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Editorial overview: Special section neuroimmunology: Neuroimmune interactions in health and disease

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Isaac M Chiu is an Associate Professor of Immunology in the Blavatnik Institute and Department of Immunology at Harvard Medical School. His laboratory studies neuronal interactions with microbes and immune cells in pain, host defense and inflammation. Dr. Chiu received his Ph.D. in immunology at Harvard University and performed his postdoctoral work in the neurobiology of pain at Boston Children's Hospital. He discovered that nociceptor sensory neurons directly detect bacterial pathogens and their secreted mediators to produce pain. He found that nociceptors signal to immune cells via neuropeptides including calcitonin-gene related peptide to regulate antimicrobial defenses at barrier sites including the gut, lungs, and skin. His lab continues to define molecular interactions between the nervous system, immune system, and microbes to develop novel approaches to treat chronic pain and inflammatory diseases.

Introduction

The nervous system and immune system communicate throughout the body and in the central nervous system (CNS). The field of neuroimmunology has enjoyed a recent renaissance. This volume of *Current Opinion in Immunology* highlights current studies and expert opinions illuminating neuro-immune interactions in health and disease. In peripheral organs and tissues, neurons bidirectionally crosstalk with innate and adaptive immune cells to regulate host defense, allergies, wound healing, and barrier immunity. We also discuss how innate and adaptive immune cell populations change dynamically in brain, spinal cord, and brain-border regions with development, aging, and disease. Immune cells play integral roles in CNS homeostasis and host defense, and their dysregulation very likely underlie autoimmune diseases and neurodegeneration. The gut microbiome and enteric nervous system (ENS) signal to neurons and immune cells to impact both peripheral and CNS inflammation.

Peripheral neuroimmune interactions

The peripheral nervous system (PNS), which includes sensory and autonomic neurons, densely innervates organs and barrier sites throughout the body. Peripheral neuroimmune interactions critically regulate systemic and local tissue immunity. The following reviews highlight how the PNS crosstalks with immune cell types (innate lymphoid cells (ILCs), mast cells, macrophages) through molecular and cellular interactions to impact homeostasis and repair, host defense, inflammatory and allergic diseases.

ILCs are tissue-resident innate lymphocytes that rapidly respond to injury, pathogen invasion, and environmental stimuli. David Artis and Hiroshi Yano describe recent studies showing that a bidirectional neuron-ILC crosstalk regulates tissue homeostasis and immunity. ILCs are functionally regulated by neural mediators including neurotrophins (e.g. GDNF), neuropeptides (e.g. VIP, CGRP), and neurotransmitters (e.g. norepinephrine). ILCs produce cytokines and neurotransmitters that signal to neurons. Targeting neuron–ILC interactions could lead to new therapies for allergy, colitis, and other inflammatory diseases.

The skin as a barrier site is both densely innervated by the nervous system and richly populated by immune cells, mediating rapid responses to noxious stimuli and environmental threats. Sophie Ugolini and colleagues discuss the roles of neuroimmune interactions in the skin in three major

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Roland Liblau was trained as a Neurologist. He then got a Ph.D. in Immunology and went for a postdoctoral fellowship with Hugh McDevitt at Stanford. Back in France he developed research projects related to the deciphering of the pathophysiology of CNS inflammatory diseases combining original animal models and study of human samples. The aim is to propose and test new therapeutic strategies based on rational ground.

topics of interest: 1) Host response to pathogens, 2) Skin allergic and inflammatory diseases, and 3) Skin homeostasis and repair. Nociceptive sensory neurons are shown to play both proinflammatory and immunoregulatory roles depending on the neuron-derived molecule, immune cell type and context of injury or inflammation.

Mast cells are innate immune cells that play critical roles in allergic inflammation, and often are juxtaposed with nerves in peripheral tissues. Nicolas Gaudenzio and Lilian Basso focus on emerging studies showing neuron-mast cell communication in allergic diseases. In particular, they discuss how sensory nerves signal to mast cells via substance P-MrgprB2 to regulate mast cell activation, and how IgE-sensitized mast cells also signal to neurons to mediate visceral sensitivity.

Gut microbiome and neuroimmune interactions

The gastrointestinal tract is home to commensal microbial flora that impacts both the ENS, immune system, and brain. The gut-brain axis is increasingly relevant to our understanding of both neurological health and disease.

Sarkis Mazmanian and colleagues describe how the gut microbiota regulates neuroinflammation. Gut microbial metabolites including short-chain fatty acids traffic via the circulation to the brain to impact inflammation in Alzheimer's disease (AD), Parkinson's disease, and multiple sclerosis (MS). Gut microbes also regulate immune cell activation and trafficking to the CNS. Moreover, gut microbes signal via the vagus nerve connecting the gut to the brainstem, which impacts neurodegeneration and depressive behaviors.

Enteric glial cells are non-neuronal cells of the ENS whose roles in inflammation were not well understood until recently. Franze Progatzky and Vassilis Pachnis discuss current work revealing how these gut-resident cells regulate gut barrier function, immunity and host defense by crosstalk with gut epithelial cells, innate and adaptive immune cells.

Physiological immune landscape of the central nervous system, casting aside the brain immune privilege concept

Currently, one of the most dynamic topics in neuroimmunology is the precise cellular and molecular definition of the immune landscape within and around the CNS and how this immune compartment bidirectionally communicates with both CNS-resident cells and the periphery. The precise function of spinal cord- and brain-border (meninges, perivascular spaces, choroid plexus) immune cells in CNS development, homeostasis and disease is being deciphered at an extraordinary pace.

Melanie Greter and colleagues provide a detailed description of the origin and function of the different populations of brain-associated macrophages based on their anatomical location, ontogeny and single-cell molecular features. Given their strategic location and functional interface with periphery signals as well as neural cells, the authors highlight how their involvement in both CNS homeostasis and disease is only beginning to be appreciated.

Menna Clatworthy and colleagues discuss the new knowledge regarding the identification and role of meningeal B cells and antibody-producing plasma cells. These authors in particular describe how IgA-producing

plasma cells can seed the dura mater, a process dependent on the gut microbiome and expanding with age. The antibody-dependent and independent functions of these meningeal B cells go far beyond CNS defense against infection.

Neuroimmune interactions in central nervous system diseases and pathology

Building on the new knowledge related to the unexpectedly diverse and dynamic CNS immune components, the refined understanding of their individual and collective functions in disease conditions, in experimental models and in humans, will likely have major therapeutic implications. Future therapeutic targeting of CNS immune cells may indeed help regulate vascular permeability and CNS homeostasis, improve CNS surveillance, and interfere with deleterious neuroinflammatory and/or neurodegenerative processes.

Following the identification of a substantial B cell population residing in the healthy meninges, Cayce Dorrier and Dorian McGavern now explore their role in infectious diseases of the CNS as well as in MS and its animal models. Whereas in infectious diseases, these B cells and plasma cells protect the CNS and its barriers from infection, they can exhibit detrimental and regulatory functions in the context of autoimmune disease.

Tissue-resident memory T cells (T_{RM}) play key roles in immune surveillance of tissues to protect against pathogens and insults. Doron Merkler, Roland Liblau and colleagues discuss how tissue-resident memory CD8+ T cells differentiate and are maintained in the CNS, and their roles in neurologic disease. They highlight studies showing how they protect the CNS against infection, but also can contribute to chronic CNS diseases including MS and neurodegeneration.

Based on recent advances in single-cell multiomic investigations of innate and adaptive immune cells, Burkhard Becher and colleagues summarize the new knowledge gained in the pathophysiology of neuroimmune diseases and discuss the requirements to bring these evolving technologies closer to routine clinical application.

AD is an age-associated neurodegenerative disease. Marco Colonna and Yun Chen highlight recent studies showing how adaptive immune responses by B and T cells regulate the outcome of AD. They discuss how T cells are primed and recruited to accumulate in AD brains. They also discuss B cell-mediated responses against Amyloid beta, and recent work showing a meningeal B cell pool in aging. Finally, therapeutic implications of targeting adaptive immune responses in AD are discussed.

Michal Schwartz and colleagues discuss data illustrating how innate and adaptive immune cells contribute to brain homeostasis and repair and how immune dysfunction occurring early in the course of neurodegenerative diseases may accelerate disease progression. As a corollary, breaking this deleterious brain-immune loop may pave the way for innovative and efficient therapies, notably for AD.

Conclusion

This collection of 12 manuscripts is merely the tip of the iceberg of new developments in the field of neuroimmunology. They, however, document how specific neuroimmune interactions in the CNS but more widely throughout the body impact tissue development, maintenance and health. We would forcefully predict that this accumulating knowledge will have major implications in the understanding of disease pathogenesis and, in all likelihood, patient care.