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Review

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Neuroimmune interactions in oral disease

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Abstract: The nervous and immune systems exhibit numerous similarities within human oral tissues, as both systems are responsible for monitoring environmental and internal stimuli, integrating these signals to maintain homeostasis, and mediating defense responses against potential threats. Recent advancements have enhanced the mechanistic understanding of neuroimmune interactions in oral tissue, highlighting the crucial role of this crosstalk in maintaining oral tissue homeostasis and modulating inflammatory and infectious oral diseases. This review aims to elucidate the pivotal role of these interactions in the initiation and progression of oral disease. Interactions mediated by neurotransmitters and neuropeptides exert a significant influence on immune-cell function, while inflammatory mediators induce peripheral and central sensitization of sensory neurons that innervate the oral cavity. These processes are extremely important in the development and progression of oral conditions such as periodontitis, pulpitis, and oral cancer. In addition, we examine the interplay between the nervous and immune systems and provide new insights into potential therapeutic interventions to target neuroimmune pathways in oral health.

Key words: Nervous system; Immunomodulation; Neuroimmune crosstalk; Neurogenic inflammation; Oral disease

1 Introduction

Oral disease represents a significant global health challenge, affecting approximately 90% of the population across various demographics at some point in their lives (Jin et al., 2016). These conditions include pulpal disease, periodontal disease, oral mucosal disease, and oral cancer. The high prevalence and chronicity of these disorders impair oral function, reduce quality of life, and are linked to systemic conditions such as cardiovascular disease (Hopkins et al., 2024), diabetes (Bitencourt et al., 2023), and neurodegenerative disorders (Nicholson and Landry, 2022). Given their impact on both oral and systemic health, a deeper understanding of the underlying mechanisms of these diseases is important for developing effective therapeutic strategies.

Traditionally, microbial factors have been viewed as the principal contributors to the pathogenesis of oral disease (Murakami et al., 2018), with bacteria, viruses, and fungi seen as playing key roles in the development and progression of disease. However, recent research has increasingly focused on the host immune response, revealing its central role in driving disease progression. For instance, in periodontitis, dysregulated T and B lymphocytes drive chronic inflammation, leading to tissue destruction (Han et al., 2023; Ye et al., 2024), while in pulpitis, immune-cell hyperactivation in response to infection prolongs inflammation and causes tissue damage (Rechenberg et al., 2016). This growing emphasis on immune regulation has prompted researchers to explore how various factors, including neural signals, influence immune behavior within the oral cavity.

Immune regulation in the oral cavity is influenced by various factors, including infections, genetic predisposition, and aging (Ebersole et al., 2016; Pandruvada et al., 2016). Beyond these, emerging neuroimmunology research highlights the critical role of the nervous system in modulating the immune response (Hafler and Sansing, 2022). This interplay between the neural and immune systems carries important implications for oral disease progression, particularly in cases involving

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persistent inflammation and chronic pain (Yi et al., 2021).

Pain is a predominant symptom in many oral diseases, including periodontitis, pulpitis, and oral cancer, and its underlying mechanisms have been extensively studied, with emphasis on neural pathways (Matsuka, 2022; Wang J et al., 2024). Neuropeptides, including calcitonin gene-related peptide (CGRP) and substance P (SP), are central to pain modulation, interacting with nociceptive neurons and glial cells. For instance, upregulation of CGRP in the trigeminal system not only induces local inflammation but also activates microglia, which release pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), amplifying the pain response (Liang et al., 2021). Similarly, SP enhances neuronal excitability by binding to neurokinin-1 (NK1) receptors, leading to both peripheral and central sensitization and contributing to persistent pain (Park et al., 2010; Sperry et al., 2021). In addition to neuropeptides, glial cells, particularly microglia and astrocytes, release inflammatory mediators such as prostaglandin E2 (PGE2) and brain-derived neurotrophic factor (BDNF), further driving central sensitization (Ye et al., 2021). Although considerable research has examined the role of neuropeptides and glial cells in pain modulation, the interactions between the nervous and immune systems in chronic inflammation are still under-researched, leaving a gap in understanding of the neuroimmune mechanisms underlying chronic pain in oral disease.

Insights derived from neuroimmune interactions, which have been previously studied in conditions such as cardiovascular (Carnevale and Lembo, 2021), allergic (Matsuda, 2022), and gastrointestinal diseases (Chesné et al., 2019), are illuminating how neural signals regulate immune pathways and influence inflammatory responses (Khanmammadova et al., 2023). These findings provide new avenues for understanding oral health, since similar neuroimmune dynamics could influence the progression of oral diseases. The orofacial region, innervated by complex neural networks such as the trigeminal, facial, and vagus nerves, is particularly susceptible to such interactions (Shoja et al., 2014a, 2014b). This means that neuroimmunology will be a crucial area for future research in oral health.

This review examines the emerging role of neuroimmune interactions in oral disease, focusing on how these mechanisms influence the pathogenesis and progression of various conditions. By clarifying these neuroimmune pathways, we seek to provide insights to guide the development of innovative therapeutic strategies for oral disease management.

2 Fundamentals of neuroimmune communication in the oral cavity

2.1 Overview of neuroimmune systems

Interaction between the nervous and immune systems spans both the central and peripheral nervous systems (CNS and PNS), orchestrating immune responses at multiple levels (Fig. 1). The PNS serves as a crucial communication link between the CNS and peripheral tissues (Murtazina and Adameyko, 2023). It is broadly divided into the somatic nervous system, which enables sensory perception and voluntary motor control, and the autonomic nervous system, which is responsible for regulating involuntary physiological processes, including homeostasis (Ferraro et al., 2022). The autonomic nervous system is further split into the sympathetic and parasympathetic divisions (Alrosan et al., 2024). Sensory neurons in the PNS relay information from peripheral tissues to the CNS, while motor neurons send signals from the CNS to muscles and organs, ensuring coordinated physiological responses.

The key components of neuroimmune communication are neuromediators released by neurons, cytokines and immune factors secreted by immune cells, and shared receptors expressed by both cell types. At specific anatomical sites, immune and neuronal cells often exist in close proximity, forming neuroimmune cell units that collaborate to modulate both local and systemic responses (Godinho-Silva et al., 2019). Neurons can detect both endogenous and exogenous signals of infection, inflammation, and tissue damage, and release neuropeptides and neurotransmitters to modulate the immune response (Deng et al., 2024).

Neurotransmitters such as acetylcholine, dopamine, serotonin, and glutamate serve as chemical messengers that transmit signals across synapses in the nervous system. They also modulate immune response by interacting with immune cells, which express receptors for these neurotransmitters. For instance, dopamine and acetylcholine have been shown to suppress inflammation by inhibiting activation of the nucleotide

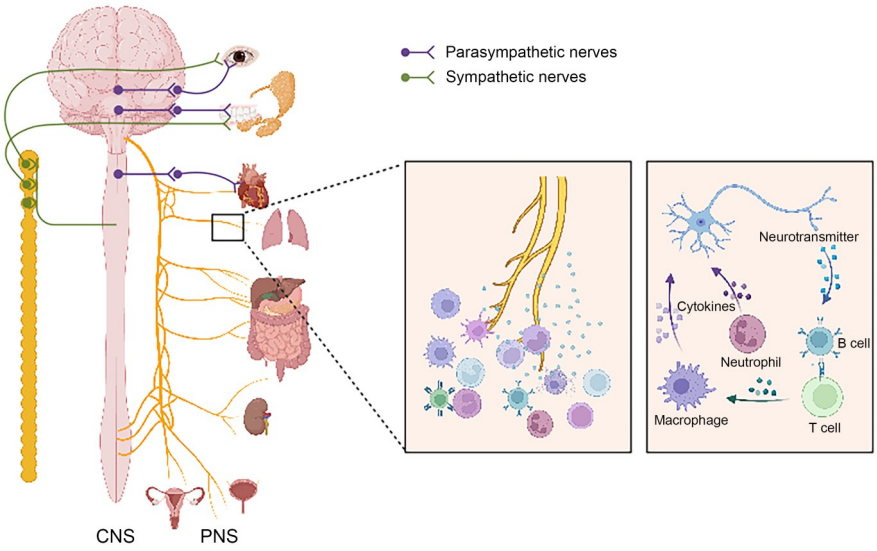


Fig. 1 Crosstalk between the nervous and immune systems. Neuroimmune communication involves neuromediators from neurons, cytokines from immune cells, and shared receptors, and forms neuroimmune cell units that regulate local and systemic responses. CNS: central nervous system; PNS: peripheral nervous system. Created with https://www.biorender.com.

binding and oligomerisation domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and by interacting with the α7 subunit of the nicotinic acetylcholine receptor (nAChR), which is expressed on cytokine-producing macrophages (Rosas-Ballina et al., 2011; Pike et al., 2022).

When sensory neurons are stimulated, neuropeptides are released from nerve terminals or synaptic clefts. These neuropeptides can act directly on neurons such as nociceptors, trigeminal ganglia (TG), and the spinal trigeminal nucleus (SpVc), or on non-neuronal targets such as glial, endothelial, and inflammatory cells. For example, in many infectious diseases, bacteria activate nociceptors, leading to the release of CGRP from nerve terminals. This release suppresses macrophage chemokine expression, neutrophil recruitment, and dural antimicrobial defenses, playing a vital role in anti-inflammatory processes and repair of tissue damage (Pinho-Ribeiro et al., 2023; Lu et al., 2024).

2.2 Nerve distribution and immune regulation in oral tissues

The trigeminal nerve provides the principal sensory innervation to the orofacial region. Numerous trigeminal primary afferent fibers terminate in the orofacial region as free nerve endings, functioning as nociceptors. These nerve endings release neuropeptides and neurotransmitters, including CGRP and SP, which modulate pain perception and inflammatory response in the oral microenvironment. When nociceptive stimuli are applied to these regions, local tissue and inflammatory cells become activated, releasing various cytokines and inflammatory mediators that alter the microenvironment surrounding the damaged peripheral nerves (Sessle, 1987; Wang J et al., 2024). This neural-immune crosstalk sets the stage for the complex interplay observed in oral disease.

Sensory nerve endings in the oral cavity also rely on ion channels to mediate pain perception and neurogenic inflammation. Transient receptor potential (TRP) channels, such as transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1), are ligand-gated cation channels that detect noxious heat, reactive electrophiles, and other harmful stimuli. Activation of these ion channels leads to pain sensation and contributes to neurogenic inflammation (Dubner and Bennett, 1983). Voltage-gated sodium channels NaV1.1–NaV1.9 are also involved in pain processing. Notably, NaV1.7, which is responsive to cold stimuli in nociceptors, has been implicated in the development of toothache (Goto et al., 2016). Together, these neural mechanisms amplify the inflammatory responses initiated by nociceptive stimuli, linking neural signaling to immune activation in oral tissues (Fig. 2).

Oral diseases such as periodontitis and pulpitis involve complex immune responses driven by both innate and adaptive immunity. Neutrophils and macrophages

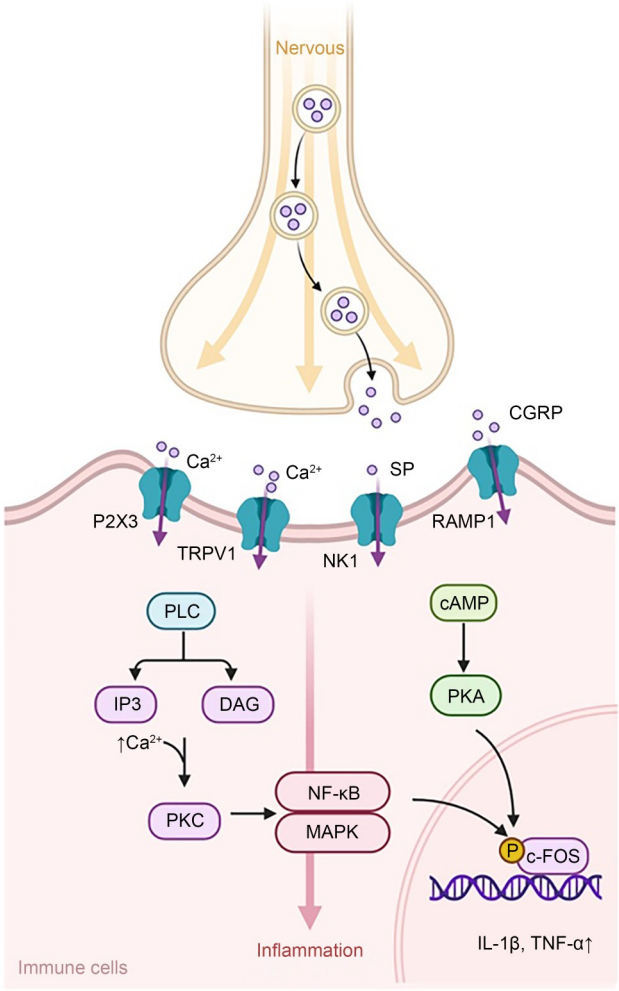


Fig. 2 Mechanisms of neuropeptide-ion channel-neuroimmune interactions. Signaling pathways of neuropeptides and ion channels play important roles in neuroimmune interactions in oral disease. CGRP: calcitonin gene-related peptide; TRPV1: transient receptor potential vanilloid 1; NK1: neurokinin-1; RAMP1: receptor activity-modifying protein 1; P2X3: purinergic receptor P2X ligand-gated ion channel 3; PLC: phospholipase C; cAMP: cyclic adenosine monophosphate; IP3: inositol 1,4,5-trisphosphate; DAG: diacylglycerol lipase; PKA: protein kinase A; PKC: protein kinase C; c-FOS: cellular proto-oncogene Fos; NF-κB: nuclear factor-κB; MAPK: mitogen-activated protein kinase; IL-1β: interleukin-1β; TNF-α: tumor necrosis factor-α. Created with https://www.biorender.com.

are pivotal in the initial phase of inflammation, controlling infection and triggering tissue responses by producing pro-inflammatory cytokines such as TNF-α and IL-1 (Cavalla et al., 2014). These cytokines activate pathways that contribute to tissue and bone breakdown (Han et al., 2023). The adaptive immune response, which particularly involves T helper cell 1 (Th1) and Th2 cells, further modulates inflammation. The Th1 cells address intracellular pathogens and the Th2 cells defend against extracellular ones (Cavalla et al., 2014). In pulpitis, the pronounced infiltration of neutrophils, macrophages, and T cells shows the distinct immune dynamics between healthy and inflamed tissues, highlighting the complex regulation of immune cells in disease progression (Wang J et al., 2023). These immune processes are linked to the neural mechanisms described earlier, forming a dynamic neuroimmune interplay in oral pathology.

The complex neural and immune systems in the oral cavity facilitate dynamic interactions between sensory perception and immune regulation (Fig. 3; Tables 1 and 2). For instance, nerves in the dental pulp not only transmit pain but also regulate inflammation in pulpitis through neurotransmitters and neuropeptides, influencing immune response and tissue repair (Zhan et al., 2021). Similarly, Wu et al. (2023) investigated the

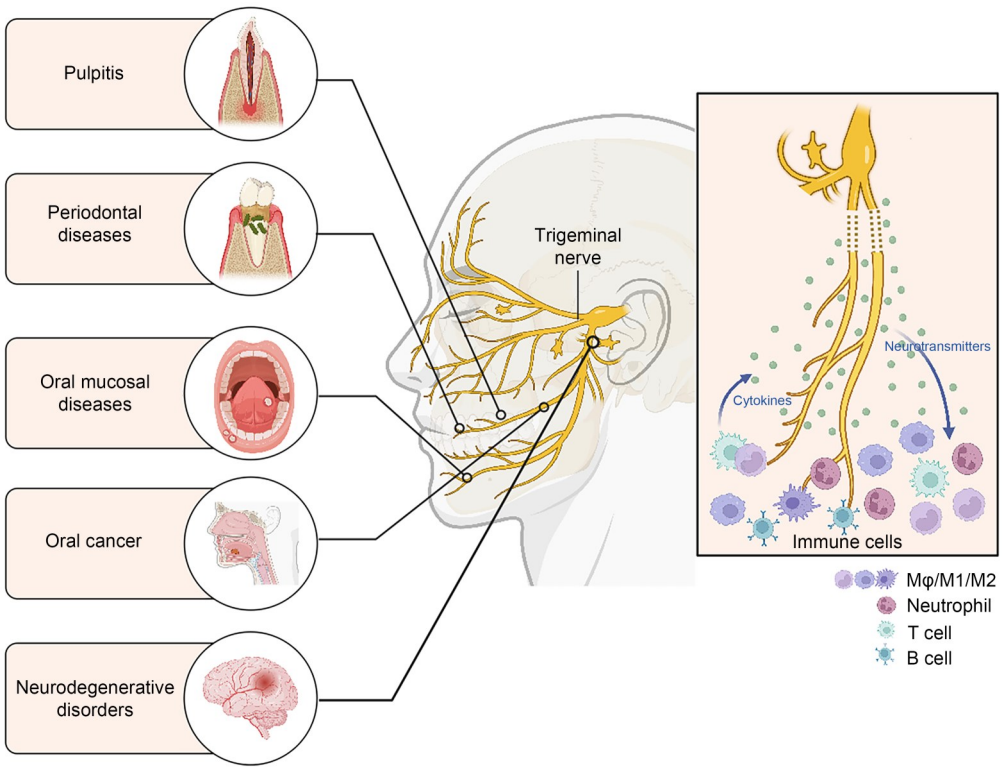


Fig. 3 Neuroimmune interactions involved in oral disease. Neuroimmune interactions involve a complex network of neurotransmitters, immune cells, and signaling pathways, and influence local immune response, inflammation, and tissue homeostasis in the oral cavity, significantly affecting the onset and progression of diseases such as pulpitis, periodontitis, and oral cancer. Created with https://www.biorender.com.

interaction between the nervous system and oral structures, revealing that this relationship modulates immune response and tissue homeostasis. The nervous system also regulates bone metabolism through neurotransmitters and neuropeptides, forming a neuro-immune-bone axis that presents potential therapeutic targets for oral disease (Richardson and Vasko, 2002; Wang et al., 2009). To help summarize the numerous signaling molecules discussed, we present Table 3, which categorizes the key neuropeptides, cytokines, and receptors involved in neuroimmune interactions across different oral diseases.

3 Neuroimmune interactions involved in oral disease

3.1 Pulpal diseases

The dental pulp is a richly innervated loose connective tissue, with nerve fibers comprising approximately 40% of its total volume. These nerves primarily consist of sensory, sympathetic, and parasympathetic fibers, with sensory nerves dominating the innervation of the pulp and predominantly originating from the trigeminal nerve (Zhan et al., 2021; Lee et al., 2023). Sensory nerves not only transmit pain signals but also play a critical role in maintaining pulp homeostasis. They protect the pulp from degenerative changes by regulating cellular proliferation, senescence, and synthesis of the extracellular matrix (Wang et al., 2024b). Research has demonstrated that the activin B/mothers against decapentaplegic homolog 2/3 (SMAD2/3) signaling pathway plays an important role in this process. Supplementation with activin B has been shown to mitigate fibrosis and calcification caused by sensory nerve ablation, thereby maintaining pulp homeostasis (Liu et al., 2020). Additionally, sensory neurons promote repair and regeneration of the pulp-dentin complex by secreting neurotrophic factors such as BDNF and nerve growth factor (NGF) (Diogenes, 2020). Conversely, dental pulp stem cells (DPSCs) secrete neurotrophic factors that act on neurons, promoting neurite outgrowth and expression of neuron-related genes (Sultan et al., 2020). This reciprocal interaction between

Table 1 Neural regulation of the immune system in oral diseases

Disease	Source and kind	Cytokines, receptors, or ion channels	Target cell	Regulatory details (key mechanisms/signaling pathways)	Reference
Pulpitis	Trigeminal neurons	CGRP	Neutrophils, monocytes	CGRP signaling through RAMP1 and calcitonin receptor-like receptor regulates immune responses.	Erdogan et al., 2024
	Trigeminal neurons	TRPV1 expression, c-FOS	Neutrophils	Upregulation of TRPV1 expression promotes pain transmission.	Cha et al., 2020
	Trigeminal neurons	P2X3 receptor	Microglia	Activation of microglia leads to an immune response.	Chen et al., 2024
	Trigeminal neurons	TACAN ion channel, TNF-α	Macrophages	Upregulation of TACAN ion channels activates immune cells.	Shang et al., 2022
Periodontitis	Trigeminal neurons	SP, PGE2, AST, ALP, MPO, IL-1β	Macrophages	SP increases vascular permeability and plasma extravasation.	Hanioka et al., 2000
	Nociceptive neurons	TRPV1, CGRP	Macrophages, neutrophils	Regulates the migration of immune cells	Wang et al., 2024b
	Nociceptive neurons	SP	Neutrophils	Promotes immune cell infiltration and osteoclast activation	Siddiqui et al., 2023
	Nociceptive neurons	TRPV1	Macrophages, osteoblast	Regulates the expression of inflammatory-related genes	Zhang et al., 2022
	Nociceptive neurons	TRPV1, CGRP	M1 macrophages	Inhibits osteoclast differentiation and reduces bone resorption	Takahashi et al., 2016
	Nociceptive neurons	NaV1.8$^+$, CGRP, SP	Macrophages, T cells	Regulates the migration of immune cells, and reduces the production of pro-inflammatory cytokines	Austah et al., 2022
OLP	Trigeminal neurons	SP, CGRP, TRPV1	Lymphocytes	TRPV1 receptor activation regulates immune responses.	Bán et al., 2010
BMS	Trigeminal neurons	NGF, SP	Mast cells	Activation of mast cells triggers degranulation and the release of pro-inflammatory mediators.	Borelli et al., 2010
Oral squamous cell carcinomas	Trigeminal neurons	CGRP	CD4$^+$ T cells, CD8$^+$ T cells, NK cells	CGRP-RAMP1 axis regulates the function of tumor-infiltrating T cells.	McIlvried et al., 2022
	Trigeminal neurons	CGRP	CD4$^+$ T cells, CD8$^+$ T cells	CGRP-RAMP1 axis regulates the activation of lymphocyte infiltration.	Darragh et al., 2024
AD	Neurons	TLR4, ER stress	Microglia, macrophages	TLR4/NF-κB pathway	Ge et al., 2024

CGRP: calcitonin gene-related peptide; RAMP1: receptor activity-modifying protein 1; TRPV1: transient receptor potential vanilloid 1; P2X3: purinergic receptor P2X ligand-gated ion channel 3; TACAN: TMEM120A, transmembrane protein 120A; TNF-α: tumor necrosis factor-α; SP: substance P; PGE2: prostaglandin E2; AST: aspartate aminotransferase; ALP: alkaline phosphatase; MPO: myeloperoxidase; IL-1β: interleukin-1β; OLP: oral lichen planus; BMS: burning mouth syndrome; NaV1.8$^+$: sodium voltage-gated channel alpha subunit 8; NGF: nerve growth factor; TLR4: Toll-like receptor 4; AD: Alzheimer's disease; NK cells: natural killer cells; ER: endoplasmic reticulum; c-FOS: cellular proto-oncogene Fos; CD4$^+$: cluster of differentiation 4-positive; NF-κB: nuclear factor-κB.

neurons and DPSCs highlights the key regulatory role of neuronal–pulp interactions in both pulp homeostasis and nerve repair.

Within the inflamed-pulp microenvironment, neuropeptides secreted by neurons also regulate immune response. Studies have demonstrated that macrophages express neuropeptide receptors, such as those for CGRP and SP, and these neuropeptides modulate immune-cell activity (Caviedes-Bucheli et al., 2006). CGRP, for instance, recruits neutrophils and monocytes to protect pulp tissue from further damage, while depletion of immune cells exacerbates sensory nerve loss and tissue injury (Erdogan et al., 2024). Beyond their role in inflammation, neuropeptides contribute to pulp

Table 2 Immune system regulation of the nervous system

Disease	Source and kind	Cytokines, receptors, or ion channels	Target cells	Regulatory details (key mechanisms/signaling pathways)	Reference
Pulpitis	Neutrophils, monocytes	TNF-α, IL-1β	Trigeminal neurons	Sensitization of neurons and induction of inflammatory pain	Erdogan et al., 2024
	Macrophages	TNF-α, IL-1β, $NaV1.7^+$	Trigeminal neurons	Activation of $NaV1.7^+$-neuronal hypersensitivity and pain response	Sunaga et al., 2024
	Microglia	NLRP3, caspase-1, P2X7 receptor	Trigeminal neurons	P2X7 receptor-NLRP3/caspase-1-inflammatory pain	Sun et al., 2023
	Macrophages, microglia	TNF-α, IL-1β	Trigeminal neurons	Upregulation of TLR2 and TLR4 expression promotes pain transmission	Lee et al., 2021
Periodontitis	Macrophages, dendritic cells	NGF	Trigeminal ganglion	NGF-TrkA signaling pathway	Gašperšič et al., 2010
Oral lichen planus	Macrophages	TNF-α, PGE2	Trigeminal ganglion	Activation of TRPA1 and TRPV1 receptors induces neurogenic inflammation	Kun et al., 2017
Oral squamous cell carcinomas	Macrophages, neutrophils	TNF-α	Sensory neurons	Activation of nerve endings and modulation of neuronal excitability	Scheff et al., 2017
AD	T cells, macrophages	IL-1β, TNF-α	Microglial cells	Systemic inflammation fosters a pro-inflammatory brain environment	Wang RPH et al., 2023
	T cells, B cells	IL-1β, TNF-α, IL-6, TGF-β, IL-10, IFN-γ	Neurons, microglial cells, astrocytes	NF-κB by TNF-α/IL-1β activates microglia via the p38-MAPK pathway	Zheng et al., 2016
	Macrophages, microglia	IL-1β, TNF-α	Neurons	Pg-LPS; activation of the complement system; neuroinflammation and neuronal damage	Costa et al., 2021
	Microglia	IL-6, IL-1, TNF-α, ROS, RNS	Neurons	Crossing the BBB; neuroinflammation; neuronal damage	Franciotti et al., 2021
	Microglia	IL-6, TNF-α, IL-1β	Neurons	IL-6; disruption of the BBB; neuroinflammation	Furutama et al., 2020
	Macrophages	IL-6, TNF-α, IL-1β	Microglia, neurons	Activation of microglia; exacerbation of neuroinflammation	Teixeira et al., 2017
PD	Microglia	TNF-α, IL-1β, IL-6	Dopaminergic neurons	Activation of TLR receptors; exacerbation of neuroinflammation	Heidari et al., 2022

IL-1β: interleukin-1β; TNF-α: tumor necrosis factor-α; $NaV1.7^+$: sodium voltage-gated channel alpha subunit 7; P2X7: P2X ligand-gated ion channel 7; TLR2: Toll-like receptor 2; NGF: nerve growth factor; TrkA: tropomyosin receptor kinase A; PGE2: prostaglandin E2; TRPA1: transient receptor potential ankyrin 1; TRPV1: transient receptor potential vanilloid 1; TGF-β: transforming growth factor-β; MAPK: mitogen-activated protein kinase; Pg-LPS: *Porphyromonas gingivalis* lipopolysaccharide; NLRP3: nucleotide binding and oligomerisation domain (NOD)-like receptor family pyrin domain containing 3; IL-6: interleukin-6; IFN-γ: interferon-γ; ROS: reactive oxygen species; RNS: reactive nitrogen species; AD: Alzheimer's disease; PD: Parkinson's disease; BBB: blood–brain barrier; NF-κB: nuclear factor-κB.

repair and regeneration (Wang et al., 2024a; Zhan et al., 2024), highlighting the significance of neuroimmune communication in managing pulp diseases.

During the progression of pulpitis, immune infiltration within the dental pulp undergoes significant changes. At the onset of inflammation, the immune-cell population in the pulp shifts from resident macrophages to neutrophils and monocytes, indicating a heightened immune response (Erdogan et al., 2023). Simultaneously, ion channels on sensory neurons, such as sodium voltage-gated channel alpha subunit 7 ($NaV1.7^+$) and TRPV1, are activated, each playing a distinct role in the stages of pain perception in the pulp. Studies have shown that in the inflamed pulp microenvironment, the expression of TRPV1 and the immediate-early gene cellular proto-oncogene Fos (c-FOS) in the PNS is significantly upregulated, directly mediating the sensation of pain (Cha et al., 2020). Furthermore, macrophages in the trigeminal ganglion become activated, leading to the upregulation of sodium channels

Table 3 Key neuropeptides, cytokines, and receptors in neuroimmune interactions of oral diseases

Molecule type	Representative molecules	Oral diseases	Functions/mechanisms
Neuropeptide	SP	Pulpitis, periodontitis, oral mucosal inflammation	Promotes inflammation by inducing IL-1β and TNF-α release; enhances immune cell activation and vascular permeability
	CGRP	Pulpitis, periodontitis, oral cancer	Anti-inflammatory; modulates vasodilation and immune cell recruitment
	VIP	SS, periodontitis	Anti-inflammatory; promotes immune tolerance
	NPY	Periodontitis, mucosal immunity	Modulates sympathetic inhibition of immune responses; promotes tissue regeneration under chronic inflammation
	Galanin	Oral pain disorders	Regulates neuronal excitability; modulates cytokine release
Cytokine	IL-1β	Pulpitis, periodontitis, OLP	Key pro-inflammatory mediator; activates immune cells and sensitizes neurons
	TNF-α	Periodontitis, oral cancer, neuroinflammation	Promotes tissue destruction; activates NF-κB pathway; contributes to pain and immune suppression
	IL-6	Pulpitis, periodontitis, oral mucosal diseases	Drives acute-phase response; involved in Th17 cell differentiation
	IL-10	Chronic inflammatory oral conditions	Anti-inflammatory; suppresses Th1 and Th17 responses
	TGF-β	Periodontitis, OLP, oral cancer	Involved in immune tolerance, tissue remodeling, and tumor progression
	IL-17	Periodontitis, OLP	Enhances neutrophil recruitment and chronic inflammation
Receptor	NK1 receptor (for SP)	Pulpitis, periodontitis	Mediates SP-driven immune activation and inflammation
	CGRP receptor (RAMP1)	Pulpitis, oral cancer	Mediates anti-inflammatory or immunosuppressive actions of CGRP
	VPAC1/VPAC2 (for VIP)	SS, oral mucosal diseases	Regulates T cells and macrophages; contributes to immune tolerance
	Toll-like receptors (e.g., TLR4)	Periodontitis, pulpitis	Recognizes microbial components; activates innate immune responses and neuronal sensitization
	IL-1R/TNF-R	Periodontitis, oral mucosal inflammation	Mediates pro-inflammatory signaling through NF-κB and MAPK pathways
	NPY receptors (Y1/Y2)	Periodontitis	Suppresses inflammation; regulates sympathetic neuroimmune signals

CGRP: calcitonin gene-related peptide; SP: substance P; OLP: oral lichen planus; SS: Sjögren's syndrome; VIP: vasoactive intestinal peptide; NPY: neuropeptide Y; IL-1β: interleukin-1β; TNF-α: tumor necrosis factor-α; TGF-β: transforming growth factor-β; NK1: neurokinin-1; IL-1R: interleukin-1 receptor; RAMP1: receptor activity-modifying protein 1; VPAC1: vasoactive intestinal polypeptide receptor 1; TLR4: Toll-like receptor 4; MAPK: mitogen-activated protein kinase; TNF-R: tumor necrosis factor-R; NF-κB: nuclear factor-κB; Th17: T helper cell 17.

(e.g., NaV1.7), which contributes to the development of ectopic pain. Inhibition of this process through depletion of macrophages results in the suppression of $NaV1.7^{+}$ overexpression and a reduction in pain symptoms (Sunaga et al., 2024). Moreover, ligand-gated ion channels in the purinergic receptor P2X family are involved. Activation of the purinergic receptor P2X ligand-gated ion channel 7 (P2X7) triggers inflammatory response through the NLRP3 inflammasome, and its inhibition reduces inflammation and increases pain thresholds (Sun et al., 2023). The purinergic receptor P2X3 regulates pain transmission via the p38-mitogen-activated protein kinase (p38-MAPK)/nuclear factor-κB (NF-κB) signaling pathway, and antagonists of P2X3 not only alleviate pain but also suppress the inflammatory response (Chen et al., 2024). These findings suggest that the interaction between the nervous and immune systems is key in the initiation and maintenance of pain through the regulation of ion channels.

Additionally, upregulation of Toll-like receptor 2 (TLR2) and transmembrane protein 120A (TMEM120A; also termed TACAN) channels has been closely associated with pain in pulpitis. TLR2 upregulation correlates with increased levels of inflammatory markers such as TNF-α and IL-1β, indicating its significant role in inflammatory pain (Lee et al., 2021). The TACAN

channel is primarily responsible for mechanical pain transmission, and its inhibition has been shown to markedly reduce pain sensitivity (Shang et al., 2022). These findings suggest that targeted interventions aimed at these channels could effectively alleviate pulpitis-induced pain.

In summary, dental pulp nerves are crucial in pain transmission, tissue homeostasis, and immune regulation. These studies suggest that the neuroimmune response in pulpitis is linked to disease severity. Mild inflammation promotes immune surveillance and tissue repair, while severe inflammation involves ion-channel dysregulation and overactive immune response. Single-cell transcriptomics reveal that the extent of inflammation correlates with immune-cell composition and expression of inflammation-related genes (Opasawatchai et al., 2022; Balic et al., 2023), highlighting the potential for neuroimmune-targeted therapies based on inflammation severity. Additionally, curcumin-based treatments, including nanoparticle-based delivery systems, have demonstrated efficacy in recent studies in modulating the neuroimmune system, reducing inflammation, inhibiting bone resorption, and promoting tissue regeneration in pulpitis (Saharkhiz et al., 2022; Dong et al., 2024). By targeting neuroimmune pathways such as those involving CGRP and immune cell recruitment, these therapies can alleviate inflammation and pain-related responses, underscoring the pivotal role of neuroimmune modulation in effective pulp treatment.

3.2 Periodontal diseases

Periodontitis is a prevalent chronic inflammatory condition primarily driven by dysregulated immune responses to pathogenic bacteria in dental plaque (Corredor et al., 2022; Fang et al., 2025). This abnormal immune response leads to localized tissue inflammation and bone resorption, gradually destroying the supporting structures of the periodontium (Monasterio et al., 2018). Neuroimmune communication plays a large role in regulating local inflammation, immune response, and maintenance of bone homeostasis in periodontitis.

Building upon this, TLR signaling is critical in driving the inflammatory processes observed in periodontal disease. Specifically, TLR signaling regulates inflammatory-cell migration and pro-inflammatory cytokine secretion, promoting osteoclastogenesis and subsequent alveolar bone resorption (Gu and Han, 2020). Periodontal pathogens activate TLR4, eliciting an innate immune response that engages gingival immune cells and trigeminal neuron nociceptors. Increased TLR4 expression in trigeminal neurons enhances immune activation and pain signaling through the neuroimmune axis, intensifying neuroinflammatory responses (Vindiš et al., 2014).

Nociceptors contribute beyond pain transmission, significantly influencing inflammation regulation and bone metabolism in periodontitis. $NaV1.8^{+}$ nociceptors mediate interactions between immune and bone cells, exerting protective effects against bone damage in apical periodontitis (Austah et al., 2022). Studies in mice lacking nociceptors reveal heightened inflammation and bone resorption, underscoring their protective roles in neuroimmune-bone dynamics (Lillis et al., 2023). Another critical player, the TRPV1 channel, modulates neuroimmune communication in periodontitis. $TRPV1^{+}$ nociceptor neurons can amplify the immune response in periodontal tissue, worsening bone resorption and tissue damage under specific conditions (Wang et al., 2022). However, TRPV1 activation also demonstrates protective effects; Li et al. (2024) reported that it suppresses pro-inflammatory M1 macrophage activity and oxidative stress via the nuclear factor erythroid 2-related factor 2 (NRF2) pathway, reducing alveolar bone loss. Furthermore, dietary capsaicin activates the TRPV1-CGRP pathway, fostering neuroprotection and mitigating bone loss (Takahashi et al., 2016). Takahashi et al. (2016) demonstrated that neural TRPV1 activity inhibited alveolar bone resorption, which means that it has potential as a therapeutic target. In diabetes-associated periodontitis, TRPV1-positive neurons shift macrophage polarization, reducing pro-inflammatory M1 macrophages while increasing anti-inflammatory M2 macrophages, and thus supporting periodontal immunoprotection (Zhang et al., 2022).

Neurotransmitters also regulate periodontitis progression, offering additional therapeutic avenues. SP exerts dual effects, amplifying inflammation and promoting bone resorption. Elevated SP levels correlate with intensified periodontal inflammation and host immune response, particularly in the presence of multiple pro-inflammatory cytokines (Hanioka et al., 2000). SP increases hypoxia-inducible factor-1α (HIF-1α) expression and raises the receptor activator of NF-κB ligand (RANKL)/osteoprotegerin (OPG) ratio, activating osteoclasts and promoting inflammatory cell

infiltration, which exacerbates the process of alveolar bone resorption (Yan et al., 2020; Siddiqui et al., 2023). Consequently, SP inhibition is a potential strategy for mitigating bone loss, with future studies likely to explore selective SP inhibitors or combined neuroimmune therapies. In contrast, neuropeptide Y (NPY) has shown potential in promoting periodontal tissue repair under chronic inflammatory conditions (Winning et al., 2022). NGF plays a complex role in the periodontal immune microenvironment. While NGF is known to promote osteogenesis in mesenchymal stem cells under normal conditions (Yang et al., 2022; Liu JY et al., 2025), its role in periodontitis is multifaceted. In the context of periodontal disease, NGF activates trigeminal ganglion neurons through its receptor tropomyosin receptor kinase A (TrkA), promoting inflammatory response and alveolar bone resorption. This pro-inflammatory effect contrasts with its osteogenic potential in mesenchymal stem cells (MSCs), which illustrates the context-dependent nature of NGF's actions. Blocking NGF with antibodies significantly reduces the expression of pro-inflammatory cytokines, such as IL-1β, in the gingiva and inhibits alveolar bone resorption (Gašperšič et al., 2010), suggesting that targeting NGF could be a promising therapeutic strategy. However, the dual role of NGF, which promotes bone formation in some contexts while exacerbating bone loss in others, highlights the need for precise modulation in clinical applications. Additionally, recent studies indicate that periodontal treatment can modulate the neuroimmune system, which has broader clinical implications. Matsuda et al. (2024) showed that periodontal treatment reduces serum IL-6 levels, so there may be benefits in terms of preventing neurodegenerative disease.

During the progression of periodontitis, neuroimmune interactions change dynamically with increasing inflammatory severity. This is manifested by shifts in immune-cell composition and alterations in the expression of inflammatory mediators (Li et al., 2020). In addition, systemic diseases such as diabetes can affect the neuroimmune characteristics of periodontitis. Studies have shown that a high-glucose environment can induce macrophage polarization toward the pro-inflammatory M1 phenotype and enhance the local expression of inflammatory cytokines (Xiang et al., 2025). Therefore, stage-specific treatment strategies should be developed based on the severity of periodontitis, with integrated management in the context of systemic diseases. Interventions through modulation of neuroimmune response can provide more precise and effective personalized treatment. In summary, neuroimmune communication in periodontal disease reveals the complex interactions between the nervous and immune systems in regulating inflammation, bone resorption, and tissue repair. Targeting the neuroimmune axis offers a multi-dimensional approach that effectively controls inflammation and bone loss while also modulating pain transmission, thus providing a novel therapeutic strategy for the treatment of periodontitis.

3.3 Oral mucosal diseases

The oral mucosa acts as a protective barrier between external environments and internal tissues, and is constantly exposed to microbial and physical stimuli (Şenel, 2021). It features dense innervation primarily composed of branches from the trigeminal nerve, which are widely distributed in both the epithelial and lamina propria layers (Moayedi et al., 2018). Consequently, its normal function depends not only on the defensive mechanisms of immune cells but also on the coordinated action of the nervous system to maintain homeostasis and regulate inflammatory response.

Within the oral mucosa, interactions between neurons and immune cells, such as macrophages, mast cells, and neutrophils, are mediated by neuropeptides, ion channels, and immunoregulatory pathways. Neuropeptides (including SP and CGRP) alongside ion channels such as TRPV1 and TRPA1 drive neurogenic inflammation. These molecules interact with immune cells to initiate or intensify inflammatory response (Chesné et al., 2019). Macrophages contribute to mucosal homeostasis by regulating local immunity through neuronal interactions, while neutrophils are recruited to inflammatory sites by chemokines released from stromal cells, in support of tissue repair (Williams et al., 2021). Mast cells further enhance immune defense; stimulation of the trigeminal nerve triggers their degranulation, releasing mediators such as histamine and TNF-α. These compounds increase vascular permeability and amplify local inflammation (Alhelal et al., 2014).

Neuroimmune interactions play a key role in the pathogenesis and progression of several oral mucosal diseases, including oral lichen planus (OLP), burning mouth syndrome (BMS), oral candidiasis (OC), and Sjögren's syndrome (SS). In OLP, upregulation of TRP

channels, specifically TRPV1 and TRPA1, intensifies neurogenic inflammation. Activation of these channels releases pro-inflammatory mediators such as TNF-α, promoting vasodilation, immune-cell activation, and tissue damage (Bán et al., 2010; Kun et al., 2017). BMS, characterized by chronic oral pain of neuropathic origin, exhibits a neuropeptide imbalance, marked by reduced neurokinin A and elevated CGRP and SP, which contribute to inflammation. Elevated NGF further heightens neural sensitization, exacerbating pain (Boras et al., 2010; Borelli et al., 2010). In OC, macrophages detect pathogens and recruit neutrophils via chemokine signaling; this process promotes pathogen clearance but also carries the risk of triggering excessive inflammation responses, which is potentially modulated by neuronal inputs (Feller et al., 2014). In SS, macrophages sustain chronic inflammation by releasing pro-inflammatory mediators, while neuroimmune crosstalk may aggravate symptoms such as pain and dryness (Yoshimoto et al., 2019).

Clinical interventions that target these interactions are emerging. Topical capsaicin, a TRPV1 agonist, is used in BMS to reduce pain, though its long-term efficacy awaits further validation (Silvestre et al., 2012). Other potential therapies include CGRP antagonists, which could be explored for BMS (Zidverc-Trajkovic et al., 2009). Future research may focus on developing selective TRPA1 or TRPV1 modulators to target neuroimmune pathways precisely.

3.4 Oral cancer

Neuroimmune interactions are important in the initiation and progression of cancer. The tumor microenvironment (TME) is not only rich in immune cells but also contains abundant neuronal components (Shurin et al., 2020). Neurons and their axon-like features can even serve as markers of the TME (Hanahan and Monje, 2023). Recent research has increasingly demonstrated that neuronal components within the TME influence cancer progression through complex neuroimmune interactions (Monje et al., 2020; Winkler et al., 2023). The PNS, particularly the autonomic nervous system, regulates immune response within the TME, thereby promoting tumor growth, invasion, and immune evasion. For example, norepinephrine maintains proliferative signaling in tumor cells via adrenergic pathways and enhances their metastatic potential (Xu et al., 2017). Cancer cells, in turn, hijack neuronal signaling pathways to resist cell death and activate pro-inflammatory factors, further driving tumor initiation and progression (Cervantes-Villagrana et al., 2020). This dynamic interplay between the nervous system, immune cells, and cancer cells forms the neuroimmune-cancer axis, which regulates tumor development and shapes immune response of the host to malignancy.

Oral squamous-cell carcinoma (OSCC), which accounts for approximately 90% of all oral cancers, severely impairs oral function and quality of life (Coletta et al., 2020). In the TME of OSCC, neuronal density, nerve diameter, and proximity of nerves to the tumor have been closely associated with tumor initiation and progression (Schmitd et al., 2022; D'Silva et al., 2023; Perez-Pacheco et al., 2023). Perineural invasion (PNI), a hallmark of OSCC, occurs when cancer cells invade surrounding nerves, leading to tumor spread and recurrence (Schmitd et al., 2018). PNI is a pathological phenomenon strongly associated with poor prognosis, and is characterized by cancer cells migrating along the nerve sheath (Zhu et al., 2019). Epidermal growth-factor receptor (EGFR) and matrix metalloproteinases (MMPs) are key in the development of PNI; cancer cells exploit these signaling pathways to disrupt the nerve sheath and increase their invasive capacity (van Vugt et al., 2017; Huang et al., 2018). Neural damage from PNI is a key driver of cancer-related pain in OSCC and induces neurogenic inflammation (Scheff et al., 2017; Salvo et al., 2020), which further promotes immune evasion by activating immunosuppressive pathways (Cervantes-Villagrana et al., 2020). In OSCC, the increased presence of immunosuppressive cells, such as regulatory T cells (Tregs) and tumor-associated macrophages, weakens anti-tumor immune response of the host. These cells secrete immunosuppressive cytokines such as IL-10 and transforming growth factor-β (TGF-β), thereby inhibiting the activity of cluster of differentiation 8-positive ($CD8^+$) T cells and facilitating tumor immune escape (Lim et al., 2014; Xue et al., 2022).

Nociceptor neurons also play a significant role in the mechanisms of immune evasion. By releasing the neuropeptide CGRP, nociceptors bind to receptor activity-modifying protein 1 (RAMP1) on $CD8^+$ T cells, leading to their functional exhaustion. This exhaustion impairs the anti-tumor activity of $CD8^+$ T cells while upregulating inhibitory markers such as programmed cell death protein 1 (PD-1), lymphocyte

activation gene-3 protein (LAG3), and T cell immunoglobulin and mucin domain-containing protein 3 (TIM3), further diminishing the immune response against tumors (Balood et al., 2022). In OSCC, CGRP not only inhibits T-cell function by binding to RAMP1 receptors but also directly promotes tumor-cell proliferation and migration, accelerating malignant progression (McIlvried et al., 2022). Research has shown that blocking CGRP signaling or performing nerve-ablation surgery significantly suppresses tumor growth and enhances the anti-tumor immune response by restoring $CD4^+$ and $CD8^+$ T-cell activity (Darragh et al., 2024). Particularly in the context of immune-checkpoint inhibitor therapy for OSCC patients, nerve ablation not only inhibits CGRP-mediated immune-evasion mechanisms but also enhances the efficacy of immunotherapy by downregulating the TGF-β signaling pathway, resulting in better tumor control and improved immune activity (Tao et al., 2024). The application of CGRP antagonists can reduce pain and tumor progression in oral cancer (Zhang et al., 2020). Currently, CGRP inhibitors such as erenumab and fremanezumab have been approved for migraine treatment (Goadsby et al., 2017). Given their action in inhibiting tumor-related angiogenesis and immune evasion, repurposing these drugs for oral cancer treatment may be a promising strategy.

Schwann cells, which support and repair nerves, also play a key role in tumor progression within the TME (Sun et al., 2022). In this environment, Schwann cells can undergo reprogramming, transitioning from functional cells that support nerves to a non-myelinating state that promotes tumor growth. Reprogrammed Schwann cells not only facilitate axonogenesis by releasing neurotrophic factors and regulating the extracellular matrix, but also help cancer cells spread along nerve axes, accelerating PNI (Deborde et al., 2022). Schwann cells are pivotal in the progression of OSCC because they undergo dedifferentiation and migrate to tumor regions, where they participate in PNI and guide cancer cells along nerves. Furthermore, Schwann cells secrete neurotrophic factors such as BDNF, which activate TrkB receptors on tumor cells. This BDNF-TrkB signaling pathway further enhances tumor-cell migration and invasion, and blocking this pathway effectively inhibits tumor spread and Schwann-cell migration (Ein et al., 2019a, 2019b). Schwann cells also promote tumor aggressiveness and dissemination through metabolic reprogramming and phenotypic changes (Santi et al., 2022). Targeting Schwann cells and their associated signaling pathways may offer a potential strategy to prevent neural invasion and improve patient outcomes. For example, inhibitors of the BDNF-TrkB pathway, such as larotrectinib (which has been approved for treating neurotrophic receptor tyrosine kinase fusion-positive cancers), could be explored as a means of reining in PNI in oral cancer (Drilon et al., 2018).

Thus, the neuroimmune regulatory mechanisms in OSCC vary across different stages of disease progression. In the precancerous stage, for example high-risk proliferative verrucous leukoplakia (PVL), although invasive tumors have not yet formed, local immune dysregulation is already evident. At this stage, the treatment with PD-1 inhibitors has been shown to activate anti-tumor immunity and delay malignant transformation (Hanna et al., 2024). As OSCC progresses to the locally advanced stage (stages III–IVA), tumor PNI becomes a major pathological feature, leading to immune suppression and tumor recurrence. In this context, neoadjuvant immunochemotherapy (NAIC) has shown potential for improving pathological response and enhancing postoperative outcomes (Liu HM et al., 2025). It has become clear that neuroimmune interactions in OSCC, neurons, nociceptors, Schwann cells, and immunosuppressive cells collectively regulate tumor growth, invasion, and immune evasion, further complicating the TME and influencing cancer progression. The emergence of technologies such as spatial transcriptomics allows for precise identification of neuroimmune interaction hotspots within the TME, providing new insights into these mechanisms. In the future, combining neuro-modulatory drugs such as CGRP antagonists and TrkB inhibitors with immunotherapy offers promising potential for innovative treatments to improve cancer treatment outcomes.

3.5 Oral diseases and neurodegenerative disorders

Oral diseases, particularly periodontitis, extend beyond chronic inflammatory conditions confined to the oral cavity. Instead, through complex neuroimmune regulatory mechanisms and interactions, they exert systemic effects and contribute significantly to the progression of neurological diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and depression (Teles et al., 2022; Ge et al., 2024). Periodontitis contributes to the progression of these neurological

disorders through various pathways (Fig. 4). Pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, are released during periodontitis and initiate the localized immune response; they disseminate via the circulatory system, potentially breaching the blood–brain barrier (BBB) to enter the CNS (Teixeira et al., 2017; Wang RPH et al., 2023). Within the brain, these cytokines activate microglia and astrocytes, triggering and amplifying neuroinflammatory response (Singh, 2022). This neuroimmune regulatory mechanism fosters chronic neuroinflammation, which damages neurons and exacerbates synaptic plasticity impairment, contributing to the progressive decline of neural function (Cohen et al., 2024).

In AD, this persistent inflammatory state accelerates the deposition of β-amyloid (Aβ) and abnormal phosphorylation of tau proteins, exacerbating neurodegeneration (Zheng et al., 2016). Similarly, in PD, it accelerates dopaminergic neuron loss, increasing motor deficits (Heidari et al., 2022). The connection between periodontitis-induced neuroinflammation and depression has also been increasingly recognized (Starhof et al., 2018). Dysregulated neurotransmitter function, partially due to overactivation of microglia and astrocytes, shows the importance of neuroimmune regulation in a variety of neurological diseases.

Moreover, pathogens associated with periodontitis, such as *Porphyromonas gingivalis* and its toxic products, including lipopolysaccharide (LPS) and Arg-gingipain B (RgpB) proteases, can infiltrate the brain via hematogenous or neural routes (Nunes et al., 2020). These pathogens interact with immune cells in the brain, such as microglia and astrocytes, activating pro-inflammatory M1 microglia which subsequently release additional IL-1β and TNF-α (Costa et al., 2021). This pathogen-driven neuroimmune response exacerbates neuronal damage, and the chronic presence of these pathogens in AD and PD patients may serve as a driving force behind neurodegenerative progression (Franciotti et al., 2021). Periodontitis further compromises BBB integrity, amplifying neuroimmune dysregulation. Pro-inflammatory cytokines and pathogens alter the expression of tight-junction proteins, e.g., zonula occludens-1 (ZO-1) and occludin, weakening BBB functionality and facilitating the entry of peripheral immune components into the CNS (Furutama et al., 2020). This effect is particularly pronounced in AD and PD patients; elevated neuroinflammatory markers

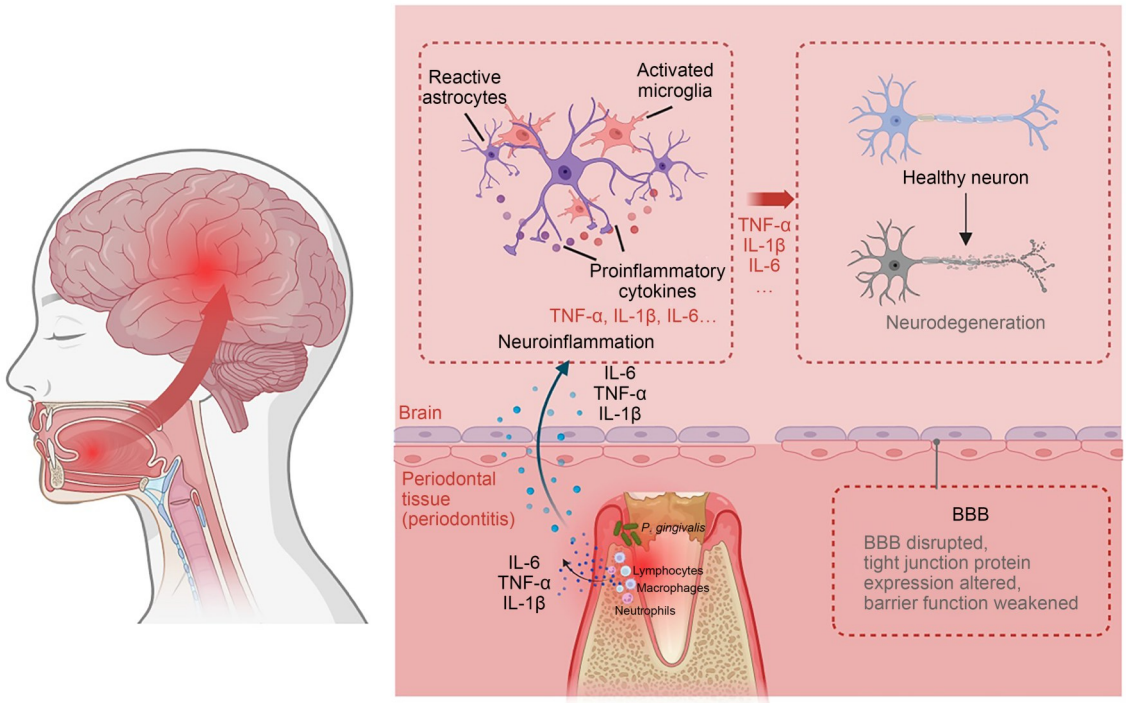


Fig. 4 Relationship between periodontitis and neurodegenerative disease. During periodontitis, pro-inflammatory factors released by immune cells cross the blood–brain barrier (BBB) and enter the central nervous system (CNS), activating microglia and astrocytes. This mediates neuroinflammation, leading to neurodegeneration. Created with https://www.biorender.com. TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; IL-1β: interleukin-1β.

such as chitinase-3-like protein 1 (CHI3L1, also named YKL-40), neurofilament light chain (NfL), and calcium-binding protein B (S100B) have been detected in individuals with periodontitis, reinforcing the association between neuroimmune imbalance and neurological decline (Brosseron et al., 2023).

In the context of endocannabinoid system (ECS) dysfunction, chronic inflammation from periodontitis heightens neuroimmune activation. Research indicates that key ECS-metabolizing enzymes, including *N*-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL), are downregulated in periodontitis and depression models, disrupting endocannabinoid signaling (Jana et al., 2024). This imbalance intensifies inflammation and aggravates depression pathophysiology by impairing neurotransmitter regulation (Kasatkina et al., 2021).

The "oral-brain axis" and "oral-gut-brain axis," which illustrate how periodontitis influences neurological health through direct and indirect pathways, are emerging areas of research in neuroimmune regulation. Periodontitis-associated pathogens can access the brain via the oral-brain axis, triggering localized neuroimmune response (Tanwar et al., 2024), while the oral-gut-brain axis modulates CNS function through alterations in gut microbiota and vagus-nerve signaling (Kerstens et al., 2024). Therapeutically, minocycline, a tetracycline derivative, has demonstrated efficacy in reducing neuronal cell death and improving cognitive deficits in studies of AD (Choi et al., 2007). These findings suggest its potential for treating neuroinflammation in AD associated with periodontitis. Additionally, probiotics targeting the oral-gut-brain axis are under investigation for their potential to mitigate systemic inflammation and enhance cognitive outcomes in neurodegenerative disorders (Taghizadeh Ghassab et al., 2024). In the future, the development of neuroimmune modulators such as cytokine inhibitors or endocannabinoid regulators, alongside personalized strategies addressing both oral and neurological health, holds promise for improving patient outcomes.

4 Future perspectives: emerging technologies for neuroimmune target discovery

4.1 Introduction to phage display technology

In recent years, with the growing demand for precision medicine and molecular targeted interventions in immune-related diseases, various advanced screening technologies have been developed to accelerate target identification. Among these, phage display has emerged as a particularly promising technique due to its flexibility and high-throughput capability. First introduced by Smith (1985), phage display involves the genetic fusion of peptides or proteins to the coat proteins of bacteriophages, so that the new peptides or proteins are then displayed on their surface. Each phage carries the corresponding DNA, linking the displayed molecule (phenotype) to its genetic code (genotype) (Xia et al., 2025). This design enables efficient screening of high-affinity ligands through iterative biopanning, and it has been used extensively for applications in antibody engineering, biomarker discovery, vaccine development, and immune regulation across cancerous, neurological, and inflammatory diseases (Peng et al., 2020a, 2020b, 2022; Jacobs-Lorena and Cha, 2024; McIlroy et al., 2025).

A key component of phage display is the biopanning process, which allows selective enrichment of phages that bind specifically to a target molecule (Bakhshinejad et al., 2016). The process typically involves incubating the phage library with an immobilized target, followed by washing to remove unbound or weakly bound phages, and then eluting the bound population using chemical or competitive methods. The recovered phages are then amplified in bacterial hosts and subjected to additional rounds of selection to progressively enrich high-affinity binders. This cycle is usually repeated three to five times, after which individual clones are isolated and characterized (Pierzynowska et al., 2024). The biopanning process is highly adaptable and can be performed against a wide range of targets, including purified proteins, cell-surface receptors, intact cells, and even tissue sections, making it a versatile tool for ligand discovery and molecular profiling in complex biological systems (Quilumba-Dutan et al., 2025).

4.2 Application of phage display in oral disease

Phage display technology offers significant advantages in identifying ligands or peptides that can target key molecules involved in neuroinflammation in oral disease. In pulpitis, peptides targeting CGRP or its receptor RAMP1 may attenuate neurogenic inflammation and reduce pain. In periodontitis, ligands that neutralize pro-inflammatory cytokines, such as TNF-α or IL-1β,

could help mitigate chronic immune activation and tissue breakdown. In OSCC, phage-derived binders targeting programmed death-ligand 1 (PD-L1) may enhance immune-checkpoint blockade strategies. For mucosal disorders and chronic orofacial pain, sensory nerve-targeting ligands are promising for both localized therapeutic delivery and diagnostic imaging, offering a potential dual benefit in disease management.

5 Conclusions

Neuroimmune crosstalk plays a critical role in the pathogenesis and progression of oral disease, influencing conditions such as pulpitis, periodontitis, oral mucosal diseases, and oral cancer. These interactions also regulate the association between oral diseases and neurological disorders by modulating immune response and neural signal transmission. In addition, the current literature shows that oral microorganisms and their products are involved in neuroimmune regulation of oral disease. By releasing factors such as endotoxins, they interact with immune cells or neurons and play important roles within the neuroimmune microenvironment. Table 4 provides a concise summary of these interactions, offering a reference for future mechanistic studies and targeted intervention strategies. However, our understanding of these mechanisms remains limited. The heterogeneity of neuroimmune response across different oral diseases, compounded by external factors such as diet, stress, and smoking, complicates the identification of consistent therapeutic targets. Furthermore, the lack of comprehensive models that integrate neural and immune dynamics hinders a full understanding of the molecular mechanisms underlying disease progression.

Recent studies suggest that phage display technology holds considerable potential for advancing neuroimmune-targeted therapies for oral disease. By enabling identification of ligands for key neuroimmune molecules, this technique supports development of more precise interventions, such as for pulpitis and periodontitis. Nevertheless, challenges remain in unraveling the exact molecular factors that govern these pathways and in understanding how environmental stimuli interact with genetic predisposition to shape neuroimmune response. A more comprehensive understanding of these interactions could reduce the need for invasive treatments and improve the management of patients with comorbid oral and neurological disorders, thereby contributing to more personalized and effective care.

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Author contributions

Xiatong ZHANG conceptualized the review topic and scope. Xiatong ZHANG, Xinyi CHEN, and Dayu WANG performed the systematic literature search, collected the data, and

Table 4 Bacterial products influencing neuroimmune interactions in oral diseases

Bacterial product/component	Source	Target cells	Receptor	Neuroimmune effects	Reference
Peptidoglycan, lipoteichoic acid, lipoproteins	Gram-positive bacteria	Immune cells, sensory neurons	TLR2	Modulates inflammatory cytokine release; contributes to inflammatory pain	Sunaga et al., 2024
LPS	Gram-negative bacteria	Immune cells, neurons	TLR4	Enhances immune activation and pain signaling	Vindiš et al., 2014
Bacterial proteases (RgpB), LPS	Gram-negative bacteria	Immune cells (microglia)	Protease-sensing pathways	Promotes pro-inflammatory phenotype and neuronal damage	Nunes et al., 2020
LPS	Oral pathogens (*Porphyromonas gingivalis*, *Streptococcus* spp.)	Brain endothelial cells	TLR4	IL-6 increases BBB permeability, impairs integrity, and allows small molecule infiltration.	Furutama et al., 2020

LPS: lipopolysaccharide; RgpB: Arg-gingipain B; IL-6: interleukin-6; BBB: blood–brain barrier; TLR2: Toll-like receptor 2.

wrote the first draft of the manuscript. Xiaoyuan HUANG and Zhuo CHEN provided supervision and project administration, contributed to the study conceptualization, secured funding, and revised the manuscript. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Xiatong ZHANG, Xinyi CHEN, Dayu WANG, Xiaoyuan HUANG, and Zhuo CHEN declare that they have no conflicts of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

Declaration on the use of generative AI tools

No generative AI tools were used in the preparation of this manuscript.

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