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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 diseases

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.*, n.d.). 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 the key roles in 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

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damage(Dk *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(Pandruvada *et al.*, 2016; Ebersole *et al.*, 2016). Beyond these, emerging neuroimmunology research highlights the nervous system's critical role in modulating immune response(Hafler and Sansing, 2022). This interplay between neural and immune systems carries important implications for oral disease progression, particularly in cases involving 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(Wang *et al.*, 2024c; Matsuka, 2022). 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 like TNF-α and IL-1β, amplifying the pain response(H *et al.*, 2021). Similarly, SP enhances neuronal excitability by binding to NK1 receptors, leading to both peripheral and central sensitization and contributing to persistent pain(Sperry *et al.*, 2021; Park *et al.*, 2010). In addition to neuropeptides, glial cells, particularly microglia and astrocytes, release inflammatory mediators like 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 from neuroimmune interactions, previously studied in conditions such as cardiovascular(Carnevale and Lembo, 2021), allergic(Matsuda, 2022), and gastrointestinal disease(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(Mm *et al.*, 2014; Shoja *et al.*, 2014). 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, orchestrating immune responses at multiple levels (Fig. 1). The peripheral nervous system (PNS) serves as a crucial communication link between the central nervous system (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, responsible for regulating involuntary physiological processes, including homeostasis(Ferraro *et al.*, 2022). The autonomic 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 NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome and by interacting with α7 subunit of the nicotinic acetylcholine receptor (nAChR) which is expressed on cytokine-producing macrophages(Pike *et al.*, 2022; Rosas-Ballina *et al.*, 2011).

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).

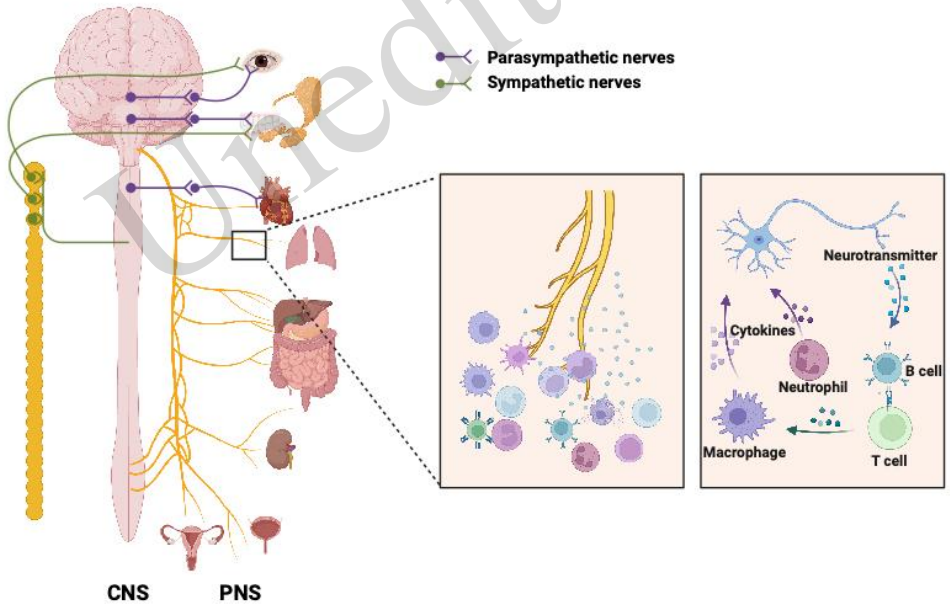

Fig. 1 Crosstalk between the nervous immune systems. Neuroimmune communication involves neuromediators from neurons, cytokines from immune cells, and shared receptors, and forms neuroimmune cell units that regulate local and systemic responses. Created with BioRender.com.

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 *et al.*, 2024c). 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 TRPV1 and 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).

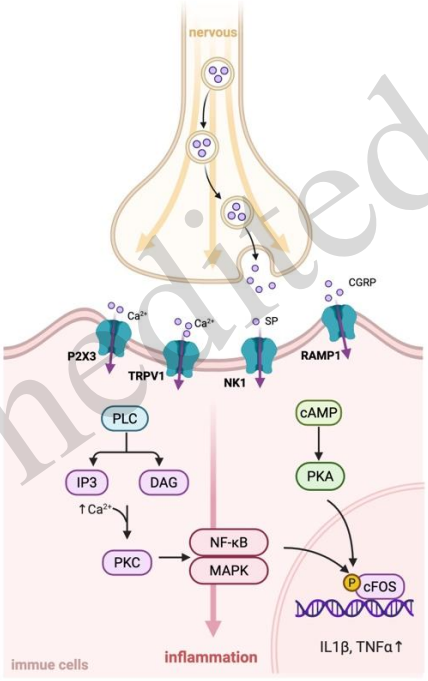

Fig. 2 Mechanisms of neuropeptide – ion channel – neuroimmune interactions. Signaling pathways of neuropeptides and ion channels play important roles in neuroimmune interactions in oral disease. Created with BioRender.com.

Oral diseases like periodontitis and pulpitis involve complex immune responses driven by both innate and adaptive immunity. Neutrophils and macrophages 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 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 *et al.*, 2023a). 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.*, 2021a). Similarly, Wu et al. investigated the interaction between the nervous system and oral structures, revealing that this relationship modulates immune response and tissue homeostasis(Wu *et al.*, 2023).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.

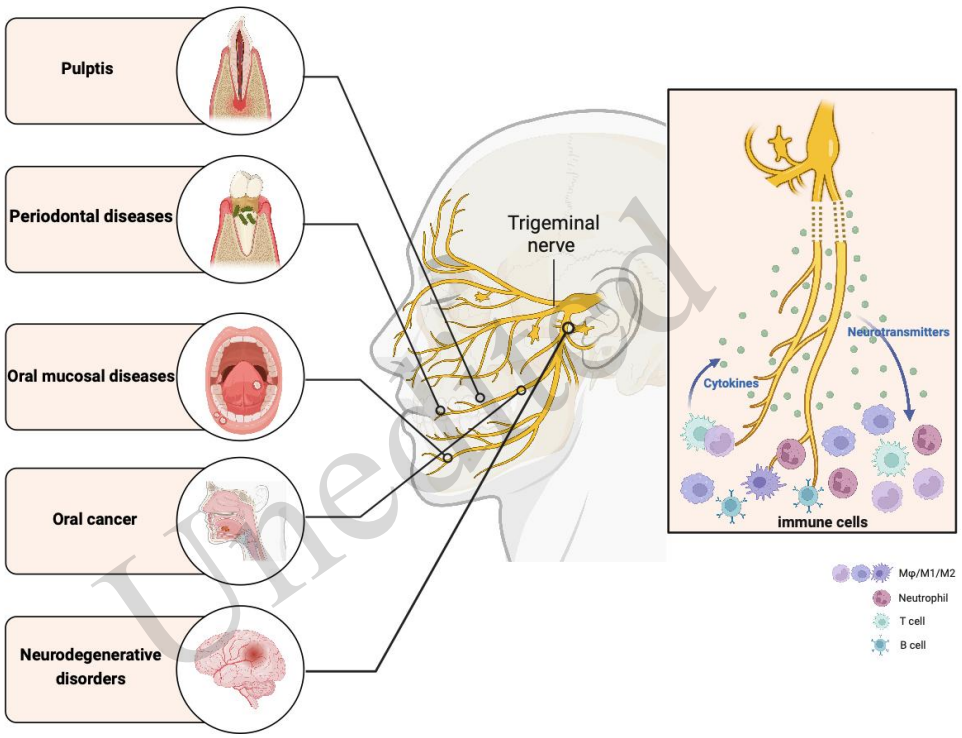

Fig. 3 Neuroimmune interactions involved in oral disease. Neuroimmune interactions involve a complex network of neurotransmitters, immune cells, and signaling pathways, and influence local immune response, inflammation, and tissue homeostasis in the oral cavity, significantly affecting the onset and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

Table 1: Neural Regulation of the Immune System in Oral Diseases (Regulatory details: Key Mechanisms/Signaling Pathways)

Diseases	Source and kind	Cytokines, Receptors, or Ion Channels	Taeget cell	Regulatory details	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 TCAN ion channels activates immune cells.	(Shang *et al.*, 2022).
Periodontitis	Trigeminal neurons	SP、PGE2、AST、ALP、MPO、IL-1b	Macrophage	SP increased vascular permeability and plasma extravasation.	(Hanioka *et al.*, 2000).
	Nociceptive neurons	TRPV1, CGRP	Macrophages neutrophils	Regulation the migration of immune cells	(Wang *et al.*, 2024b).
	Nociceptive neurons	SP	Neutrophils	Promotes immune cell infiltration and osteoclast activation	(Yd *et al.*, 2023).
	Nociceptive neurons	TRPV1	Macrophages、Osteoblast.	Regulating 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	Regulation the migration of immune cells, reduce the production of pro-inflammatory cytokines.	(On *et al.*, 2022).

Table 1: Neural Regulation of the Immune System in Oral Diseases（Regulatory details：Key Mechanisms/Signaling Pathways

Diseases	Source and kind	Cytokines, Receptors, or Ion Channels	Taeget cell	Regulatory details	Reference
Oral Lichen Planus	Trigeminal neurons	SP、CGRP、TRPV1	Lymphocyte	TRPV1 receptor activation regulates immune responses.	(Bán *et al.*, 2010).
Burning Mouth Syndrome	Trigeminal neurons	NGF、SP	Mast cell	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 cell, CD8+ Tcll，NK cell	CGRP-RAMP1 axis regulates the function of tumor-infiltrating T cells.	(McIlvried *et al.*, 2022).
	Trigeminal neurons	CGRP	CD4+T cell, CD8+ Tcll	CGRP-RAMP1 axis regulates the activation of Lymphocyte Infiltration	(Darragh *et al.*, 2024).
Alzheimer's disease (AD)	Neurons	TLR4、ER Stress	Microglia 、 Macrophage	Toll-like receptors (TLR4)/NF-κB pathway	(Ge *et al.*, 2024).

Table 2. Immune System Regulation of the Nervous System (Regulatory details: Key Mechanisms/Signaling Pathways)

Diseases	Source and kind	Cytokines, Receptors, or Ion Channels	Taeget cell	Regulatory details	Reference
Pulpitis	Neutrophils、Monocytes	TNF-α、IL-1β	Trigeminal neurons	Sensitize neurons and drive inflammatory pain.	(Erdogan *et al.*, 2024).
	Mcrophages	TNFα、IL-1β、Nav1.7^{+} ion channel	Trigeminal neurons	Activation of Nav1.7^{+}-neuronal hypersensitivity and pain response	(Sunaga *et al.*, 2024).
	Microglia	NLRP3、Caspase-1、P2X7receptor	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	Macrophage Dendritic cells	NGF	Trigeminal ganglion	NGF-TrkA siganlling pathway	(Gašperšič *et al.*, 2010).
Oral Lichen Planus	Macrophage	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	Activating nerve endings and altering neuronal excitability	(Scheff *et al.*, 2017).

Table 2. Immune System Regulation of the Nervous System（Regulatory details：Key Mechanisms/Signaling Pathways）

Diseases	Source and kind	Cytokines, Receptors, or Ion Channels	Taeget cell	Regulatory details	Reference
Alzheimer's disease (AD)	T cells、Macrophages	IL-1β,、TNF-α	Microglial cells	Systemic inflammation fosters a pro-inflammatory brain environment.	(Wang *et al.*, 2023b).
	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 the complement system/neuroinflammation and neuronal damage	(Costa *et al.*, 2021).
	Microglia	IL-6, IL-1, TNF-α , ROS , RNS	Neurons	Crossing the blood-brain barrier/ neuroinflammation/neuronal damage	(Franciotti *et al.*, 2021).
	Microglia	IL-6, TNF-α, and IL-1β	Neurons	IL-6 /disruption of the blood-brain barrier/neuroinflammation.	(Furutama *et al.*, 2020).
	Macrophages	IL-6, TNF-α, and IL-1β	Microglia、Neurons	Activation of microglia/ exacerbates neuroinflammation	(Teixeira *et al.*, 2017).
Parkinson's disease (PD)	Microglia	TNF-α、IL-1β、IL-6	Dopaminergic neural	Activation of TLR receptors/exacerbates neuroinflammation	(Heidari *et al.*, 2022).

Table 3 Key Neuropeptides, Cytokines, and Receptors in Neuroimmune Interactions of Oral Diseases

Molecule Type	Representative Molecules	Oral Diseases	Functions/Mechanisms
Neuropeptides	Substance P (SP)	Pulpitis, Periodontitis, Oral Mucosal Inflammation	Promotes inflammation by inducing IL-1β and TNF-α release; enhances immune cell activation and vascular permeability
	Calcitonin Gene-Related Peptide (CGRP)	Pulpitis, Periodontitis, Oral Cancer	Anti-inflammatory; modulates vasodilation and immune cell recruitment;
	Vasoactive Intestinal Peptide (VIP)	Sjögren's syndrome, Periodontitis	Anti-inflammatory; promotes immune tolerance
	Neuropeptide Y (NPY)	Periodontitis, Mucosal Immunity	Modulates sympathetic inhibition of immune responses; promotes tissue regeneration under chronic inflammation
	Galanin	Oral pain disorders	Regulates neuronal excitability and modulates cytokine release
Cytokines	IL-1β	Pulpitis, Periodontitis, Oral Lichen Planus	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, Oral Lichen Planus, Oral Cancer	Involved in immune tolerance, tissue remodeling, and tumor progression
	IL-17	Periodontitis, Oral Lichen Planus	Enhances neutrophil recruitment and chronic inflammation
Receptors	NK1 Receptor (for SP)	Pulpitis, Periodontitis	Mediates SP-driven immune activation and inflammation
	CGRP Receptor (RAMP1)	Pulpitis, Oral Cancer	Mediates CGRP's anti-inflammatory or immunosuppressive actions
	VPAC1/VPAC2 (for VIP)	Sjögren's syndrome, Oral Mucosal Diseases	Regulates T cells and macrophages, contributes to immune tolerance
	Toll-like Receptors (e.g., TLR4)	Periodontitis, Pulpitis	Recognize microbial components; activate innate immune responses and neuronal sensitization
	IL-1R / TNF-R	Periodontitis, Oral Mucosal Inflammation	Mediate pro-inflammatory signaling through NF-κB and MAPK pathways
	Neuropeptide Y Receptors (Y1/Y2)	Periodontitis	Suppress inflammation; regulate sympathetic neuroimmune signals

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.*, 2021b; 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.*, 2024a). Research has demonstrated that the activin B/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 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 repair and regeneration(Wang *et al.*, 2024b; 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 transient receptor potential vanilloid 1 (TRPV1), are activated, each playing a distinct role in the stages of pain perception in the pulp. Studies have shown that in the inflammed pulp microenvironment, expression of TRPV1 and the immediate early gene c-Fos in the peripheral nervous system 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 (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 P2X7 triggers inflammatory response through the nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3) inflammasome, and its inhibition reduces inflammation and increases pain thresholds(Sun *et al.*, 2023). The purinergic receptor P2X3 (P2X3) regulates pain transmission via the p38 mitogen-activated protein kinase (P38MAPK)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, and antagonists of P2X3 not only alleviate pain but also suppress 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 regulation of ion channels.

Additionally, upregulation of Toll-like receptor 2 (TLR2) and TACAN channels has been closely associated with pain in pulpitis. TLR2 upregulation correlates with increased levels of inflammatory markers

such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (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 relieve pulpitis-induced pain.

In summary, dental pulp nerves are crucial in pain transmission, tissue homeostasis, and immune regulation. These studies suggest that 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(Dong *et al.*, 2024; Saharkhiz *et al.*, 2022). 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). 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, Toll-like receptor (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 Toll-like receptor 4 (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(On *et al.*, 2022). Studies in mice lacking nociceptors reveal heightened inflammation and bone resorption, underscoring their protective role 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(S *et al.*, 2022). However, TRPV1 activation also demonstrates protective effects; Li et al. reported that it suppresses pro-inflammatory M1 macrophage activity and oxidative stress via the NRF2 pathway, reducing alveolar bone loss(Y *et al.*, 2024). Furthermore, dietary capsaicin activates the TRPV1-CGRP pathway, fostering neuroprotection and mitigating bone loss (N *et al.*, 2016). Tahakashi et al. demonstrated that neural TRPV1 activity inhibited alveolar bone resorption, which means that it has potential as a therapeutic target(Takahashi *et al.*, 2016). 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.*, n.d.). SP increases hypoxia-inducible factor 1-alpha (HIF-1α) expression and raises the RANKL/OPG ratio, activating osteoclasts and promoting inflammatory cell infiltration, which exacerbates the process of alveolar bone resorption(Yd *et al.*, 2023; Yan *et al.*, 2020). 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.*, n.d.). Nerve growth factor (NGF) plays a complex role in the periodontal immune microenvironment. While NGF is known to promote osteogenesis in mesenchymal stem cells (MSCs) under normal conditions(Liu *et al.*, 2025b; Yang *et al.*, 2022), its role in periodontitis is multifaceted. In the context of periodontal disease, NGF activates trigeminal ganglion neurons through its receptor TrkA, promoting inflammatory response and alveolar bone resorption. This pro-inflammatory effect contrasts with its osteogenic potential in 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. showed that periodontal treatment reduces serum IL-6 levels, so there may be benefits in terms of preventing neurodegenerative disease (Matsuda *et al.*, 2024).

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 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 like 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 (Dw *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 transient receptor potential (TRP) channels, specifically TRPV1 and TRPA1, intensifies neurogenic inflammation. Activation of these channels releases pro-inflammatory mediators like TNF-α, promoting vasodilation, immune-cell activation, and tissue damage (Bán *et al.*, 2010; Kun *et al.*, n.d.). BMS, characterized by chronic oral pain of neuropathic origin, exhibits a neuropeptide imbalance, marked by reduced neurokinin A (NKA) and elevated CGRP and substance P, which contribute to inflammation. Elevated nerve growth factor (NGF) further heightens neural sensitization, exacerbating pain (Borelli *et al.*, 2010; Boras *et al.*, 2010). In OC, macrophages detect pathogens and recruit neutrophils via chemokine signaling; this is helpful in pathogen clearance but risks increasing inflammation, 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 like 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 tumor microenvironment(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 peripheral nervous system, 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 the host's immune response 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 tumor microenvironment of OSCC, neuronal density, nerve diameter, and proximity of nerves to the tumor have been closely associated with tumor initiation and progression(Perez-Pacheco *et al.*, 2023; D'Silva *et al.*, 2023; Schmitd *et al.*, 2022). 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(C *et al.*, 2018; van Vugt *et al.*, 2017). Neural damage from PNI is a key driver of cancer-related pain in OSCC and induces neurogenic inflammation(Salvo *et al.*, 2020; Scheff *et al.*, 2017), 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 (TAMs), weakens the host's anti-tumor immune response. These cells secrete immunosuppressive cytokines such as IL-10 and TGF-β, thereby inhibiting the activity of CD8+ T cells and facilitating tumor immune escape(Xue *et al.*, 2022; Lim *et al.*, 2014).

Nociceptor neurons also play a significant role in the mechanisms of immune evasion. By releasing the neuropeptide calcitonin gene-related peptide (CGRP), nociceptors bind to RAMP1 receptors on CD8+ T cells, leading to their functional exhaustion. This exhaustion impairs CD8+ T cells' anti-tumor activity while upregulating inhibitory markers such as PD-1, LAG3, and 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 NTRK 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 leukoplakia (PVL), although invasive tumors have not yet formed, local immune dysregulation is already evident. At this stage, 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 (stage 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 *et al.*, 2025a). 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 tumor microenvironment and influencing cancer progression. The emergence of technologies such as spatial transcriptomics allows for precise identification of neuroimmune interaction hotspots within the tumor microenvironment, 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 cancertreatment 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(Ge *et al.*, 2024; Teles *et al.*, 2022). Periodontitis contributes to the progression of these neurological disorders through various pathways （Figure 3）. 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 central nervous system (Teixeira *et al.*, 2017; Wang *et al.*, 2023b). 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)

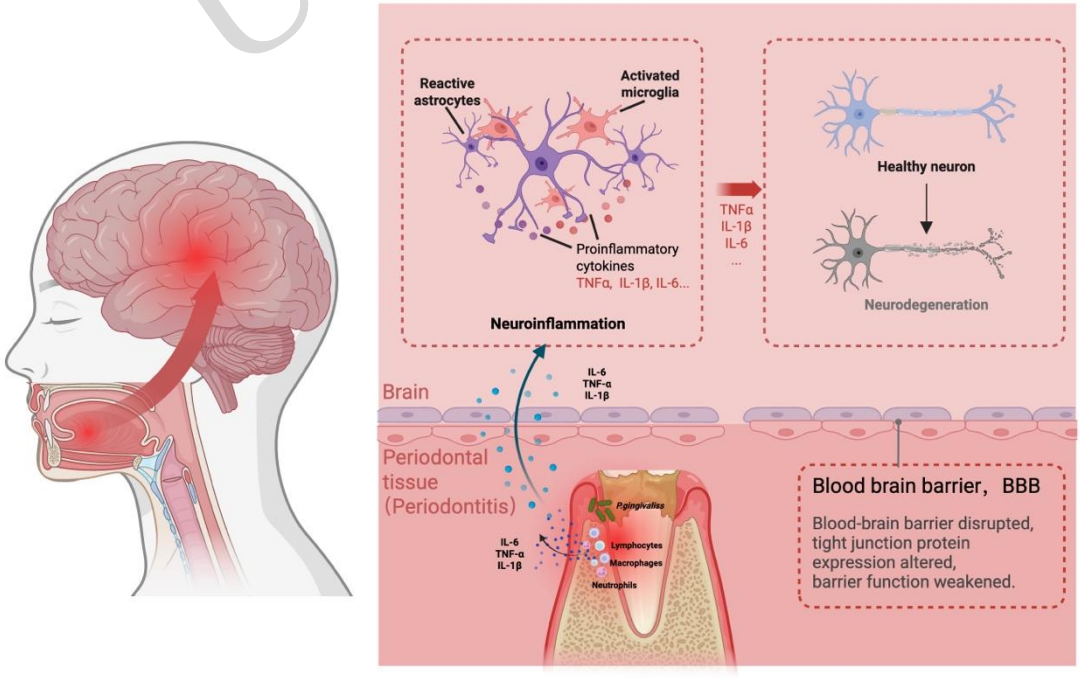

Fig. 4 The relationship between periodontitis and neurodegenerative disease. During periodontitis, pro-inflammatory factors released by immune cells cross the blood-brain barrier and enter the central nervous system, activating microglia and astrocytes. This mediates neuroinflammation, leading to neurodegeneration. Created with BioRender.com.

In Alzheimer's disease, 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 Parkinson's disease, 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 lipopolysaccharides (LPS) and RgpB proteases), can infiltrate the brain via hematogenous or neural routes(Kell *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., ZO-1 and occludin), weakening BBB functionality and facilitating the entry of peripheral immune components into the central nervous system(Furutama *et al.*, 2020). This effect is particularly pronounced in AD and PD patients; elevated neuroinflammatory markers such as YKL-40, NfL, and 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 (EC) dysfunction, chronic inflammation from periodontitis heightens neuroimmune activation. Research indicates that key EC-metabolizing enzymes, including NAPE-PLD and 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 central nervous system 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 Alzheimer’s disease (Choi *et al.*, 2007). These findings suggest its potential for treating neuroinflammation in Alzheimer’s disease 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 George P. Smith in 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(Smith, 1985). 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(McIlroy *et al.*, 2025; Jacobs-Lorena and Cha, 2024; Peng *et al.*, 2022, 2020b, 2020a).

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 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.

Table 4 Bacterial products influencing neuroimmune interactions in oral diseases

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

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Author contributions

Xiatong ZHANG conceptualized the review topic and scope. Xiatong ZHANG, Xinyi WANG and Dayu WANG performed the systematic literature search, collected the data, and wrote the first draft of the manuscript. Xiaoyuan WANG and Zhuo CHEN reviewed and edited the manuscript. Both authors have read and approved the final manuscript.

Compliance with ethics guidelines

Xiatong ZHANG, Xinyi WANG, Dayu WANG, Xiaoyuan WANG and Zhuo CHEN declare that they have no

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

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