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Type 2 neuroimmune interaction-mediated functional homeostasis and tissue repair

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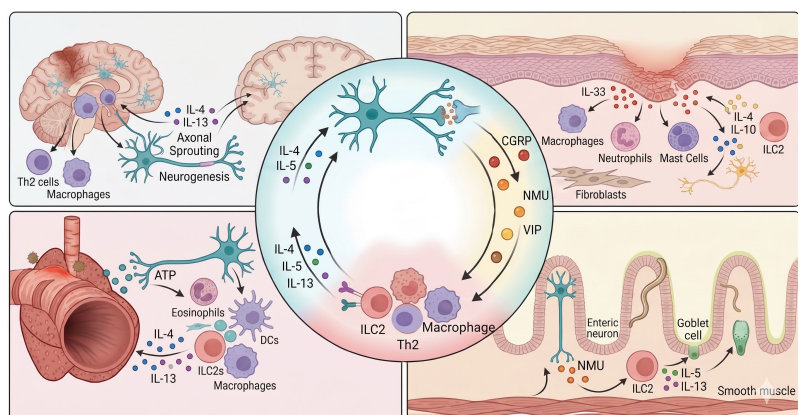
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ABSTRACT: The functional interdependence between type 2 immunity and the nervous system plays a critical role in maintaining tissue homeostasis and promoting repair across multiple organs. These systems act in concert through bidirectional crosstalk to preserve systemic physiological equilibrium. The nervous system, including its peripheral components, releases neuropeptides and neurotransmitters in response to signals from type 2 immune cells, such as T helper 2 (Th2) cells and group 2 innate lymphoid cells (ILC2s), thereby inducing cytokine production and immunomodulatory effects. Conversely, type 2 immune cells and their cytokines can sensitize peripheral nociceptors and regulate neurotransmitter release, forming a reciprocal feedback loop. This review summarizes the molecular mechanisms underlying type 2 neuroimmune interactions and their roles in physiological homeostasis and tissue repair across multiple organ systems, including the nervous system, skin, gastrointestinal tract, respiratory tract, and oral cavity. In addition, we highlight current controversies and knowledge gaps to identify critical molecular targets that confer specificity to type 2 neuroimmune interactions, and to propose emerging conceptual frameworks and research directions for the clinical management of related disorders.



KEYWORDS: type 2 immunity, neuroimmunology, homeostasis, cytokines, neurotransmitters, tissue repair

1 Introduction

The immune and nervous systems are two of the principal regulatory systems. Environmental threat signals, such as tissue injury and microbial invasion, are transmitted via the peripheral nervous system to the central nervous system (CNS), which subsequently orchestrates protective and defensive responses^[1,2]. Type 2 immunity represents a major immunological program involved in antiparasitic.

defense, tissue repair, and metabolic homeostasis. It integrates danger signals generated by tissue injury or pathogen-derived factors and directs effector cells to mount appropriately regulated immune responses^[3-5].

Type 2 immunity and the nervous system do not function independently. The nervous system conveys precise information regarding the location and severity of infection or tissue injury to immune cells; conversely, immune cells and cytokines can sensitize peripheral nociceptors and modulate neurotransmitter release. Together, these systems coordinate neuroimmune responses through interactions at peripheral nerve endings that innervate immune organs. Moreover, they utilize a diverse array of cytokines, growth factors, and signaling mediators to enable bidirectional communication, thereby maintaining tissue homeostasis and coordinating responses to infection, injury, and repair^[6,7]. Elucidating the mechanisms underlying type 2 neuroimmune interactions, as well as exploring therapeutic strategies targeting the neuroimmune axis, may provide novel opportunities for the treatment of helminth infections, allergic diseases, tissue injury, and chronic neurodegenerative disorders.

In recent years, accumulating evidence has indicated that type 2 neuroimmune crosstalk is a key regulator of functional homeostasis

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and tissue repair. Interactions between type 2 immune cells and peripheral neurons that innervate immune organs can influence neuronal survival, proliferation, and differentiation, as well as axonal and synaptic development. Meanwhile, immune signals are not passive; rather, they are actively monitored and modulated through the regulation of neural responses to maintain systemic equilibrium^[8,9]. Conversely, immune cells are directly regulated by the nervous system via neurotransmitters, such as acetylcholine and norepinephrine, and neuropeptides, including calcitonin gene-related peptide (CGRP) and neuromedin U (NMU).

Cytokines, neuropeptides, and related signaling molecules serve as key mediators of bidirectional communication between the nervous system and type 2 immunity, thereby ensuring coordinated physiological responses. Type 2 immune cells modulate neural activity and contribute to tissue repair in part through the release of cytokines and immunoregulatory mediators. For example, interleukin IL-4 and IL-13 secreted by meningeal T cells are closely associated with cognitive function; deficiency of these cytokines leads to cognitive impairment, whereas their supplementation improves memory performance^[10–14]. Moreover, overexpression of IL-4 and IL-13 confers neuroprotection in CNS injuries, including stroke and traumatic brain injury (TBI)^[15,16]. Administration of IL-4, alone or in combination with IL-13, in APP/PS1 mice enhances amyloid plaque clearance and attenuates memory deficits in models of neurodegeneration^[17].

Neuropeptides released by neurons also regulate the function of type 2 immune cells. Substance P (SP), produced by cutaneous sensory neurons, induces mast cell degranulation and promotes the release of histamine and vascular endothelial growth factor (VEGF), thereby facilitating inflammation, angiogenesis, and inflammatory cell infiltration^[18]. NMU, expressed by mucosal neurons, activates IL-25–stimulated ILC2s, promoting proinflammatory responses and eosinophilia that facilitate the expulsion of intestinal helminths^[19–22]. In asthma pathogenesis, C fibers-derived vasoactive intestinal peptide (VIP) enhances the activation of both CD4⁺ T cells and ILC2s, leading to increased production of type 2 cytokines, including IL-4, IL-5, and IL-13, and thereby exacerbating airway hyperresponsiveness and allergic inflammation in the lung^[23].

2 Type 2 neuroimmune crosstalk and its signaling molecules

2.1 Type 2 neuroimmune interactions

Barrier tissues, including the brain, skin, lung, and intestine, are characterized by the spatial co-localization and functional integration of neuronal terminals and immune cells. These components cooperate to maintain tissue homeostasis through the regulation of key physiological functions; collectively, this functional unit is termed the neuroimmune unit (NIU)^[24–28]. The NIU comprises diverse neuronal subtypes as well as innate and adaptive immune cells, whose coordinated activities depend on a wide array of molecular mediators, including neurotransmitters, neuropeptides/cytokines, growth factors, antibodies, and components of the complement system (Fig. 1)^[29,30].

Bidirectional neuroimmune crosstalk is particularly prominent in the intestine. Intrinsic enteric neurons (iENs) express IL-13 receptors and can directly respond to IL-13 released by ILC2s, leading to increased β -CGRP expression and subsequent suppression of ILC2-mediated anti-helminth immunity^[31]. In the

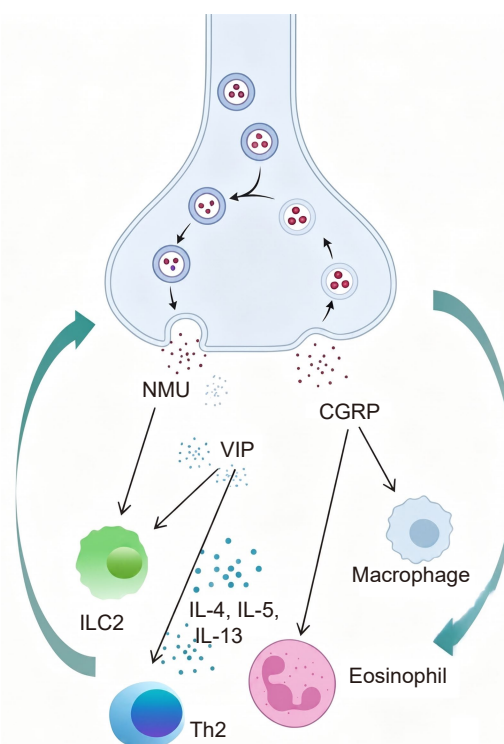


Figure 1 Key signaling molecules involved in type 2 neuroimmune interactions. Type 2 immune cells—including Th2, ILC2, macrophages, etc.—secrete a variety of cytokines, particularly IL-4, IL-5, and IL-13. Neurons synthesize neuropeptides, such as CGRP, NMU, and VIP. The dynamic interactions between type 2 immune cells and their effector cytokines, neurons and neuropeptides constitute a basic molecular framework that supports a broad range of physiological and pathological processes. Among these molecules, NMU acts on ILC2 cells to promote intestinal helminth expulsion; VIP promotes the activation of ILC2 and Th2, exacerbating airway hyperresponsiveness and pulmonary allergic inflammation; CGRP acts on macrophages to accelerate wound healing. Th2: T helper 2 cells; ILC2: group 2 innate lymphoid cells; CGRP: calcitonin gene-related peptide; NMU: neuromedin U; VIP: vasoactive intestinal peptide.

skin, nociceptor terminals extend into sites of injury, where CGRP released from these terminals acts on neutrophils and macrophages, enhancing phagocytosis and promoting macrophage polarization toward a reparative phenotype, thereby facilitating wound healing^[32].

Within the meningeal immune microenvironment, ILC2s establish direct contacts with vagal and trigeminal nerve endings, forming a specialized neuroimmune interface. Crosstalk between type 2 immune cells, their cytokines, and the nervous system mediates both neuroprotective and neuroregenerative effects, in addition to immunomodulation. In healthy meninges, abundant ILC2s can be activated by the alarmin IL-33 following CNS injury. Upon activation, these cells proliferate and upregulate CGRP expression, promoting the regeneration of sensory neurons both within the CNS and in peripheral tissues^[33]. During the early stages of ischemic stroke, ILC2s infiltrate the brain parenchyma, suppress neuroinflammation, restore immune homeostasis, and release α -CGRP to promote vascular sprouting and enhance regional perfusion, thereby supporting long-term sensorimotor recovery^[34].

The sympathetic and parasympathetic nervous systems release neurotransmitters, including norepinephrine, acetylcholine, and catecholamines, which regulate the distribution and functional

activity of type 2 immune cells within or entering the brain^[35]. The microbiota–gut–brain axis represents a dynamic process through which the intestinal microbiota continuously shape neuroendocrine function and indirectly modulate intestinal immunity^[36,37]. Acetylcholine secreted by the parasympathetic nervous system can specifically bind to cholinergic receptors on the surface of ILC2s, mediating pulmonary inflammatory responses and significantly enhancing type II immune responses in the lungs of mice after feeding^[38]. In contrast, in the intestinal mucosa, parasympathetic cholinergic signaling enhances type 2 immune responses during helminth infection via acetylcholine-dependent mechanisms^[39].

2.2 Key signaling molecules in type 2 neuroimmune crosstalk

Type 2 immunity is orchestrated by a range of immune cells that function as initiators, transducers, or effectors, including Th2, ILC2s, macrophages, eosinophils, basophils, mast cells, and dendritic cells. These cell populations and their associated cytokines act in concert to regulate a broad spectrum of physiological processes, including defense against exogenous pathogens (particularly helminths), modulation of type 1 immune responses to prevent dysregulation, suppression of autoimmune pathogenesis, and the maintenance of tissue repair and metabolic homeostasis^[40–43].

Among these mediators, interleukin IL-4 and IL-13 directly influence neuronal function by enhancing synaptic activity, regulating synaptic plasticity, and improving spatial learning and memory^[44]. The upstream alarmin IL-33 activates Th2 cells, thereby amplifying type 2 immune responses, and also stimulates sensory neurons associated with itch and pain^[45,46]. Furthermore, IL-4 and IL-13 have been shown to reduce infarct size, ameliorate motor dysfunction, promote long-term neurological recovery following stroke, and attenuate brain atrophy^[47,48].

Acetylcholine receptor agonists exert inhibitory effects on the proliferation and functional activity of ILC2s, thereby reducing airway hyperresponsiveness in allergic airway inflammation^[49]. CGRP and SP induce mast cells to secrete inflammatory cytokines, including tumor necrosis factor- α (TNF- α), IL-1, and IL-4, thereby establishing a localized proinflammatory microenvironment. These neuropeptides also promote vasodilation, plasma extravasation, and increased vascular permeability, while modulating immune cell recruitment and phenotypic polarization through their actions on vascular endothelial and smooth muscle cells^[50–52]. NMU binds to its cognate receptor, NMUR1, which is selectively expressed on ILC2s, Th2 cells, and eosinophils, and promotes goblet cell differentiation, thereby facilitating the expulsion of intestinal helminths^[53].

3 Roles of type 2 neuroimmune interactions in functional homeostasis and tissue repair

3.1 Central nervous system: neuroinflammation and regenerative repair

Traumatic brain injury (TBI) is characterized by pathological alterations in neuroimmune crosstalk, including reduced numbers of regulatory T cells, neuroinflammation, lymphocyte infiltration into the brain parenchyma, reactive astrogliosis, and transient motor dysfunction^[54,55]. The type 2 cytokine interleukin IL-4 exerts significant reparative effects by promoting the polarization of macrophages and microglia toward anti-inflammatory phenotypes,

suppressing neuronal apoptosis, reducing lesion volume, enhancing neuronal activity, and accelerating brain tissue repair^[56,57]. Neutrophils also contribute to wound healing following TBI and may facilitate neural recovery^[58,59]. In addition, fibroblast-derived IL-33 acts on ILC2s to limit acute infiltration of pathogenic cells into the brain and preserve hippocampal structure during the chronic phase^[60].

Existing research has fully confirmed that type II immune responses exert neuroprotective effects; however, some studies have also pointed out that following TBI, CD4⁺CD11b⁺T cells can infiltrate damaged brain tissue through the damaged blood-brain barrier, thereby mediating and exacerbating the pathological damage associated with acute brain injury^[61]. Collectively, these findings underscore the importance of the type 2 neuroimmune microenvironment in TBI pathogenesis and recovery, supporting the development of therapeutic strategies aimed at optimizing immune responses and promoting neurogenesis.

Ischemic stroke is characterized by severe cerebral hypoperfusion, resulting in cellular damage and neuronal death^[62]. Type 2 neuroimmune interactions exert bidirectional effects on disease progression and prognosis. On the one hand, cytokines regulate the activation, proliferation, and differentiation of T and B cells. IL-4 and IL-13 produced by activated T cells reduce infarct size and improve motor function, with IL-4 playing a particularly critical role in microglial/macrophage M2 polarization and long-term neurological recovery^[44,45]. IL-13 also exhibits anti-inflammatory and reparative properties; in murine models of permanent cerebral ischemia, it promotes macrophage polarization toward the M2 phenotype, enhances anti-inflammatory responses, and reduces neuronal apoptosis^[63]. Conversely, accumulating evidence suggests that dysregulated type 2 cytokine signaling may exacerbate neuroinflammation and worsen CNS injury^[64]. Further studies are required to delineate the precise regulatory mechanisms through which type 2 neuroimmune interactions influence stroke outcomes (Fig. 2).

3.2 Barrier systems: physical injury and microbial defense

As the largest organ and primary interface between the body and the external environment, the skin plays a critical role in host defense. Following cutaneous injury, microbial invasion, immune cell infiltration, neuroimmune crosstalk, and tissue remodeling collectively contribute to wound repair. The skin is richly innervated by sensory fibers originating from the dorsal root ganglia, which communicate bidirectionally with resident and infiltrating immune cells to regulate healing. In the early phase, mast cells release IL-33, histamine, and other mediators that recruit immune cells to the injury site^[65]. Subsequently, sensory neuronal signals stimulate macrophages, neutrophils, and mast cells to secrete anti-inflammatory cytokines, including IL-4 and IL-10, thereby promoting tissue repair^[66,67]. Transforming growth factor- β (TGF- β) induces IL-31 production in dermal dendritic cells, which activates sensory neurons and contributes to wound-associated pruritus^[68]. Conversely, IL-31 signaling in sensory neurons can suppress type 2 skin inflammation induced by chronic allergen exposure^[69]. These mechanisms provide a conceptual framework for the clinical management of wound-associated itch (Fig. 2).

In the intestine, type 2 immunity and the nervous system interact in a context-dependent manner to maintain homeostasis while also contributing to pathology. Macrophages play a crucial role in the

Neuroimmune Interaction Panorama

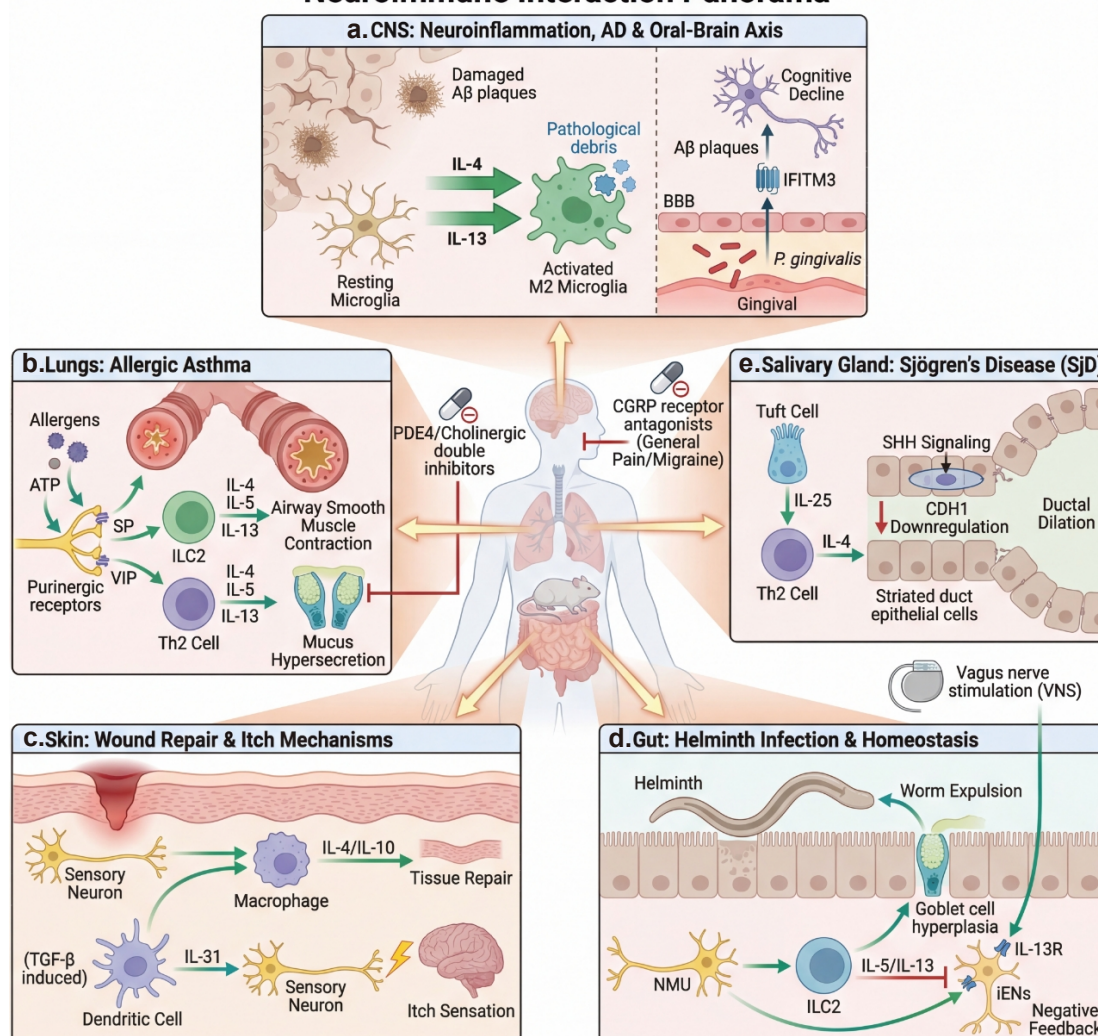


Figure 2 Schematic overview of the type 2 neuroimmune circuit across organ systems. Neuropeptides—including CGRP, NMU, vasoactive intestinal peptide (VIP), and SP—are released from peripheral nerve endings, while cytokines secreted by type 2 immune cells (e.g., Th2 cells, ILC2s, and macrophages), such as IL-4, IL-5, and IL-13, form reciprocal signaling loops with neuronal mediators. This bidirectional circuit operates across multiple organ systems: Central nervous system (CNS): IL-4 and IL-13 derived from Th2 cells and macrophages promote neuronal repair and functional recovery following injury. Skin barrier: Upon injury, IL-33 recruits immune cells to the wound site; macrophages, neutrophils, and mast cells subsequently release IL-4 and IL-10, which act on neurons to accelerate tissue repair. Intestinal mucosa: Neuron-derived NMU activates ILC2s to produce IL-5 and IL-13, facilitating helminth expulsion. Respiratory system: Neuron-released ATP activates eosinophils, dendritic cells, ILC2s, and macrophages, inducing IL-4 and IL-13 production, thereby contributing to bronchoconstriction and impaired lung function.

development, maintenance, and repair of the enteric nervous system (ENS), including synaptic pruning and the removal of dysfunctional neurons during early development^[70]. Co-administration of NMU and CGRP restores impaired host defense against the gastrointestinal helminth *Heligmosomoides polygyrus* in *Il13ra1*-deficient mice, while enhancing local immune responses^[71]. NMU also stimulates ILC2s to produce IL-5 and IL-13, thereby increasing resistance to helminth infection^[72]. Additionally, sensory neuron-derived CGRP, SP, and VIP regulate intestinal inflammation and anti-helminth immunity by acting on immune cells, vascular smooth muscle cells, endothelial cells, and epithelial cells. These mediators support type 2 immune responses and exert pleiotropic protective effects on the intestinal barrier under both homeostatic and host-defense conditions^[73].

Pathologically, dysregulated type 2 neuroimmune crosstalk contributes to intestinal disorders. For example, submucosal

macrophage–neuron interactions are closely associated with the pathogenesis of irritable bowel syndrome. Macrophage depletion disrupts intestinal motility, sensitizes enteric neurons, and promotes intestinal dysfunction, thereby contributing to disease development^[74]. Mouse intestinal ILC2 cells express β 2-adrenergic receptors (β 2AR) and are subject to neuroregulation by intestinal adrenergic neurons. Deletion of the β 2AR gene induces excessive activation of intestinal ILC2 cells, thereby exacerbating intestinal inflammation. Furthermore, the vagus nerve transmits peripheral nerve signals to choline acetyltransferase (ChAT)-positive T cells, which further act on macrophages and inhibit the secretion of TNF- α . This neuro-immune regulatory axis is inextricably linked to the development and progression of intestinal inflammation and dysfunction. Therefore, the dual biological effects of type II neuroimmunity on intestinal function, as well as their underlying molecular mechanisms, warrant further systematic investigation^[75–76].

3.3 Respiratory system: allergen exposure and airway inflammation

Allergic asthma is one of the most prevalent chronic inflammatory lung diseases worldwide, and its pathogenesis is closely linked to type 2 neuroimmune crosstalk. Allergens directly activate ILC2s and Th2 cells in the airway epithelium, inducing the production of IL-4, IL-5, and IL-13, key cytokines that drive disease progression. Clinical studies have demonstrated increased density of sensory nerve endings in the airways of patients with asthma, contributing to bronchoconstriction and enhanced inflammation. Airway sensory neurons are highly responsive to purinergic signaling, particularly adenosine triphosphate (ATP, released by almost all immune cells and neurons during a wide range of physiological processes), which amplifies cough reflexes and inflammatory responses. ATP also activates innate immune cells, including eosinophils, dendritic cells, ILC2s, and macrophages, thereby promoting cytokine release and further impairing pulmonary function^[77,78]. These findings highlight neuroimmune interactions as promising therapeutic targets in asthma (Fig. 2).

Recent advances have focused on bifunctional therapeutic strategies that exploit synergistic effects. Dual IL-4/IL-13 antagonists reduce IgE production and attenuate airway hyperresponsiveness and inflammation. Phosphodiesterase 4 (PDE4) inhibitors suppress T-cell activation and neutrophil infiltration, while combined inhibition of PDE4 and cholinergic signaling may yield enhanced anti-inflammatory effects. Additional approaches targeting neural signaling, including denervation or modulation of neuronal sensitivity, show potential in reducing airway hyperreactivity, although clinical efficacy remains variable and standardized treatment protocols are lacking. Further research is needed to evaluate the long-term safety and effectiveness of these strategies^[79,80].

3.4 Current advances in oral type 2 neuroimmune research

Periodontitis is a prevalent chronic inflammatory disease driven by interactions between dysbiotic oral microbiota and host immune responses. Increasing evidence links periodontitis to the development and progression of Alzheimer's disease (AD), a neurodegenerative disorder characterized by cognitive decline and memory loss and behavioral abnormalities. Pathological markers of AD mainly include β -amyloid ($A\beta_{1-42}$) deposition in the brain, tau protein hyperphosphorylation leading to neurofibrillary tangles, and neuronal apoptosis induced by persistent neuroinflammation. Existing research has clearly confirmed that dysregulated type 2 cytokines (e.g., IL-4 and IL-5), together with proinflammatory mediators such as IL-1 β , IL-6, and TNF- α , contribute to neuroinflammation, neuronal apoptosis, and cognitive impairment in AD^[81].

Currently confirmed oral-brain axis regulatory mechanisms show that periodontitis-related pathogenic factors can affect AD pathology through multiple pathways. Recent studies have found that the core pathogen of periodontitis—*Porphyromonas gingivalis*—and its secreted virulence factors (such as *Porphyromonas gingivalis* lipopolysaccharide) can be detected in the brain tissue of patients with AD. These pathogens can directly induce inflammatory responses in the brain, promote tau protein hyperphosphorylation and $A\beta_{1-42}$ accumulation, providing important direct evidence for the association between periodontitis and AD^[82,83]. In addition to those direct mechanisms, the systemic

inflammatory response triggered by periodontitis is also an important link between the two diseases. During periodontitis pathogenesis, the Th2 immune response often exhibits dynamic antagonism with the Th1 and Th17 immune responses, collectively forming a complex immune microenvironment. Multiple studies have indicated that periodontitis can participate in the development and progression of neuroinflammation by regulating central immune homeostasis^[84-85]. Periodontitis-associated neuroinflammation also activates the interferon-induced transmembrane protein 3 (IFITM3)– $A\beta$ axis, contributing to AD-like pathology and cognitive decline^[86].

Emerging evidence indicates that type 2 immunity is involved in the pathogenesis of Sjögren's disease (SjD) (Fig. 2). IL-4 signaling via the Sonic Hedgehog (SHH) pathway in salivary gland epithelial cells disrupts cell–cell adhesion by upregulating SNAIL and downregulating CDH1, leading to ductal dilation and impaired glandular function^[87]. Furthermore, IL-25 secreted by tuft cells in dilated ducts stimulates Th2 cells to produce IL-4 and IL-13, amplifying type 2 inflammation in SjD^[88].

4 Clinical translation and therapeutic prospects

Therapeutic strategies targeting neuroimmune interactions are gaining increasing attention. CGRP receptor antagonists have been approved for trigeminal neuralgia and exhibit high specificity with minimal adverse effects^[89]. β_2 -adrenergic receptor agonists function as bronchodilators, inhibit ILC2-mediated responses, and provide bronchoprotective effects, making them valuable in asthma management^[90]. Vagus nerve stimulation, a form of bioelectronic medicine with established anti-inflammatory properties, is approved for epilepsy and depression and shows promise in inflammatory bowel disease^[91]. Future therapies targeting NMU–NMUR1 and VIP–VIPR2 signaling pathways may offer novel approaches for treating allergic diseases and promoting tissue regeneration.

Harnessing type 2 neuroimmune crosstalk for regenerative medicine represents a promising avenue. Activation of ILC2s by IL-33 has demonstrated efficacy in preclinical models of chronic wounds, including diabetic ulcers^[92]. However, excessive activation may lead to adverse outcomes such as fibrosis, hypertrophic scarring, and neuropathic pain. Therefore, precise spatiotemporal regulation of type 2 neuroimmune interactions remains a major challenge for clinical translation.

Despite the significant clinical value and application potential of these treatment strategies, numerous challenges remain for their clinical translation. First, tissue specificity remains insufficient. For example, although CGRP receptors are primarily distributed in the trigeminal ganglion, they are also expressed at low levels in various normal tissues^[93]; long-term use of CGRP receptor antagonists may therefore affect normal tissue function. Improving targeting precision while minimizing off-tissue effects remains a key research priority. Second, the potential risk of systemic adverse reactions cannot be ignored. Some local interventions may trigger systemic responses via neural conduction or humoral circulation, making the monitoring and management of adverse reactions essential throughout clinical application. Third, clear and unified criteria for intervention timing are lacking. Neuroimmune interactions exhibit distinct mechanisms at different stages of disease progression, and the efficacy of the same treatment strategy varies considerably between early, middle, and late stages. Precisely selecting the

optimal intervention window remains a major translational challenge. Fourth, the risks of fibrosis and immunosuppression limit the clinical applicability of such strategies. Overactivation of type II neuroimmune interactions can induce tissue fibrosis, whereas prolonged vagal nerve stimulation may suppress local immunity, thereby increasing infection risk. Therefore, fine-tuning the intensity of immune responses has become a central focus of future research. Finally, species differences between mice and humans reduce the efficiency of translating basic research into clinical practice. Most preclinical studies currently rely on mouse models, yet inherent differences exist between mice and humans in neuroimmune pathway regulation, immune cell subset distribution, and pharmacokinetics. These discrepancies may lead to inconsistent efficacy between animal models and human clinical outcomes, increasing both translational costs and risks. In summary, neuroimmune-based therapeutic strategies hold substantial advantages and broad application prospects. However, inadequate tissue specificity, systemic adverse reactions, unclear intervention timing, risks of fibrosis and immunosuppression, and species differences still seriously impede their clinical translation. Future research should focus on addressing these key limitations by optimizing treatment targeting, establishing evidence-based criteria for intervention timing, precisely modulating immune response intensity, and developing animal models that more faithfully recapitulate human disease characteristics.

5 Conclusions and perspectives

Recent advances highlight the critical role of type 2 neuroimmune crosstalk in maintaining tissue homeostasis and promoting repair across multiple organ systems. Coordinated interactions between the nervous and immune systems are essential for physiological stability and recovery following injury. Future research should focus on elucidating organ-specific regulatory mechanisms and the complex networks of cytokines and neuropeptides involved under diverse physiological and pathological conditions. These efforts will enhance our understanding of neuroimmune regulation and inform the development of targeted therapies for conditions such as neuroinflammation, asthma, helminth infections, and tissue injury.

However, the field of type II neuroimmune interactions still faces numerous controversies and knowledge gaps. First, the organ-specific regulatory mechanisms of type II neuroimmune interactions under different physiological and pathological states are not fully understood, particularly regarding the link between type II neuroimmunity in the oral cavity and systemic diseases (such as Alzheimer's disease). Furthermore, the precise spatiotemporal regulation of type II neuroimmune interactions is controversial; the regulatory nodes that balance immune activation and overactivation remain unclear. Second, within the complex signaling network composed of cytokines and neuropeptides, the key molecular targets specific to type II neuroimmune interactions have not been precisely identified, and the synergistic or antagonistic mechanisms between different signaling molecules require further exploration. Addressing these controversies and targets, we construct an "organ-specific precise regulation" framework to develop personalized intervention strategies targeting the type II neuroimmune characteristics of different organs (central nervous system, skin, oral cavity, etc.). Furthermore, we can establish a "signal molecule precise regulation" system, using organ-specific key molecular targets as the core, to develop highly specific

intervention drugs (such as CGRP receptor antagonists and NMUR1-targeting agents). Finally, advancing the spatiotemporal regulation of key pathways in type II neuroimmune interactions will help overcome clinical translation challenges such as fibrosis and immunosuppression, ultimately providing new diagnostic and therapeutic insights for related diseases.

Precise therapeutic modulation of neuroimmune interactions—through regulation of immune cell activation, targeted control of cytokine and neuropeptide signaling, and inhibition of aberrant neural-immune communication—holds promise for improving tissue homeostasis and clinical outcomes. Continued advances in this field may ultimately lead to more effective and comprehensive strategies for disease prevention and treatment.

Compared with existing reviews in this field, this review's additional academic value and unique contributions are mainly reflected in three aspects. First, this review focuses on the sub-field of type II neuroimmune interactions, unlike existing reviews which often center on the overall neuroimmune cross-dialogue model. It systematically reviews the core molecular mechanisms of this field, clarifying the bidirectional regulatory roles of key signaling mediators such as cytokines and neuropeptides, filling the gap in the mechanism analysis of this sub-field. Second, this review integrates relevant research results on multiple organ systems, for the first time incorporating the central nervous system, skin, gastrointestinal tract, respiratory tract, and oral cavity into a unified research framework. In particular, it supplements the research on the association between oral cavity and periodontitis, Sjögren's syndrome, and Alzheimer's disease, improving the research content of multi-organ system integrated analysis in this field. Finally, this review emphasizes the combination of basic research and clinical application, while objectively analyzing the core challenges in the clinical translation process. This differs from existing reviews that often focus on basic theory and lack clinical translation, providing a more targeted reference for basic research and clinical diagnosis and treatment.

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Data available statement

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Author contribution

F.W. contributed to conception and critically revised the manuscript. F.W. and X.C. wrote the manuscript. J.Z., J.L. and L.L. revised the manuscript and participated in the drawing of the figures. All authors read and approved the final manuscript.

Ethics approval and consent

N/A

Consent for publication

All authors agree to publish.

Conflicts of interest

Author Fu Wang is an editorial board member of this journal, but he is not involved in the peer-review or decision of this article.

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