1051 DOI 10.1111/jcpe.13684.
- He Y, Bright R, Vasilev K, Zilm P. 2024. Development of “Intelligent particles” for the treatment of dental caries. *European Journal of Pharmaceutics and Biopharmaceutics* 202:114374 DOI 10.1016/j.ejpb.2024.114374.
- He Z, Jiang W, Jiang Y, Dong J, Song Z, Xu J, Zhou W. 2022. Anti-biofilm activities of coumarin as quorum sensing inhibitor for *Porphyromonas gingivalis*. *Journal of Oral Microbiology* 14(1):2055523 DOI 10.1080/20002297.2022.2055523.
- He X, Jiang W, Luo Z, Qu T, Wang Z, Liu N, Zhang Y, Cooper PR, He W. 2017. IFN- γ regulates human dental pulp stem cells behavior via NF- κ B and MAPK signaling. *Scientific Reports* 7:40681 DOI 10.1038/srep40681.

- He R, Li Y, Han C, Lin R, Qian W, Hou X. 2019. L-Fucose ameliorates DSS-induced acute colitis via inhibiting macrophage M1 polarization and inhibiting NLRP3 inflammasome and NF- κ B activation. *International Immunopharmacology* 73:379–388 DOI 10.1016/j.intimp.2019.05.013.
- He X, Wei Z, Zhou E, Chen L, Kou J, Wang J, Yang Z. 2015. Baicalein attenuates inflammatory responses by suppressing TLR4 mediated NF- κ B and MAPK signaling pathways in LPS-induced mastitis in mice. *International Immunopharmacology* 28(1):470–476 DOI 10.1016/j.intimp.2015.07.012.
- Hirai K, Furusho H, Hirota K, Sasaki H. 2018. Activation of hypoxia-inducible factor 1 attenuates periapical inflammation and bone loss. *International Journal of Oral Science* 10(2):12 DOI 10.1038/s41368-018-0015-0.
- Hozhabri NS, Benson MD, Vu MD, Patel RH, Martinez RM, Nakhaie FN, Kim HK, Varanasi VG. 2015. Decreasing NF- κ B expression enhances odontoblastic differentiation and collagen expression in dental pulp stem cells exposed to inflammatory cytokines. *PLOS ONE* 10(1):e0113334 DOI 10.1371/journal.pone.0113334.
- Huang Y, Jiang H, Gong Q, Li X, Ling J. 2015. Lipopolysaccharide stimulation improves the odontoblastic differentiation of human dental pulp cells. *Molecular Medicine Reports* 11(5):3547–3552 DOI 10.3892/mmr.2014.3120.
- Huang J, Liu L, Jin S, Zhang Y, Zhang L, Li S, Song A, Yang P. 2020. Proanthocyanidins promote osteogenic differentiation of human periodontal ligament fibroblasts in inflammatory environment via suppressing NF- κ B signal pathway. *Inflammation* 43(3):892–902 DOI 10.1007/s10753-019-01175-y.
- Ikeda M, Karakawa A, Takizawa H, Azetsu Y, Sakai N, Chatani M, Suzuki N, Takami M. 2022. Effects of anti-receptor activator of nuclear factor kappa B ligand antibody and zoledronic acid on periapical lesion development in mice. *Journal of Endodontics* 48(5):632–640 DOI 10.1016/j.joen.2022.02.002.
- Iotsova V, Caamaño J, Loy J, Yang Y, Lewin A, Bravo R. 1997. Osteopetrosis in mice lacking NF- κ B1 and NF- κ B2. *Nature Medicine* 3(11):1285–1289 DOI 10.1038/nm1197-1285.
- Jang YE, Kim Y, Kim SY, Kim BS. 2024. Predicting early endodontic treatment failure following primary root canal treatment. *BMC Oral Health* 24:327 DOI 10.1186/s12903-024-03974-8.
- Kang IA, Njimbouom SN, Kim JD. 2023. Optimal feature selection-based dental caries prediction model using machine learning for decision support system. *Bioengineering* 10(2):245 DOI 10.3390/bioengineering10020245.
- Karin M, Cao Y, Greten FR, Li ZW. 2002. NF- κ B in cancer: from innocent bystander to major culprit. *Nature Reviews Cancer* 2(4):301–310 DOI 10.1038/nrc780.
- Kawada-Matsuo M, Komatsuzawa H. 2017. Role of *Streptococcus mutans* two-component systems in antimicrobial peptide resistance in the oral cavity. *Japanese Dental Science Review* 53(3):86–94 DOI 10.1016/j.jdsr.2016.12.002.
- Keller MK, Kressirer CA, Belstrøm D, Twetman S, Tanner ACR. 2017. Oral microbial profiles of individuals with different levels of sugar intake. *Journal of Oral Microbiology* 9(1):1355207 DOI 10.1080/20002297.2017.1355207.
- Khajavi A, Radvar M, Moeintaghavi A. 2022. Socioeconomic determinants of periodontitis. *Periodontology 2000* 90(1):13–44 DOI 10.1111/prd.12448.
- Kim SY, Kim YJ, Kim S, Momeni M, Lee A, Treanor A, Kim S, Kim RH, Park NH. 2023. GV1001 inhibits the severity of the ligature-induced periodontitis and the vascular lipid deposition associated with the periodontitis in mice. *International Journal of Molecular Sciences* 24:12566 DOI 10.3390/ijms241612566.

- Kim JS, Kim KD, Na HS, Jeong SY, Park HR, Kim S, Chung J. 2012.** Tumor necrosis factor- α and interleukin-1 β expression pathway induced by *Streptococcus mutans* in macrophage cell line RAW 264.7. *Molecular Oral Microbiology* 27(3):149–159 DOI 10.1111/j.2041-1014.2012.00639.x.
- Kittaka M, Shiba H, Kajiya M, Ouhara K, Takeda K, Kanbara K, Fujita T, Kawaguchi H, Komatsuzawa H, Kurihara H. 2013.** Antimicrobial peptide LL37 promotes vascular endothelial growth factor- α expression in human periodontal ligament cells. *Journal of Periodontal Research* 48(2):228–234 DOI 10.1111/j.1600-0765.2012.01524.x.
- Lee SY, Auh QS, Kang SK, Kim HJ, Lee JW, Noh K, Jang JH, Kim EC. 2014.** Combined effects of dentin sialoprotein and bone morphogenetic protein-2 on differentiation in human cementoblasts. *Cell and Tissue Research* 357(1):119–132 DOI 10.1007/s00441-014-1831-y.
- Lee SY, Yi JK, Yun HM, Bae CH, Cho ES, Lee KS, Kim EC. 2016.** Expression of Caveolin-1 in periodontal tissue and its role in osteoblastic and cementoblastic differentiation in vitro. *Calcified Tissue International* 98(5):497–510 DOI 10.1007/s00223-015-0095-1.
- Lepetos P, Papavassiliou KA, Papavassiliou AG. 2019.** Redox and NF- κ B signaling in osteoarthritis. *Free Radical Biology and Medicine* 132(4):90–100 DOI 10.1016/j.freeradbiomed.2018.09.025.
- Li J, Jin F, Cai M, Lin T, Wang X, Sun Y. 2022.** LncRNA nron inhibits bone resorption in periodontitis. *Journal of Dental Research* 101(2):187–195 DOI 10.1177/00220345211019689.
- Li YF, Sun HW, Gao R, Liu KY, Zhang HQ, Fu QH, Qing SL, Guo G, Zou QM. 2015.** Inhibited biofilm formation and improved antibacterial activity of a novel nanoemulsion against cariogenic *Streptococcus mutans* in vitro and in vivo. *International Journal of Nanomedicine* 10:447–462 DOI 10.2147/ijn.S72920.
- Li H, Wang D. 2014.** *Streptococcus mutans* wall-associated protein A promotes TLR4-induced dendritic cell maturation. *Scandinavian Journal of Immunology* 80(2):121–126 DOI 10.1111/sji.12194.
- Li H, Wang Q, Ding Y, Bao C, Li W. 2017.** Mangiferin ameliorates Porphyromonas gingivalis-induced experimental periodontitis by inhibiting phosphorylation of nuclear factor- κ B and Janus kinase 1-signal transducer and activator of transcription signaling pathways. *Journal of Periodontal Research* 52(1):1–7 DOI 10.1111/jre.12360.
- Liang D, Li F, Fu Y, Cao Y, Song X, Wang T, Wang W, Guo M, Zhou E, Li D, Yang Z, Zhang N. 2014.** Thymol inhibits LPS-stimulated inflammatory response via down-regulation of NF- κ B and MAPK signaling pathways in mouse mammary epithelial cells. *Inflammation* 37(1):214–222 DOI 10.1007/s10753-013-9732-x.
- Lin JJ, Du Y, Cai WK, Kuang R, Chang T, Zhang Z, Yang YX, Sun C, Li ZY, Kuang F. 2015.** Toll-like receptor 4 signaling in neurons of trigeminal ganglion contributes to nociception induced by acute pulpitis in rats. *Scientific Reports* 5:12549 DOI 10.1038/srep12549.
- Liu Z, Jiang T, Wang X, Wang Y. 2013.** Fluocinolone acetonide partially restores the mineralization of LPS-stimulated dental pulp cells through inhibition of NF- κ B pathway and activation of AP-1 pathway. *British Journal of Pharmacology* 170(6):1262–1271 DOI 10.1111/bph.12404.
- Liu X, Wang C, Pang L, Pan L, Zhang Q. 2022.** Combination of resolvin E1 and lipoxin A4 promotes the resolution of pulpitis by inhibiting NF- κ B activation through upregulating sirtuin 7 in dental pulp fibroblasts. *Cell Proliferation* 55(5):e13227 DOI 10.1111/cpr.13227.
- Liu Y, Zhang Z, Li W, Tian S. 2020b.** PECAM1 combines with CXCR4 to trigger inflammatory cell infiltration and pulpitis progression through activating the NF- κ B signaling pathway. *Frontiers in Cell and Developmental Biology* 8:593653 DOI 10.3389/fcell.2020.593653.

- Liu S, Zhou M, Li J, Hu B, Jiang D, Huang H, Song J. 2020a. LIPUS inhibited the expression of inflammatory factors and promoted the osteogenic differentiation capacity of hPDLs by inhibiting the NF- κ B signaling pathway. *Journal of Periodontal Research* 55(1):125–140 DOI 10.1111/jre.12696.
- Long P, Xiong L, Ding C, Kuang Y, He Y, Li G, Xiao J, Li S. 2023. Connexin43 reduces LPS-induced inflammation in hDPCs through TLR4-NF- κ B pathway via hemichannels. *Oral Diseases* 30(5):3239–3249 DOI 10.1111/odi.14767.
- Lu Q, Xu W, Liu L, Zhou X, Ye L, Song D, Zhang L, Huang D. 2020. Traumatic compressive stress inhibits osteoblast differentiation through long chain non-coding RNA Dancr. *Journal of Periodontology* 91(11):1532–1540 DOI 10.1002/JPER.19-0648.
- Luo X, Wan Q, Cheng L, Xu R. 2022. Mechanisms of bone remodeling and therapeutic strategies in chronic apical periodontitis. *Frontiers in Cellular and Infection Microbiology* 12:908859 DOI 10.3389/fcimb.2022.908859.
- Ma N, Yang D, Okamura H, Teramachi J, Hasegawa T, Qiu L, Haneji T. 2017. Involvement of interleukin-23 induced by Porphyromonas endodontalis lipopolysaccharide in osteoclastogenesis. *Molecular Medicine Reports* 15(2):559–566 DOI 10.3892/mmr.2016.6041.
- Meng R, Li D, Feng Z, Xu Q. 2019. MyD88 hypermethylation mediated by DNMT1 is associated with LTA-induced inflammatory response in human odontoblast-like cells. *Cell and Tissue Research* 376(3):413–423 DOI 10.1007/s00441-019-02993-0.
- Nam OH, Kim JH, Kang SW, Chae YK, Jih MK, You HH, Koh JT, Kim Y. 2024. Ginsenoside Rb1 alleviates lipopolysaccharide-induced inflammation in human dental pulp cells via the PI3K/Akt, NF- κ B, and MAPK signalling pathways. *International Endodontic Journal* 57(6):759–768 DOI 10.1111/iej.14058.
- Pai P, Sukumar S. 2020. HOX genes and the NF- κ B pathway: a convergence of developmental biology, inflammation and cancer biology. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer* 1874(2):188450 DOI 10.1016/j.bbcan.2020.188450.
- Pei F, Wang HS, Chen Z, Zhang L. 2016. Autophagy regulates odontoblast differentiation by suppressing NF- κ B activation in an inflammatory environment. *Cell Death & Disease* 7(3):e2122 DOI 10.1038/cddis.2015.397.
- Qiao W, Huang Y, Bian Z, Sun X, Wang X, Gao Q, Peng Y, Meng L. 2019. Lipopolysaccharide-induced DNA damage response activates nuclear factor κ B signalling pathway via GATA4 in dental pulp cells. *International Endodontic Journal* 52(12):1704–1715 DOI 10.1111/iej.13180.
- Rider D, Furusho H, Xu S, Trachtenberg AJ, Kuo WP, Hirai K, Susa M, Bahammam L, Stashenko P, Fujimura A, Sasaki H. 2016. Elevated CD14 (Cluster of Differentiation 14) and toll-like receptor (TLR) 4 signaling deteriorate periapical inflammation in TLR2 deficient mice. *The Anatomical Record* 299(9):1281–1292 DOI 10.1002/ar.23383.
- Ruben SM, Klement JF, Coleman TA, Maher M, Chen CH, Rosen CA. 1992. I-Rel: a novel rel-related protein that inhibits NF-kappa B transcriptional activity. *Genes & Development* 6(5):745–760 DOI 10.1101/gad.6.5.745.
- Ryseck RP, Bull P, Takamiya M, Bours V, Siebenlist U, Dobrzanski P, Bravo R. 1992. RelB, a new Rel family transcription activator that can interact with p50-NF-kappa B. *Molecular and Cellular Biology* 12(2):674–684 DOI 10.1128/MCB.12.2.674.
- Sabeti M, Simon J, Kermani V, Valles Y, Rostein I. 2005. Detection of receptor activator of NF-kappa beta ligand in apical periodontitis. *Journal of Endodontics* 31(1):17–18 DOI 10.1097/01.DON.0000134210.95473.A7.

- Sakamoto M, Fukunaga T, Sasaki K, Seiryu M, Yoshizawa M, Takeshita N, Takano-Yamamoto T. 2019. Vibration enhances osteoclastogenesis by inducing RANKL expression via NF- κ B signaling in osteocytes. *Bone* 123:56–66 DOI 10.1016/j.bone.2019.03.024.
- Sen R, Baltimore D. 1986. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. *Cell* 46(5):705–716 DOI 10.1016/0092-8674(86)90346-6.
- Shen S, Shang L, Liu H, Liang Q, Liang W, Ge S. 2021. AGGF1 inhibits the expression of inflammatory mediators and promotes angiogenesis in dental pulp cells. *Clinical Oral Investigations* 25(2):581–592 DOI 10.1007/s00784-020-03498-9.
- Shi J, Zhang Y, Zhang X, Chen R, Wei J, Hou J, Wang B, Lai H, Huang Y. 2021. Remodeling immune microenvironment in periodontitis using resveratrol liposomes as an antibiotic-free therapeutic strategy. *Journal of Nanobiotechnology* 19(1):429 DOI 10.1186/s12951-021-01175-x.
- Siddiqui Z, Acevedo-Jake AM, Griffith A, Kadincesme N, Dabek K, Hindi D, Kim KK, Kobayashi Y, Shimizu E, Kumar V. 2022. Cells and material-based strategies for regenerative endodontics. *Bioactive Materials* 14(9):234–249 DOI 10.1016/j.bioactmat.2021.11.015.
- Silva-García O, Valdez-Alarcón JJ, Baizabal-Aguirre VM. 2019. Wnt/ β -Catenin signaling as a molecular target by pathogenic bacteria. *Frontiers in Immunology* 10:2135 DOI 10.3389/fimmu.2019.02135.
- Siqueira JF Jr, Rôças IN. 2009. Diversity of endodontic microbiota revisited. *Journal of Dental Research* 88(11):969–981 DOI 10.1177/0022034509346549.
- Sjögren U, Figdor D, Persson S, Sundqvist G. 1997. Influence of infection at the time of root filling on the outcome of endodontic treatment of teeth with apical periodontitis. *International Endodontic Journal* 30(5):297–306 DOI 10.1046/j.1365-2591.1997.00092.x.
- Song Y, Cao P, Gu Z, Xiao J, Lian M, Huang D, Xing J, Zhang Y, Feng X, Wang C. 2018. The role of neuropilin-1-FYN interaction in odontoblast differentiation of dental pulp stem cells. *Cellular Reprogramming* 20(2):117–126 DOI 10.1089/cell.2017.0041.
- Song F, Sun H, Wang Y, Yang H, Huang L, Fu D, Gan J, Huang C. 2017. Pannexin3 inhibits TNF- α -induced inflammatory response by suppressing NF- κ B signalling pathway in human dental pulp cells. *Journal of Cellular and Molecular Medicine* 21(3):444–455 DOI 10.1111/jcmm.12988.
- Song J, Wu Q, Jiang J, Sun D, Wang F, Xin B, Cui Q. 2020. Berberine reduces inflammation of human dental pulp fibroblast via miR-21/KBTBD7 axis. *Archives of Oral Biology* 110(Suppl. 1):104630 DOI 10.1016/j.archoralbio.2019.104630.
- Stark GR, Kerr IM, Williams BR, Silverman RH, Schreiber RD. 1998. How cells respond to interferons. *Annual Review of Biochemistry* 67(1):227–264 DOI 10.1146/annurev.biochem.67.1.227.
- Sun SC. 2011. Non-canonical NF- κ B signaling pathway. *Cell Research* 21(1):71–85 DOI 10.1038/cr.2010.177.
- Tian Y, Li Y, Liu J, Lin Y, Jiao J, Chen B, Wang W, Wu S, Li C. 2022. Photothermal therapy with regulated Nrf2/NF- κ B signaling pathway for treating bacteria-induced periodontitis. *Bioactive Materials* 9:428–445 DOI 10.1016/j.bioactmat.2021.07.033.
- Tibúrcio-Machado CS, Michelon C, Zanatta FB, Gomes MS, Marin JA, Bier CA. 2021. The global prevalence of apical periodontitis: a systematic review and meta-analysis. *International Endodontic Journal* 54(5):712–735 DOI 10.1111/iej.13467.
- Wang J, Du Y, Deng J, Wang X, Long F, He J. 2019. MicroRNA-506 is involved in regulation of the occurrence of lipopolysaccharides (LPS)-induced pulpitis by sirtuin 1 (SIRT1). *Medical Science Monitor* 25:10008–10015 DOI 10.12659/MSM.918172.

- Wang Q, Jiang H, Li Y, Chen W, Li H, Peng K, Zhang Z, Sun X. 2017. Targeting NF- κ B signaling with polymeric hybrid micelles that co-deliver siRNA and dexamethasone for arthritis therapy. *Biomaterials* 122(Suppl 2):10–22 DOI 10.1016/j.biomaterials.2017.01.008.
- Wang L, Jin H, Ye D, Wang J, Ao X, Dong M, Niu W. 2016. Enterococcus faecalis lipoteichoic acid-induced NLRP3 inflammasome via the activation of the nuclear factor kappa B pathway. *Journal of Endodontics* 42(7):1093–1100 DOI 10.1016/j.joen.2016.04.018.
- Wang J, Wang B, Lv X, Wang L. 2020. NIK inhibitor impairs chronic periodontitis via suppressing non-canonical NF- κ B and osteoclastogenesis. *Pathogens and Disease* 78(7):2377 DOI 10.1093/femspd/ftaa045.
- Wang Y, Wang L, Sun T, Shen S, Li Z, Ma X, Gu X, Zhang X, Peng A, Xu X, Feng Q. 2023. Study of the inflammatory activating process in the early stage of Fusobacterium nucleatum infected PDLSCs. *International Journal of Oral Science* 15(1):8 DOI 10.1038/s41368-022-00213-0.
- Wang Y, Xie Y, Xue N, Xu H, Zhang D, Ji N, Chen Q. 2024. TSG-6 inhibits the NF- κ B signaling pathway and promotes the odontogenic differentiation of dental pulp stem cells via CD44 in an inflammatory environment. *Biomolecules* 14(3):368 DOI 10.3390/biom14030368.
- Wang X, Yu Y, Ji L, Geng Z, Wang J, Liu C. 2021. Calcium phosphate-based materials regulate osteoclast-mediated osseointegration. *Bioactive Materials* 6(12):4517–4530 DOI 10.1016/j.bioactmat.2021.05.003.
- Wei W, Li J, Liu X, Pan W, Wang M, Li J, Yue Y, Hao L. 2022. Inhibition of RGS10 aggravates periapical periodontitis via upregulation of the NF- κ B pathway. *Journal of Endodontics* 48(10):1308–1318.e1305 DOI 10.1016/j.joen.2022.07.009.
- Wu H, He M, Yang R, Zuo Y, Bian Z. 2018. Astrocyte elevated gene-1 participates in the production of pro-inflammatory cytokines in dental pulp cells via NF- κ B signalling pathway. *International Endodontic Journal* 51(10):1130–1138 DOI 10.1111/iej.12921.
- Xiao J, Jiang R, Yin W, Zhang Y, Cao P, Li J, Gong Y, Ding X, Shi S, Hao J. 2022. NOD2 is involved in regulating odontogenic differentiation of DPSCs suppressed by MDP through NF- κ B/p65 signaling. *Cytotechnology* 74(2):259–270 DOI 10.1007/s10616-022-00526-2.
- Xie X, Chen W, Xu M, Chen J, Yang T, Wang C, Su Y, Zhao J, Xu J, Liu Q. 2024. IKK/NF- κ B and ROS signal axes are involved in Tenacissoside H mediated inhibitory effects on LPS-induced inflammatory osteolysis. *Cell Proliferation* 57(1):e13535 DOI 10.1111/cpr.13535.
- Yang SY, Hu Y, Zhao R, Zhou YN, Zhuang Y, Zhu Y, Ge XL, Lu TW, Lin KL, Xu YJ. 2024. Quercetin-loaded mesoporous nano-delivery system remodels osteoimmune microenvironment to regenerate alveolar bone in periodontitis via the miR-21a-5p/PDCD4/NF- κ B pathway. *Journal of Nanobiotechnology* 22(1):94 DOI 10.1186/s12951-024-02352-4.
- Yang Y, Rossi FM, Putnins EE. 2010. Periodontal regeneration using engineered bone marrow mesenchymal stromal cells. *Biomaterials* 31(33):8574–8582 DOI 10.1016/j.biomaterials.2010.06.026.
- Yao S, Jiang C, Zhang H, Gao X, Guo Y, Cao Z. 2021. Visfatin regulates Pg LPS-induced proinflammatory/prodegradative effects in healthy and inflammatory periodontal cells partially via NF- κ B pathway. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 1868(8):119042 DOI 10.1016/j.bbamcr.2021.119042.
- Yu H, Lin L, Zhang Z, Zhang H, Hu H. 2020. Targeting NF- κ B pathway for the therapy of diseases: mechanism and clinical study. *Signal Transduction and Targeted Therapy* 5(1):209 DOI 10.1038/s41392-020-00312-6.
- Zhang L, Cui Y, Yang Y, Wei J, Liu W, Cai L, Wang L, Zhang D, Xie J, Cheng L. 2021a. The virulence factor GroEL promotes gelatinase secretion from cells in the osteoblast lineage:

- implication for direct crosstalk between bacteria and adult cells. *Archives of Oral Biology* **122**(4):104991 DOI [10.1016/j.archoralbio.2020.104991](https://doi.org/10.1016/j.archoralbio.2020.104991).
- Zhang Q, Ma Q, Wang Y, Wu H, Zou J. 2021b.** Molecular mechanisms of inhibiting glucosyltransferases for biofilm formation in *Streptococcus mutans*. *International Journal of Oral Science* **13**(1):30 DOI [10.1038/s41368-021-00137-1](https://doi.org/10.1038/s41368-021-00137-1).
- Zhang X, Peng B. 2005.** Immunolocalization of receptor activator of NF kappa B ligand in rat periapical lesions. *Journal of Endodontics* **31**(8):574–577 DOI [10.1097/01.don.0000153839.74546.66](https://doi.org/10.1097/01.don.0000153839.74546.66).
- Zhang Z, Song J, Kwon SH, Wang Z, Park SG, Piao X, Ryu JH, Kim N, Kim OS, Kim SH, Koh JT. 2023.** Pirfenidone inhibits alveolar bone loss in ligature-induced periodontitis by suppressing the NF-κB signaling pathway in mice. *International Journal of Molecular Sciences* **24**(10):8682 DOI [10.3390/ijms24108682](https://doi.org/10.3390/ijms24108682).
- Zhang X, Wang X, Wu J, Wang M, Hu B, Qu H, Zhang J, Li Q. 2022.** The global burden of periodontal diseases in 204 countries and territories from 1990 to 2019. *Oral Diseases* **30**(2):754–768 DOI [10.1111/odi.14436](https://doi.org/10.1111/odi.14436).
- Zhang L, Xiao X, Arnold PR, Li XC. 2019.** Transcriptional and epigenetic regulation of immune tolerance: roles of the NF-κB family members. *Cellular & Molecular Immunology* **16**(4):315–323 DOI [10.1038/s41423-019-0202-8](https://doi.org/10.1038/s41423-019-0202-8).
- Zhao Z, Dai J, Yin C, Wang X, Wang J, Jia X, Zhao Q, Fu H, Zhang Y, Xia H. 2019.** Transcription factor 7-like 2-associated signaling mechanism in regulating cementum generation by the NF-κB pathway. *Journal of Cellular Physiology* **234**(11):20790–20800 DOI [10.1002/jcp.28685](https://doi.org/10.1002/jcp.28685).
- Zhou W, Su L, Duan X, Chen X, Hays A, Upadhyayula S, Shivde J, Wang H, Li Y, Huang D, Liang S. 2018.** MicroRNA-21 down-regulates inflammation and inhibits periodontitis. *Molecular Immunology* **101**:608–614 DOI [10.1016/j.molimm.2018.05.008](https://doi.org/10.1016/j.molimm.2018.05.008).
- Zhu N, Chatzistavrou X, Ge L, Qin M, Papagerakis P, Wang Y. 2019.** Biological properties of modified bioactive glass on dental pulp cells. *Journal of Dentistry* **83**(1):18–26 DOI [10.1016/j.jdent.2019.01.017](https://doi.org/10.1016/j.jdent.2019.01.017).