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Editorial overview: Brain, gut and immune system interactions

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Isaac Chiu is Assistant Professor of Immunology at Harvard Medical School. After receiving an undergraduate degree in Biochemistry from Harvard College, he completed a PhD in Immunology at Harvard Medical School. During his postdoctoral work at Boston Children's Hospital, he discovered that nociceptor sensory neurons directly detect bacterial pathogens to produce pain. Dr Chiu's research has focused on neuro-immune interactions in host defense against pathogens. In the lungs, his lab found that vagal sensory neurons signal to T cells and neutrophils to regulate lethal bacterial pneumonia. In the skin, his lab found that *Staphylococcus aureus* activates nociceptors through pore-forming toxins and TRPV1 to produce pain. Neuro-immune interactions regulate *Streptococcus pyogenes* invasive infections and blocking this signaling could lead to a treatment for necrotizing fasciitis. In the gut, he found that nociceptor neurons regulate Peyer's patch M cells and the gut microbiome to protect against *Salmonella* enteric infections. His lab currently focuses their research on neuro-immune interactions in barrier immunity, pain, and neurodegenerative diseases.

This volume of *Current Opinion in Neurobiology* covers the latest papers that support interactions between the nervous system, immune system, and the gut microbiome. The brain is no longer considered isolated from the immune system. Immune signaling and microbial factors influence both neurological behavior and function. Neurons have also taken on non-traditional roles of regulating immunity at peripheral tissues including the skin, gastrointestinal tract, and internal organs. Finally, microbes, whether pathogenic or commensal, have been shown to signal to both neurons and immune cells to regulate physiology and inflammation. Microbes that reside at our barriers, in particular in the gut, have been shown to affect neuro-immune function.

In this volume, we focus on fundamental aspects of neuro-immune communication, how these interactions are affected by the microbiome, and how from the integrative physiology perspective, they affect health and disease.

Neuro-immune interactions occur in a bidirectional manner, where immune cells modulate neuronal function and neurons control immune function. Kaplan and colleagues discuss the parallels and interactions between the peripheral nervous system (PNS) and the immune system. The authors first discuss co-evolution of the PNS and immune system with parallel mechanisms and roles. They highlight how neurons fit into 'non-immune cells' of the innate immune system, possessing pathogen recognition and response mechanisms. Immune cells express receptors for neuron-derived ligands. Finally, they describe recent studies showing that different branches of the PNS, including both sensory and autonomic neurons coordinate immune responses.

Pain (Dolor) is a cardinal sign of inflammation driven by neuro-immune crosstalk. Ji and colleagues focus on the role of neuron–macrophage communication in pain. During tissue inflammation, macrophages release cytokines that act on nociceptor neurons to produce pain. Macrophages, in turn, respond to neuron-derived neuropeptides and chemokines. In resolution of inflammation, macrophages produce pro-resolving cytokines that inhibit nociceptor neurons and pain. MicroRNAs play an emerging role in this macrophage–neuron crosstalk.

Recent work in the model host *Caenorhabditis elegans* have revealed that neuro-immune communication plays an ancient, fundamental role in host defense. Aballay and Singh discuss two aspects of how the nervous system

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Asya Rolls is Associate Prof. at the Rappaport Medical School, Technion, Israel Institute of Technology. She is an International Howard Hughes Medical Institute (HHMI)-Wellcome investigator. Rolls studies the physiological mechanisms whereby emotions and thoughts affect physical health. Her laboratory uses chemogenetic, optogenetic, and behavioral approaches to investigate how specific brain activity affects the immune response. For example, they found that activation of the brain's reward system, a brain area active during positive expectations (e.g. placebo response), boosts antibacterial and anti-tumor imunity. By deciphering the mechanisms mediating brain-immune signals, her work aims to harness the brain's therapeutic potential.

defends against pathogens: behavioral immunity and molecular immunity. In behavioral immunity, *C. elegans* neurons sense pathogen-derived mediators to drive behavioral avoidance and protection from bacterial pathogens. In molecular immunity, *C. elegans* neural circuits control immune mechanisms in tissue protection and defense. Specific neuro-immune circuits were found to modulate unfolded protein responses, antimicrobial genes, and other key molecular pathways in innate immunity.

Irazoqui and colleagues describe how neuro-immune mechanisms in *C. elegans* relate to parallel mechanisms in mammals, with a major focus on the gastrointestinal tract. Both mammalian and *C. elegans* neurons signal to gut epithelial and immune cells to modulate antimicrobial gene expression and inflammation. Acetylcholine, dopamine, and neuropeptides play a key role in this neuro-immune signaling at the gut mucosal barrier. Therefore, studies in *C. elegans* and mammals advance basic principles of neuroimmunology and how they are conserved across evolution.

The gut is a complex mucosal barrier tissue with crosstalk between the nervous system, immune system, and microbiome. Boeckstaens and colleagues describe interactions between gut-innervating neurons and three major immune cells: macrophages, mast cells, and innate lymphoid cells (ILC). Enteric neurons crosstalk with muscularis macrophages to maintain gut homeostasis and modulate inflammation. Neurons closely associate with mast cells, and their crosstalk contributes to irritable bowel syndrome. Neurons also communicate with gut ILCs to modulate tissue homeostasis and inflammation. The gut neuro-immune axis is a rich area for future study.

Nissan Yissachar discusses how the enteric nervous system and immune system closely interact to control gut homeostasis. He attempts to untangle the complex interactions between enteric neurons, enteric glial cells, macrophages, effector and regulatory T-cells and innate lymphoid cells to highlight the major knowledge gaps in our understanding of these cellular interactions in health and disease.

The vagus nerve is a key anatomical link that connects the gut to the brain. Chang and colleagues describe recent advances in understanding vagal sensory neurons in the gut-brain-axis. Newly defined vagal afferent neuron subsets sense gut luminal contents and signal to specific brain regions (e.g. nucleus of the solitary tract, hypothalamus) to regulate food intake and satiety. The gut microbiome may regulate vagal afferent activity and neuro-immune signaling. Vagal sensory neurons also detect cytokines and immune mediators in gut inflammatory conditions.

Neuroimmunology is a field where conceptual boundaries are often broken. Traditionally, neurons are classified as producing-specific mediators, such as the neurotransmitter Acetylcholine. Olofsson and colleagues discuss the emerging role of Acetylcholine-producing lymphocytes in physiology and immunobiology. Choline acetyltransferase $(ChAT)^{+}$ T cells were discovered as part of the 'inflammatory reflex', where autonomic neurons signal to these cells to regulate splenic cytokine production. ChAT+ T cells mediate antiviral responses and modulate vasodilation, with implications for treatment of hypertension. ChAT+ B cells were also recently found to mediate antibacterial and innate immunity.

The brain was previously thought to be immune-privileged, with few avenues of communication with peripheral immune cells. Breaking this concept, Louveau and Federick highlight the recent (re)discovery of the

meningeal lymphatic system connecting the brain to peripheral immune system. The meninges is a brain-border region with a diverse immune compartment. The authors describe the meningeal lymphatic system in regulating molecular homeostasis of the cerebrospinal fluid and antigen drainage to the cervical lymph nodes. The authors discuss how dysregulation of the meningeal system may contribute to Alzheimer's disease, stroke, and other neurological diseases.

The involvement of the microbiota in neurological conditions is discussed in this volume from different perspectives; neurodegeneration, mood disorders, stroke and stress. Sauma & Casaccia, focus on the effects of gut-brain communication in demyelinating disorders such as Multiple Sclerosis (MS). MS and other autoimmune disorders are often associated with genetic predisposition and environmental variables, including gut microbiota, diet and lifestyle factors. The authors describe some of the emerging evidence that the course of the disease and immunomodulatory therapies designed to cope with it, are affected by diet and gut microbial species.

Järbrink-Sehgal & Andreasson focus on the bidirectional gut microbiota–brain axis in mental health studies in humans. These studies include evidence from interventions such as probiotic treatments and fecal transplants and highlight the relevance of microbiota modulation for depression, bipolar disorder, anxiety and stress. However, these studies are still limited and confounded by a cross-sectional design, small sample sizes, and multiple comparisons.

Specific focus on the effects of microbiota–gut–brain axis in stroke is provided by Kumar & Wong. Major risk factors of stroke are associated with gut dysbiosis and gut dysfunction, which are prevalent in clinical and experimental stroke. In this light, the authors examine the potential role of the gut microbiota in the onset, progression and recovery phase of stroke.

Koren and colleagues discuss the effects of microbiota in the establishment of the hypothalamus-pituitary-adrenocortical (HPA) axis, a crucial mediator of the stress response. The authors describe recent evidence suggesting a role for the maternal and commensal microbiota in the development of the HPA axis and of the stress response.

Some of these effects of microbiota and the gut–brain axis on the brain activity can be mediated via changes in the brain's immune compartment. Hajjo & Geva-Zatorsky discuss how the immune system can partially mediate the effects of the gut microbiota on brain development, physiology and pathology. They discuss the emerging effects of microbiota on resident microglia cells as well as the peripheral immune cells that infiltrate the brain.

Neuro-immune–microbiota interactions represent the emerging field of integrative physiology. This field attempts to understand the interactions between different physiological systems. Miguel-Aliaga and colleagues cover the effects of microbiota, nutrients, sex and ageing on the morphology and function of gastrointestinal innervation in mammals and discuss how this plasticity shapes gut-brain crosstalk and whole-body physiology.

Ezra-Nevo, Henriques & Ribeiro discuss the different components of diet such as amino acids, carbohydrates, vitamins and fatty acids and their interactions with the microbiome. They propose that diet shapes microbiome composition, and in turn, the microbiome composition can shape the effect of diet on the host. The authors propose that the effect of diet–microbiome interactions on behavior relies on the action of nutrients or diet-derived metabolites on different host cell types and organ systems.

Ronai and colleagues provide a different perspective on the systemic implications of the microbiota–neuro-immune interactions discussing the impact of the gut microbiome on anti-tumor immunity. Commensal gut microbiota or pathobionts secrete metabolites that can directly impact proximal tissues or have a systemic effect via the bloodstream. Some of these effects on the immune system have major implications on anti-tumor immunity. However, as most aspects of this field, there are major gaps in our knowledge that preclude our ability to develop Microbiota-based therapies for cancer.

In summary, the neuro-immune-microbiome axis is an area of research that is transforming our understanding of many aspects of biology and physiology. However, the field has many open questions, and translation of neuroimmunology into disease applications is nascent. Future work into interactions between the nervous system, immune system, and microbiome will require boundary-breaking and cross-disciplinary interrogations.