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Feature Review

The Regulation of Immunological Processes by Peripheral Neurons in Homeostasis and Disease

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The nervous system and the immune system are the principal sensory interfaces between the internal and external environment. They are responsible for recognizing, integrating, and responding to varied stimuli, and have the capacity to form memories of these encounters leading to learned or 'adaptive' future responses. We review current understanding of the cross-regulation between these systems. The autonomic and somatosensory nervous systems regulate both the development and deployment of immune cells, with broad functions that impact on hematopoiesis as well as on priming, migration, and cytokine production. In turn, specific immune cell subsets contribute to homeostatic neural circuits such as those controlling metabolism, hypertension, and the inflammatory reflex. We examine the contribution of the somatosensory system to autoimmune, autoinflammatory, allergic, and infectious processes in barrier tissues and, in this context, discuss opportunities for therapeutic manipulation of neuro-immune interactions.

Introduction

The idea of mutual influences between the manifestations of neuronal activity and the other organ systems of the body can be traced back to antiquity when the Roman poet Decimus Iunius Iuvenalis (1st to 2nd Century AD) famously coined the phrase '*mens sana in corpore sano*' ('sound mind in a sound body'). For centuries, this concept has stimulated countless explorations by philosophers, psychologists, clinicians, and biologists who traditionally have focused their inquiries on interactions between neuroendocrine and/or higher cerebral functions with non-neuronal organs, including the innate and adaptive immune system. However, research during the past few years has generated mounting experimental evidence for an additional functional link that is based on interactions between the peripheral nervous system (PNS) and the immune system.

Early observations of commonalities between these two systems date back to the original discovery of some of their key components. Indeed, some canonical molecules and cell types that have become a focus of research for either neuroscientists or immunologists were actually discovered in tissues whose primary function was considered to be the domain of the other field.

Trends

Homeostasis: macrophages have been identified as key components of neurally-mediated circuits in various tissues including the gut, where they contribute to motility, and in adipose tissue, where they aid in thermogenesis.

Barrier tissues: dendritic cells are found in close proximity to sensory neurons in the skin, gut, and lung, and the evidence suggests that they integrate signals from distinct neuronal subsets with either pro- or anti-inflammatory outcomes.

Infection: pain during some cutaneous bacterial infections can be a direct result of bacterial products acting on sensory neurons rather than secondary to inflammatory processes.

Subsets: an enhanced molecular understanding of neural and immune cell ontogeny and function has led to the generation of tools for ablation or functional modulation of specific cell subsets.

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A prominent example is the description by Paul Langerhans in 1868 of an epidermal subset of dendritic cells (DCs), which he hypothesized to function as sensory neurons [1]. It took over a century for biologists to recognize that what we now call Langerhans cells are actually not of neuronal but of hematopoietic origin, and that they function as prototypical antigen-presenting cells (APCs) [2,3].

Similarly, acetylcholine, a hallmark neurotransmitter of cholinergic neurons, was originally isolated from a major lymphoid organ, the spleen [4]. While acetylcholine was soon understood to have a crucial role as a neurotransmitter at neuromuscular junctions and in the parasympathetic nervous system, its source and role in splenic immunity took decades to decipher [5–8]. Recent work has identified a subset of memory T cells (Tmem) as a key source of acetylcholine in the spleen, while splenic innervation is predominantly adrenergic in nature [7–9].

Does then acetylcholine belong to the nervous system, and are Langerhans cells and other DCs merely of relevance in immunology? All too often, the serendipitous history of discovery of a biological process dictates its perceived relevance to a given field [10,11]. The emergence of field-specific vocabulary and the use of buzzwords as shorthand to describe complex biological processes often stymie the uninitiated and impede information exchange. Notwithstanding, classifications are often helpful and even necessary [12–14]. However, as our understanding of interactions between the nervous system and the immune system continues to deepen, the once clear-cut material and functional boundaries have faded.

In this review we aim to integrate classical work and thinking in the field of neuro-immunology [15] with our contemporary cellular and molecular understanding of both systems [16,17]. We start with an overview of the PNS and provide a toolbox (Box 1) for how neuro-immune interactions can be studied. We then discuss how the autonomic and somatosensory PNS regulates the development, deployment, and homeostasis of the immune system. Finally, we explore the role of the somatosensory system in autoimmune, autoinflammatory, allergic, and infectious processes, particularly in barrier tissues, and we contemplate opportunities for therapeutic manipulation of neuro-immune interactions.

Box 1. Experimental Strategies to Study Neuro-Immune Interactions

The standard techniques to investigate neuro-immune interactions include several experimental strategies. The most reductionist approach relies on exposing leukocyte subsets *in vitro* to specific neurotransmitters or neurotransmitter receptor agonists and/or antagonists. This strategy provides high mechanistic resolution and allows exacting investigations of the underlying cellular biology, but it typically cannot identify a neuronal source, location, or physiological role. A related approach employs receptor agonists or antagonists *in vivo*. This strategy can provide clues that a candidate pathway is active in a physiological setting, but it can be difficult to assess if the observed effects on the immune system are direct or indirect. One approach to address this question involves technically-demanding co-cultures of isolated DRG neurons with purified leukocyte subsets [212]. A more widely used *in vivo* strategy makes use of selective elimination of specific neuronal activities. For example, pharmacological agents, such as capsaicin and resiniferatoxin (RTX) can ablate $TRPV1^+$ heat-sensing neurons, and 6-hydroxydopamine (6-OHDA) can transiently deplete catecholamine stores by interfering with neurotransmitter recycling [247,248]. These agents enable pharmacological interrogation of specific neuronal subsets, but are typically used on a systemic level. More recently, investigators have implemented genetic models of neural ablation based on the diphtheria toxin system to either constitutively or conditionally ablate neurons by targeted expression of diphtheria toxin or its receptor in neuronal populations that are defined by expression of lineage-specific markers [27,28,30,249]. These systems allow the cleanest genetic interrogation of specific neuro-immune interactions, but their interpretation can be challenging in light of the complex and dynamic expression patterns of ion channels during neuronal development.

In-depth molecular understanding of the PNS together with the recent advent of chemicogenetic and optogenetic approaches afford an unprecedented opportunity to genetically target neuronal populations of interest for functional studies [250,251]. So far, these tools have been utilized mainly to map neural circuits in fine detail by activating or inhibiting specific populations of neurons in a genetically and regionally defined fashion. Their use should also be very informative to study neuro-immune interactions.