

Deciphering peripheral neuroimmune crosstalk for translational therapeutics

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INTRODUCTION

Linkage between the nervous and immune systems dates to ancient times when Celsus identified the four cardinal signs of inflammation as redness, swelling, heat, and pain. Recent elucidation of neurogenic inflammation and inflammatory pain has brought renewed focus on the bidirectional neuroimmune crosstalk from physiological to pathological conditions. Advancements in mechanistic investigations have identified novel therapeutic targets by leveraging neuroimmune interaction.

This perspective outlines the framework of peripheral neuroimmune interactions *via* diverse neurons, immune cells and their mediators. What follows are examples of targeted therapies for pain and cancer at the neuroimmune interface. Lastly, outstanding questions for basic and clinical research on neuroimmune crosstalk, together with concerns and pitfalls for its targeted therapies, are outlined for consideration.

THE PERIPHERAL ORGANIZATION OF NEUROIMMUNE CROSSTALK

Distinct immune and neuronal cell subsets are key players in peripheral neuroimmune crosstalk, maintaining homeostasis through receptor-ligand interactions mediated by neurotransmitters, neuropeptides, cytokines, and chemokines.^[1] Sensory neurons have fixed anatomical locations and extensive innervation, enabling rapid signal detection and transmission. In contrast, innate and adaptive immune cells are mobile and dispersed, mediating inflammation and

tissue repair. This structural and functional contrast underscores their complementary cooperation, enhancing reaction speed and systemic impact.

Peripheral neuroimmune crosstalk functions hierarchically, integrating localized and systemic regulation. Sensory neurons rapidly detect threats, releasing neuropeptides that modulate immune cells, while local axonal reflexes facilitate signal transmission. For example, the vagus nerve mediates an anti-inflammatory reflex that suppresses cytokine production. Systemically, neuroimmune signals drive immune responses and protective behaviors like coughing, vomiting, and sneezing, enhancing host defense. These responses are modulated by both conscious CNS control and unconscious immune regulation. Therefore, the complexity of neuroimmune regulation across hierarchical levels presents promising avenues for research and therapeutic innovation.

NEUROIMMUNE CROSSTALK IN PAIN RELIEF

Pain serves as a protective warning against external and internal threats but becomes pathological when prolonged immune and nervous system activation requires intervention.^[2] Recent identification of nociceptor-immune interactomes as insult-specific pain signatures,^[3] highlights the potential of neuroimmune targets for translational therapies (Figure 1).

Therapeutics targeting sensory neuron ion channels and neuromodulation techniques are increasingly applied in pain management.

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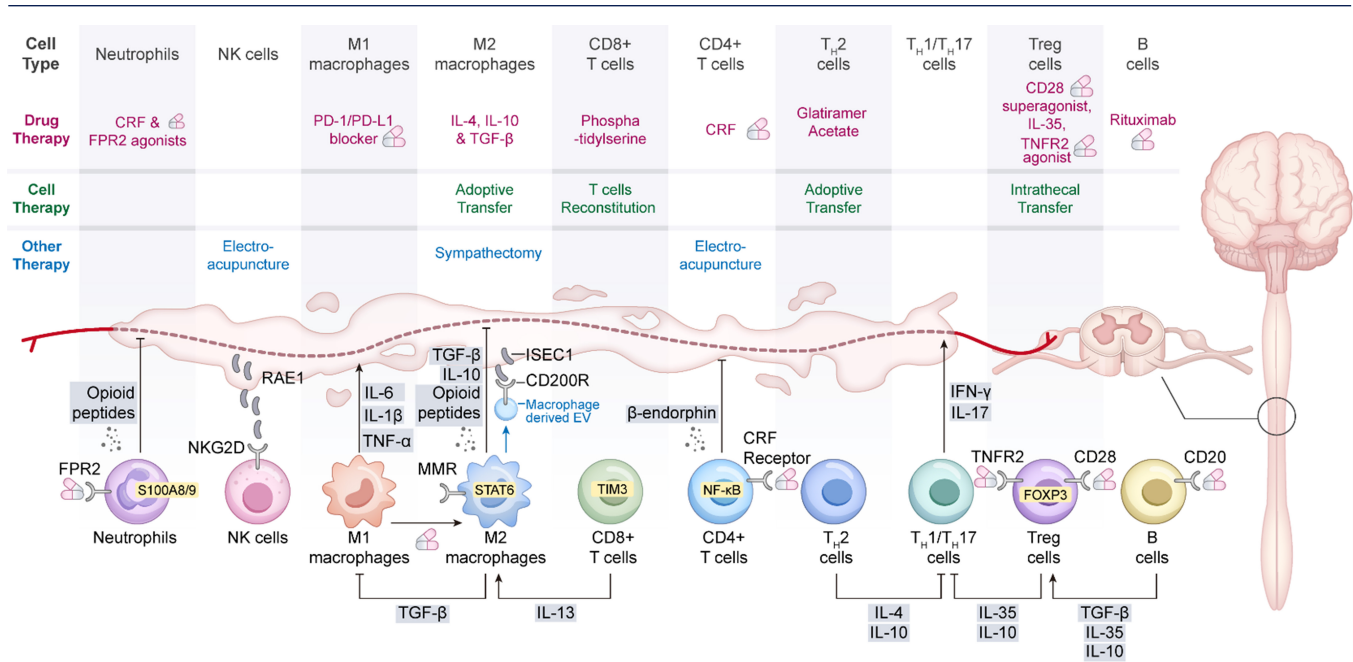


Figure 1: Therapeutic strategies to alleviate pain via targeting neuroimmune crosstalk in peripheral nervous system. (Details in Supplementary file).

TRPV1 antagonists (*e.g.*, capsaicin) desensitize nociceptors, while Nav1.7 blockers directly inhibit pain-inducing action potentials. Inhibitors of ASICs, P2X receptors, and modulators of Piezo channels offer additional targeted approaches. Neuromodulation of the peripheral nervous system *via* a 2-week sacral nerve stimulation reduced visceral pain in irritable bowel syndrome (IBS),^[4] where the crosstalk among gut macrophages, microbiota, and enteric neurons contributes to IBS pathology.^[5] Additionally, deep transcranial magnetic stimulation (dTMS) for the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) has demonstrated efficacy in laser-induced pain. Therefore, the involved neurocircuits and neurotransmitters can serve as biomarkers for brain stimulation interventions aimed at specific peripheral pain sites. Targeting the overlapping neural mechanisms between pain and emotion is crucial in developing holistic approaches to pain management and comorbidity.^[6]

NEUROIMMUNE CROSSTALK IN CANCER THERAPIES

Heterotypic neuroimmune signaling in tumors is increasingly recognized for investigation mechanism and therapies for cancer. Early evidence highlights the role of peripheral nerves in cancer progression, as neurotransmitters and neuropeptides (*e.g.* Substance P [SP] and calcitonin gene-related peptide [CGRP]) modulate immune cell phenotypes in the tumor microenvironment (TME), promoting tumor growth and metastasis.^[7] Further, the density of nerve fibers in tumors correlate with morbidity, thereby pointing to

therapeutic strategies targeting the neuroimmune interface in various malignant tumors.

Clinical trials targeting the neuroimmune axis have been initiated for breast cancer and melanoma.^[8] These involve using propranolol, a non-selective β-adrenergic receptor antagonist. A Phase 1b/2 trial for the combination therapy with propranolol and pembrolizumab (an anti-PD1 blocker) was conducted for melanoma patients (NCT03384836). Although results indicated a response rate of 78% without dose-limiting toxicities, the Phase 3 trials did not demonstrate an independent prognostic effect on recurrence-free survival (NCT02362594). This emphasizes further mechanistic investigations for viable neuroimmune targets and the identification of eligible patient populations. In a clinical trial involving breast cancer patients undergoing surgical resection (NCT02839668), intravenous administration of lidocaine downregulated neutrophil extracellular trap formation, potentially reducing tumor recurrence. With intratumor microbes now recognized as key in tumor metabolics and immunotherapy responses,^[9] the various ways commensal microbiota impact neuroimmune therapies must be carefully considered.^[10] Identification of neuroimmune biomarkers for disease prediction and prevention could further advance the field for both basic research and clinical practice.

CONCLUSIONS AND PERSPECTIVES

Preclinical research and clinical trials have identified

numerous potential therapeutic strategies targeting neuroimmune crosstalk, showing promise for enhancing current medications. In cancer, for example, blocking neuroimmune crosstalk can suppress tumor initiation and metastasis. This approach is valuable both as a standalone intervention and in combination with conventional chemotherapy, radiotherapy, and immunotherapy. Revealing neuroimmune interactions in either promoting or alleviating disease progression across different pathologies and disease states is crucial. When particular neuroimmune crosstalk leads to therapeutic resistance, integrating interventions along with surgical denervation and cytotoxic therapy may yield synergistic outcomes.

Particular attention should be placed on the intricate implication involved in exploring integrated therapeutic approaches by the incorporation of targeting neuroimmune crosstalk. In considering the synergetic effects of modulating neuroimmune crosstalk and targeted immunotherapies such as CAR-T cell therapies, it is crucial to consider case-by-case. In this context, the immune-mediated eradication of tumor cells must outpace cancer cell proliferation to prevent tumor progression, otherwise, it may inadvertently promote tumor growth. Furthermore, tailoring neurotransmitters and neuropeptides that modulate immune cells holds significant promise in shaping microenvironments conducive to immunotherapies with higher efficacy.

Embracing a unified portrait of disease mechanisms, wherein the nervous system and immune system are considered as one integrated framework with intertwined functions, primes our comprehensive understanding of pathology across conditions such as infection, pain, allergy and cancer. Such a paradigm shift not only enhances our diagnostic acumen but also opens up novel vistas for therapeutic breakthroughs.

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Not applicable.

Informed Consent

Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

Use of Large Language Models, AI and Machine Learning Tools

None declared.

Data Availability Statement

No additional data is available.

REFERENCES

1. Talbot S, Foster SL, Woolf CJ. Neuroimmunity: Physiology and Pathology. *Annu Rev Immunol* 2016;34:421–447.
2. Zheng Q, Dong X, Green DP, Dong X. Peripheral mechanisms of chronic pain. *Med Rev* (2021) 2022;2:251–270.
3. Chen O, Luo X, Ji R. Macrophages and microglia in inflammation and neuroinflammation underlying different pain states. *Medical Review* 2023;3:381–407.
4. Wang X, Chen JD. Therapeutic potential and mechanisms of sacral nerve stimulation for gastrointestinal diseases. *J Transl Int Med* 2023;11:115–127.
5. Zhang H, Wang X, Zhang J, He Y, Yang X, Nie Y, *et al.* Crosstalk between gut microbiota and gut resident macrophages in inflammatory bowel disease. *J Transl Int Med* 2023;11:382–392.
6. Ju P, Zhao D, Ma L, Chen J. Biomarker development perspective: Exploring comorbid chronic pain in depression through deep transcranial magnetic stimulation. *J Transl Int Med* 2024;12:123–128.
7. Yaniv D, Mattson B, Talbot S, Gleber-Netto FO, Amit M. Targeting the peripheral neural-tumour microenvironment for cancer therapy. *Nat Rev Drug Discov* 2024;23:780–796.
8. Khanmammadova N, Islam S, Sharma P, Amit M. Neuro-immune interactions and immuno-oncology. *Trends Cancer* 2023;9:636–649.
9. Cai Q, Deng W, Zou Y, Chen Z, Tang H. Histone lactylation as a driver of metabolic reprogramming and immune evasion. *Medical Review* 2024; Ahead of print.
10. Zou Y, Zhang H, Liu F, Chen ZS, Tang H. Intratumoral microbiota in orchestrating cancer immunotherapy response. *J Transl Int Med* 2025;12:540–542.

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