Immunity
Review

Mechanisms and Therapeutic Relevance of Neuro-immune Communication

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http://dx.doi.org/10.1016/j.immuni.2017.06.008

Active research at the frontiers of immunology and neuroscience has identified multiple points of interaction and communication between the immune system and the nervous system. Immune cell activation stimulates neuronal circuits that regulate innate and adaptive immunity. Molecular mechanistic insights into the inflammatory reflex and other neuro-immune interactions have greatly advanced our understanding of immunity and identified new therapeutic possibilities in inflammatory and autoimmune diseases. Recent successful clinical trials using bioelectronic devices that modulate the inflammatory reflex to significantly ameliorate rheumatoid arthritis and inflammatory bowel disease provide a path for using electrons as a therapeutic modality for targeting molecular mechanisms of immunity. Here, we review mechanisms of peripheral sensory neuronal function in response to immune challenges, the neural regulation of immunity and inflammation, and the therapeutic implications of those mechanistic insights.

Introduction

The immune system and the nervous system evolved to provide regulation of physiological homeostasis and protect against threats. The immune system defends against infection and injury through inflammation. If unresolved, however, inflammation can also be deleterious, for instance, in inflammatory and autoimmune disorders. The nervous system integrates biological functions and provides a nearly instantaneous homeostatic control mechanism by releasing neurotransmitters and other regulatory molecules. These two systems have perfected evolutionary features that allow for the recognition of alterations and threats in the ever-changing microenvironment, the mounting of protective responses, and memory development to facilitate these protective responses upon encounters with similar alterations in the future. Interaction between neurons and immune cells, and their communication and functional cooperation, is integral to homeostasis and species survival.

Neuro-immune interaction with biological consequences have been identified in evolutionarily ancient animals: neurons in the primitive nervous system of the soil nematode *Caenorhabditis elegans* regulate innate immune responses, including a non-canonical unfolded protein response pathway (Sun et al., 2011). Studies in rodents and humans have identified molecular components of neuro-immune interaction reciprocally shared between the two systems. In addition to immune cells, the expression of pattern-recognition receptors (PRRs), including Toll-like receptors (TLRs), and cytokine receptors has been demonstrated on neurons, providing a molecular substrate for simultaneous modulation of immune and neuronal function by pathogen-associated molecular patterns (PAMPs), cytokines, and other immune molecules (Hosoi et al., 2005; de Lartigue et al., 2011; Li et al., 2005; Steinberg et al., 2016; Park et al., 2014; Xu et al., 2015). The expression of receptors for neurotransmitters, including acetylcholine receptors and adrenergic receptors, has been identified on macrophages, dendritic cells, T cells, and other immune cells, facilitating neural regulation of immune responses (Wang et al., 2003; Kawashima et al., 2012; Kawashima et al., 2015). Immune cells also synthesize and release substances classically designated as neurotransmitters and neuromodulators, including acetylcholine, dopamine, and other catecholamines with a role in local immune regulation and in more complex neuroimmunomodulatory circuitry (Rosas-Ballina et al., 2011; Kawashima et al., 2012; Marino and Cosentino, 2013). This common repertoire is utilized in the integration of immune and neural communication through neural circuits triggered by a stimulus (e.g., infection or injury) and culminating in a response-regulating immune function (e.g., inhibition of tumor necrosis factor [TNF] or stimulation of dendritic cells).

Reflexes are composed of sensory (afferent) neurons activated by a stimulus and motor (efferent) neurons that release molecules to generate a response. As discussed here, recent discoveries have revealed several neuroimmunoregulatory circuits organized by these principles of reflex regulation (Tracey, 2002; Chavan and Tracey, 2017; Talbot et al., 2016). Here, we provide an analytical review of mechanisms interfacing the immune and the nervous system and the role of neural pathways in the regulation of immunity. We also provide an abridged summary of the therapeutic implications of neuromodulation in animal models of inflammatory and autoimmune disease, and the recent successful translation of these findings in clinical trials.

Mechanisms and Principles of Neuro-immune Communication

Interactions between neurons and immune cells are multifactorial and multidimensional. In the central nervous system (CNS), interactions between myeloid cells and neurons play an important role in CNS homeostasis, as well as in pathophysiological states, including autoimmunity, neurodegeneration, infection, and mechanical injury (Herz et al., 2017, in this issue of *Immunity*). CNS injuries also elicit astrocyte protective and harmful phenotypes (Liddelow and Barres, 2017, in this issue of

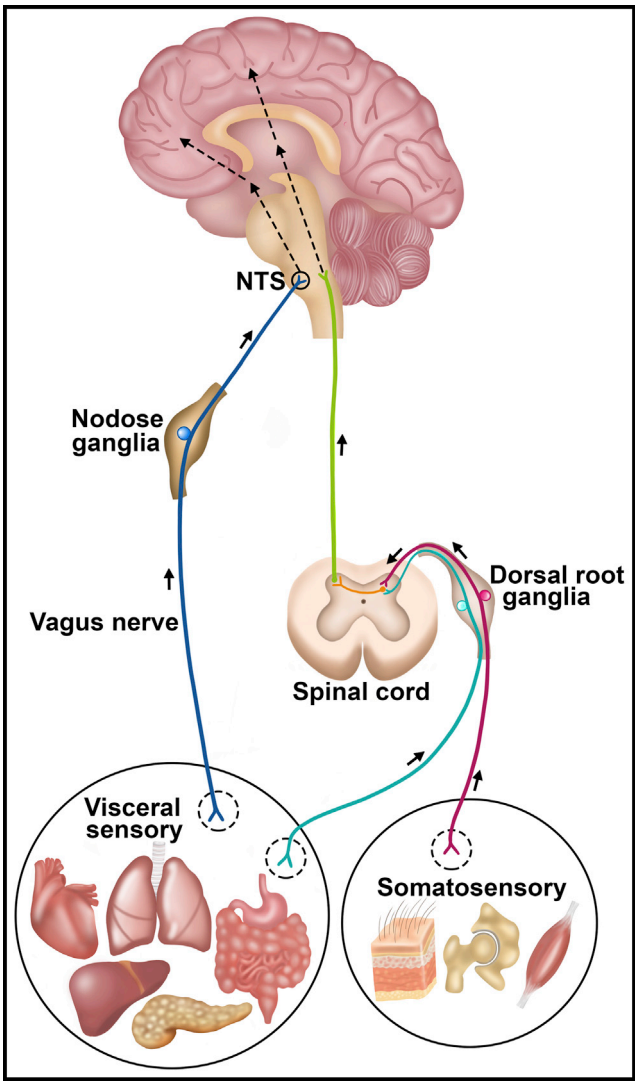

Figure 1. Anatomy of Sensory Neurons with a Role in Neuro-immune Interaction

Sensory neurons with cell bodies in the dorsal root ganglia are somatosensory and visceral. Somatosensory neurons (innervating the skin, joints, and muscles) and visceral neurons (innervating the gastrointestinal track, pancreas, liver, lungs, heart, and other organs) enter the spinal cord via the dorsal horn. In the spinal cord, central axonal terminals of these neurons make synaptic contacts with interneurons and relay neurons transmitting the signals to the brainstem and other brain areas. Vagus sensory neurons originate in the nodose ganglia (anatomically divided into nodose and jugular ganglia in rats and humans) and innervate visceral organs, including the gastrointestinal tract, pancreas, liver, lungs, heart, and other organs. Most of their central axons terminate in the nucleus tractus solitarius (NTS) and project to other brainstem and forebrain areas. The activity of somatosensory and visceral neurons communicating peripheral information to the CNS is altered in inflammatory and autoimmune conditions affecting the innervated areas in visceral and somatic organs and tissues.

Immunity). A complex interplay between neuro-protective and damaging innate and adaptive immune responses has been described in CNS infections (Klein and Hunter, 2017, in this issue of *Immunity*). In addition to occurring in the CNS, neuro-immune interactions with an important role in homeostasis occur in the gut, where neurons of the enteric nervous system and immune cells communicate in responding to a variety of dietary products and pathogens (Yoo and Mazmanian, 2017, in this issue of *Immunity*). Neuro-immune communication in peripheral sites of injury and infection and integrated neuromodulatory responses have been actively studied. The activity of afferent (sensory) neurons is modulated by alterations in immune cell function, and sensory neurons importantly participate in immune regulation. Neural output from efferent (motor) autonomic neurons is also a potent regulator of immunity. Afferent and efferent neural circuits organized in a reflexive manner operate to regulate immune responses and inflammation. In the next sections, we review important aspects of the current understanding of the neuro-immune dialog and its functional anatomy, molecular mechanisms, and clinical relevance.

The Immune Impact on Afferent Neuronal Function

Sensory neurons transmit information about alterations in the environment to the CNS. Somatosensory neurons innervate the skin, muscles, and joints, whereas visceral sensory neurons innervate virtually all internal organs. Sensory neurons are also classified as spinal, in which cell bodies are located in the dorsal root ganglia (DRGs) and project to the spinal cord, and vagal (visceral), in which cell bodies are located in the nodose and jugular ganglia and project to the brainstem (Mazzone and Undem, 2016; Berthoud and Neuhuber, 2000) (Figure 1). Peripheral alterations that activate sensory neurons importantly include immune cell activation with the release of cytokines and other signaling molecules (Figure 2). Immune cell activation occurs in response to pathogen invasion and sterile tissue injury and is triggered by the interaction between PAMPs or damage-associated molecular patterns (DAMPs) and PRRs (Akira et al., 2006; Takeuchi and Akira, 2010). These receptors include TLRs and the nucleotide-binding domain, leucine-rich-repeat-containing proteins (NLRs) on macrophages and other immune cells (Akira et al., 2006; Takeuchi and Akira, 2010; Davis et al., 2011). These interactions result in the activation of intracellular pathways mediated by NF-κB, AP-1, and other transcription factors, as well as activation of the inflammasome and increased synthesis of cytokines, including TNF, interleukin-6 (IL-6), IL-1β, chemokines, and other immune molecules (Akira et al., 2006; Takeuchi and Akira, 2010; Davis et al., 2011). These molecules mediate inflammation by acting on immune cells and the endothelium, leading to enhanced cytokine production, vasodilation, increased vascular permeability, and attraction of leukocytes and plasma proteins to the inflammatory loci (Akira et al., 2006; Medzhitov, 2008; Takeuchi and Akira, 2010; Tracey, 2002; Nathan and Ding, 2010).

Peripheral immune cell activation with the release of cytokines and other inflammatory molecules has an impact on sensory neurons in the sites of infection or injury and triggers or alters signaling to the CNS—the spinal cord and brain (Chiu et al., 2013; Niijima, 1996; Goehler et al., 2000; Ordovas-Montanes et al., 2015; Binshtok et al., 2008; Lai et al., 2017; Figure 2). A major class of sensory (somatosensory) neurons is the nociceptors, which are preferentially sensitive to noxious stimuli, including heat and mechanical stimulation, or to a stimulus that would become noxious if prolonged (Dubin and Patapoutian, 2010). One of the cardinal features of inflammation is pain, and nociceptors are important peripheral mediators of pain perception (Dubin and Patapoutian, 2010; Pinho-Ribeiro et al., 2017).

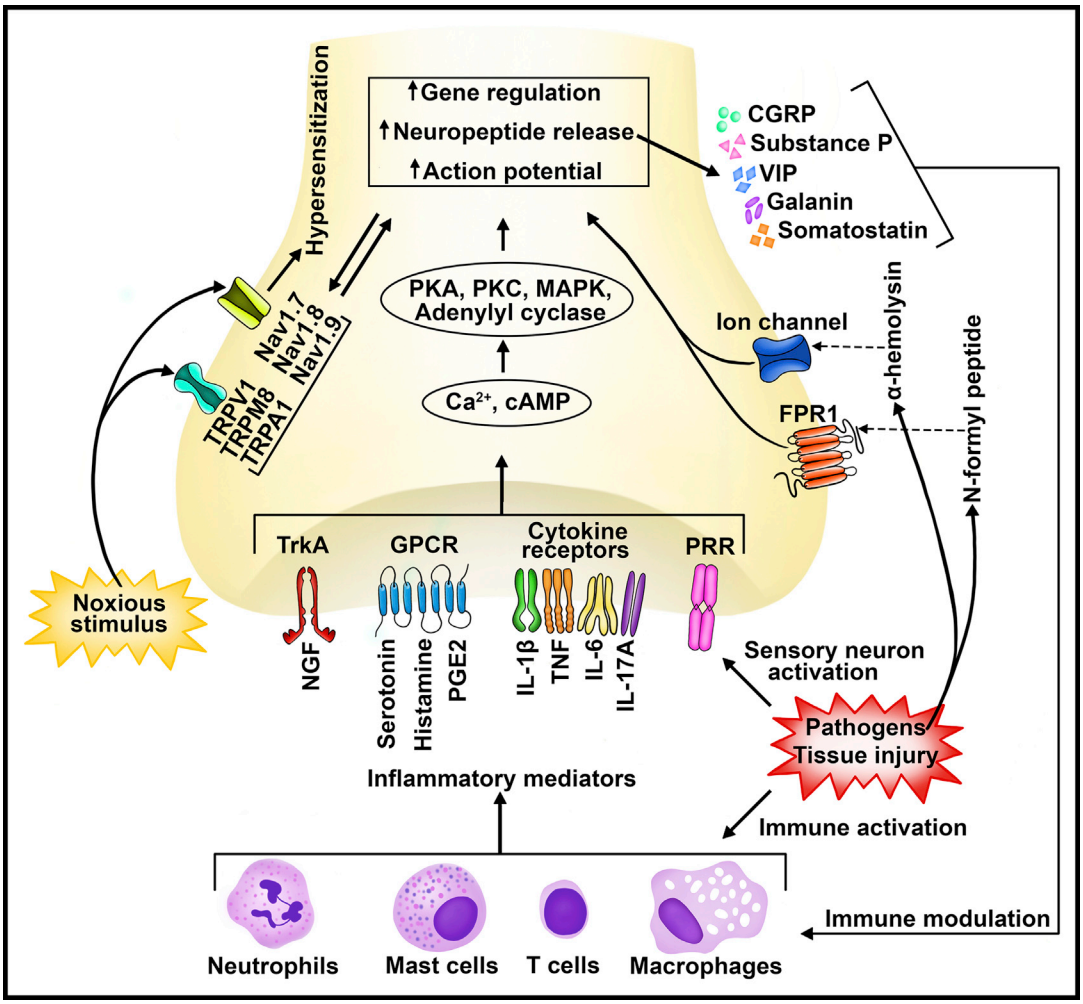

Figure 2. Molecular Mechanisms at the Immune-Sensory-Neuron Interface

Pathogens or tissue injury results in the release of inflammatory mediators, such as pro-inflammatory cytokines (tumor necrosis factor [TNF], interleukin-1β, IL-6, and IL-17), nerve growth factor (NGF), prostaglandins (PGE2), serotonin, and histamine, by immune cells. Both pathogens and inflammatory mediators can modulate the activity of sensory neurons in the local area. Cytokines and other inflammatory mediators act on receptors expressed on peripheral axonal terminals of sensory neurons, including cytokine receptors, G-protein-coupled receptors (GPCRs), and tyrosine kinase receptor type 1 (TrkA). As with immune activation, pathogens can cause sensory neuronal activation mediated by the interaction between pathogen-associated molecular patterns (PAMPs) and pattern-recognition receptors (PRRs, such as TLR4) on neurons. The secretion of *N*-formyl peptide and α-hemolysin by the pathogen *S. aureus* can directly activate sensory neurons by binding to formyl peptide receptor 1 (FPR1) or ion channel oligomerization and depolarization. Activation of sensory neurons by pathogens or inflammatory mediators leads to the generation of secondary messengers such as Ca^{2+} and cAMP, which in turn activate intracellular kinases such as adenylyl cyclase, protein kinases A (PKA) and C (PKC), and mitogen-activated protein kinase (MAPK). Activation of this signaling cascade results in action-potential generation and plasticity-associated gene regulation. It also decreases the threshold for activation of key neuronal receptors, such as transient receptor potential cation channel subfamily A member 1 (TRPA1), TRPV1, and TRPM8, as well as the voltage-gated sodium channels $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$, by noxious stimuli, e.g., hypersensitization. Neuronal activation by pathogens and inflammatory stimuli also causes the release of neuropeptides, which in turn modulate inflammatory responses. Vasoactive intestinal peptide (VIP), substance P, and calcitonin gene-related peptide (CGRP) are involved in the generation of neurogenic inflammation. CGRP, somatostatin, and galanin suppress lymphadenopathy and inflammation in bacterial infection.

Somatosensory neurons, including nociceptors, are pseudounipolar cells with a single process that is a bidirectional axon; peripheral axon terminals innervate the skin, joins, and other peripheral tissue, and the central axon projects to spinal cord neurons in the dorsal horn (Dubin and Patapoutian, 2010; Figure 1). The central axonal branches release glutamate and other substances and synapse with spinal interneurons and relay neurons. The spinal relay neurons in turn project to the brainstem, thalamus, and other brain areas. Neural networks between these regions and the somatosensory and anterior cingulate cortex mediate cognitive aspects of pain and homeostatic coordination (Heinricher et al., 2009; Dubin and Patapoutian, 2010). Descending brain neural pathways provide modulatory control of spinal nociceptive loci (Heinricher et al., 2009). Nociceptors include two major types of neurons, which can be further subdivided according to the molecular expression profile of the receptors, ion channels, and release of specific neuropeptides. Non-myelinated, slow-conducting C-fiber nociceptor neurons are generally associated with thermal pain sensitivity and are capsaicin sensitive. Myelinated faster-conducting Aβ and lightly myelinated Aδ

nociceptor neurons are major mediators of mechanical stimuli, resulting in pain (Pinho-Ribeiro et al., 2017). Peripheral axons of nociceptive neurons and their somata contain voltage-gated sodium channels, including $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$, which play an important role in depolarization and the generation of action potentials initiated by noxious stimuli. Another class of important protein molecules mediating thermal and mechanical pain is the family of transient receptor potential (TRP) ion channels (Julius, 2013). Two abundantly expressed members of this family are TRPV1 and TRPM8; TRPV1 is capsaicin sensitive and plays a critical role in the induction of heat hypersensitivity, whereas TRPM8 mediates cold hypersensitivity. In addition, TRPA1 mediates chemical and mechanical pain sensitivity (Pinho-Ribeiro et al., 2017).

Peripheral axon terminals of nociceptors are located in proximity to macrophages, neutrophils, mast cells, and other immune cells, and this proximity and the expression of receptors for cytokines, lipids, growth factors, and other immune signaling molecules on nociceptors facilitate immune modulation of nociceptor function. Cytokines (such as TNF, IL-1β, IL-6, and IL-17A) and other inflammatory molecules (including serotonin [5-HT], histamine, prostaglandins, and nerve growth factor) activate these receptors in allergy, infection, and tissue damage (Schaible, 2014; Pinho-Ribeiro et al., 2017; Nicol et al., 1997; Woolf et al., 1997; Figure 2). In addition, interactions between cytokines and sensory neurons have been described in itch; for instance, the epithelial-cell-derived cytokine thymic stromal lymphopoietin acts on a subset of TRPA1-positive sensory neurons to trigger itch in atopic dermatitis, a condition of chronic itch and skin inflammation (Wilson et al., 2013). Sensory neurons are also activated by pathogenic and commensal bacteria via specific metabolites and toxins (Chiu et al., 2013; Lai et al., 2017). This activation triggers intracellular mechanisms, resulting in modulation of the gating properties of $Na_v1.7$, $Na_v1.8$, $Na_v1.9$, TRPV1, and TRPA1 and in a reduced threshold for nociceptor neurons to fire action potentials. This ultimately leads to increased pain sensitivity or "hyperalgesia" in inflammatory conditions (Binshtok et al., 2008; Pinho-Ribeiro et al., 2017; Talbot et al., 2016; Schaible, 2014; Figure 2). IL-1β and other cytokines can also activate sensory neurons directly through interaction with their receptors (Binshtok et al., 2008). TRPV1-expressing nociceptors innervating the gastrointestinal tract are important mediators of abdominal pain in inflammatory bowel disease (IBD). These fibers can be also activated by cytokines, other immune cell products, and bacterial toxins (Lai et al., 2017; Goehler et al., 2000). Cytokines and other immune signaling molecules also act on the somata of nociceptor neurons in the DRGs and affect neuroplasticity and long-term pain sensitization (Schaible, 2014; Pinho-Ribeiro et al., 2017). Particular mechanisms of cytokine sensitization and activation of nociceptors and their role in mechanical and thermal hyperalgesia have been reviewed elsewhere (Talbot et al., 2016; Pinho-Ribeiro et al., 2017; Lai et al., 2017; Woolf et al., 1997; Nicol et al., 1997; Jin and Gereau, 2006; Binshtok et al., 2008).

In addition to providing a primary neuronal output for processing pain sensation to the CNS, nociceptors are potent regulators of immune cell function and inflammation. Activation of peripheral axon terminals of nociceptors by noxious stimuli and bacterial infection causes the release of calcitonin gene-related peptide (CGRP), substance P (SP), vasoactive intestinal peptide (VIP), and other neuropeptides. These substances act via their cognate receptors on immune cells and vasculature and promote or suppress inflammation (Talbot et al., 2016; Pinho-Ribeiro et al., 2017; Chiu et al., 2013). For instance, the release of SP, CGRP, and VIP from spinal nociceptors innervating the gastrointestinal tract has been shown to have protective or deleterious effects on the regulation of colonic inflammation, as shown in IBD mouse models (Lai et al., 2017). Spinal sensory neurons also play a role in the regulation of inflammation in arthritis (Schaible, 2014). The interplay between immune cells and sensory neurons could occur via axon reflex mechanisms described in one of the next sections of this review.

Afferent vagus nerve fibers have their cell bodies localized in the nodose ganglion and in the jugular ganglion (Mazzone and Undem, 2016; Figure 1). These neurons are also pseudounipolar cells with peripheral axonal terminals in internal organs (including the airways, lungs, gastrointestinal tract, pancreas, liver, bile ducts, and portal vein) and central axon terminals projecting predominantly to the nucleus tractus solitarius (NTS) (Mazzone and Undem, 2016; Berthoud, 2004; Berthoud and Neuhuber, 2000). Afferent vagus innervations of the dorsal motor nucleus of the vagus (DMN), area postrema, and the trigeminal islands have also been shown (Berthoud and Neuhuber, 2000). The nodose and jugular ganglia are anatomically distinct in rats and humans in that the jugular ganglion is much smaller, whereas in mice the two ganglia are fused and are commonly designated as the nodose ganglion (Mazzone and Undem, 2016). Vagal afferents are about 80% of the vagus nerve, and the central axon terminal releases glutamate as a main neurotransmitter in the NTS, which is viscerotopically organized (Browning et al., 2017; Berthoud and Neuhuber, 2000). Whereas nodose ganglion neurons provide abundant innervations to visceral organs, vagal afferents in the jugular ganglion preferentially innervate the airways and the esophagus (Mazzone and Undem, 2016; Kollarik et al., 2010). Vagal sensory neurons can be classified according to fiber conduction velocities and mechanical and chemical sensitivity. The proportion of non-myelinated, slow-conducting C-fibers to myelinated A-fibers (Aδ and Aβ) is about 8:1, and subdiaphragmatic afferent neurons are almost entirely unmyelinated (Mazzone and Undem, 2016). On the basis of physiological responsiveness, vagal afferents can be grouped into mechanosensitive fibers represented by C-fibers and chemical-sensitive afferents activated by a variety of chemical stimuli but less sensitive to mechanical stimuli (Mazzone and Undem, 2016). Vagal afferents are important mediators of satiety and respond to alterations in the levels of cholecystokinin, leptin, glucagon-like peptide 1, peptide YY, and other nutrients and metabolic molecules (Browning et al., 2017; Pavlov and Tracey, 2012). Their activity is also modulated by gut motility and intestinal distention, and the recent genetic molecular profiling of gastrointestinal vagal afferents has characterized subsets of neurons specifically associated with these functions (Williams et al., 2016). Vagal sensory neurons with properties of nociceptors have also been described and are predominantly C-fibers (Mazzone and Undem, 2016). The expression of the capsaicin-sensitive TRPV1, which is frequently co-localized with TRPA1, is commonly associated with this subtype of vagal sensory neuron (Nassenstein et al., 2008; Mazzone and Undem, 2016; Kollarik et al., 2010).

These fibers with cell bodies in both the nodose and jugular ganglia have different molecular phenotypes and central locations and are associated with different physiological responses (Kimura et al., 2016). The expression of $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ has also been determined in nociceptor-type vagal sensory neurons, specifically in the airways (Mazzone and Undem, 2016).

Vagal sensory neurons are activated during viral or bacterial infection, tissue damage, and allergenic exposure in the airways (Mazzone and Undem, 2016). The release of cytokines (such as IL-1β and TNF) and other inflammatory mediators (including prostaglandins, serotonin, and ATP from macrophages, neutrophils, mast cells, and eosinophils) has a major impact on vagal afferent terminals in the airways and lungs (Mazzone and Undem, 2016). These immune cell signaling molecules cause peripheral neuron sensitization, characterized by a decreased threshold needed for evoking action potentials or directly inducing neuronal activation (Mazzone and Undem, 2016; Browning et al., 2017). Afferent neurons within the subdiaphragmatic vagus nerve, innervating the gastrointestinal tract, are in position to detect gastrointestinal pathogens, including *Campylobacter jejuni*, and signal the brain (Lai et al., 2017; Goehler et al., 2005). Oral inoculation with *C. jejuni* results in increased c-Fos immunoreactivity in vagal sensory ganglia and, in a time-dependent manner, in the NTS and other brainstem and forebrain regions, including the area postrema, the ventrolateral medulla, the locus coeruleus, the thalamus, different hypothalamic nuclei, the amygdala, and the insular cortex. This neuronal activation occurs in the absence of increased circulating levels of pro-inflammatory cytokines, including TNF and IL-1β. Although the mechanisms of the pathogen-sensory-neuron interactions leading to neuronal activation remain to be elucidated, these findings establish vagus sensory neurons as a pathway for early signaling of gut infection to the brain. A similar profile of c-Fos brain neuronal alterations has been shown to follow peripheral endotoxin (liposaccharide [LPS]) administration in association with symptoms of behavioral depression, including social withdrawal (Marvel et al., 2004). Interestingly, transient neuronal inactivation in the dorsal vagus complex (DVC), where primary vagal afferents terminate, abolishes this pattern of c-Fos brain activation and alleviates behavioral derangements (Marvel et al., 2004). The release of IL-1β and other cytokines from macrophages, neutrophils, dendritic cells, and other immune cells in inflammatory conditions activates vagal afferent signaling to the brain, which plays a role in mediating fever and sickness (Goehler et al., 2000; Capuron and Miller, 2011). Early studies have demonstrated activation of viscerosensory vagal afferent signaling by peripheral (intraperitoneal [i.p.]) administration of LPS or IL-1β (Gaykema et al., 1998; Goehler et al., 1998; Goehler et al., 1999). Intravenous IL-1β activates rat vagal afferents directly or in a prostaglandin-dependent manner supported by the expression of IL-1 and prostaglandin E2 receptors on peripheral axonal endings and the somata of these neurons in the nodose ganglion (Ek et al., 1998). Activation of vagal afferents by cytokines or bacterial products is mediated by cytokine receptors or PRRs (TLR4) expressed on these neurons or via chemosensory cells in the associated vagal paraganglia (Hosoi et al., 2005; de Lartigue et al., 2011; Goehler et al., 2000; Goehler et al., 1999; Figure 2). A very recent study provided an important insight into the mechanisms underlying the information transfer of inflammatory conditions to afferent nerves (Steinberg et al., 2016). Electrophysiological recording of cervical vagus nerve activity in mice after peripheral (i.p.) administration of TNF or IL-1β demonstrated neuronal activation and specific patterns of compound action potentials by these pro-inflammatory cytokines. Sensory vagus neurons express TNF and IL-1 receptors, as well as receptors for other cytokines. Transecting the vagus nerve distal to the recording electrode ablates the electrical signals, indicating that this neuronal activity is mainly associated with afferent signaling. Genetic ablation of cytokine receptor expression abolishes the cytokine-induced vagus nerve activation. These observations demonstrate specific patterns of vagus nerve activity, e.g., "cytokine neurograms," in response to inflammatory challenges (Steinberg et al., 2016).

Efferent Neurocircuitry in the Regulation of Immunity

Efferent autonomic (visceral) nerves provide a conduit for brain-to-periphery communication with important regulatory functions. Efferent vagus nerve fibers originate in the DMN and nucleus ambiguus (NA) in the brainstem medulla oblongata. The DMN, NTS, and area postrema constitute the DVC, an important regulatory and integrative unit in the brainstem (Berthoud and Neuhuber, 2000; Pavlov et al., 2003). Efferent vagus neurons with somata in the DMN give preganglionic projections to visceral organs in the thoracic and abdominal cavity, including the lungs, heart, liver, gastrointestinal tract, kidneys, and pancreas (Figure 3). Efferent vagus neurons with cell bodies in the NA predominantly innervate the heart, and to a lesser extent, other visceral organs. Vagus nerve preganglionic fibers interact with postganglionic vagus nerve fibers in close proximity to or within the innervated organs through the release of acetylcholine. Postganglionic fibers predominantly release acetylcholine, which interacts with muscarinic acetylcholine receptors (mAChRs; five subtypes of G-protein-coupled receptors) on cardiac myocytes, smooth muscle cells, and glandular cells to modulate bronchoconstriction, gastrointestinal motility and secretion, heart rate, pancreatic exocrine and endocrine secretion, and other physiological functions.

Experiments with electrical vagus nerve stimulation nearly 20 years ago demonstrated for the first time that efferent vagus nerve fibers provide a conduit for brain-to-immune communication to control the production of TNF and other pro-inflammatory cytokines through the release of acetylcholine (Borovikova et al., 2000). This neuronal circuit was termed "the cholinergic anti-inflammatory pathway" (Borovikova et al., 2000; Pavlov et al., 2003; Tracey, 2007). In contrast to its classical regulatory functions, which are mediated through muscarinic receptors, the vagus nerve cholinergic anti-inflammatory activity is exerted through alpha 7 nicotinic acetylcholine receptor (α7nAChR) expressed on macrophages, dendritic cells, and other immune cells (Wang et al., 2003; Gallowitsch-Puerta and Pavlov, 2007; Olofsson et al., 2012). Delineating intracellular mechanisms downstream of α7nAChR has indicated a role for inhibition of the nuclear translocation of the transcription factor NF-κB and activation of the JAK2-STAT-3 pathway in the suppression of pro-inflammatory cytokine production (Guarini et al., 2003; de Jonge et al., 2005). An inflammasome-mediated anti-inflammatory effect of acetylcholine has been also reported (Lu et al.,

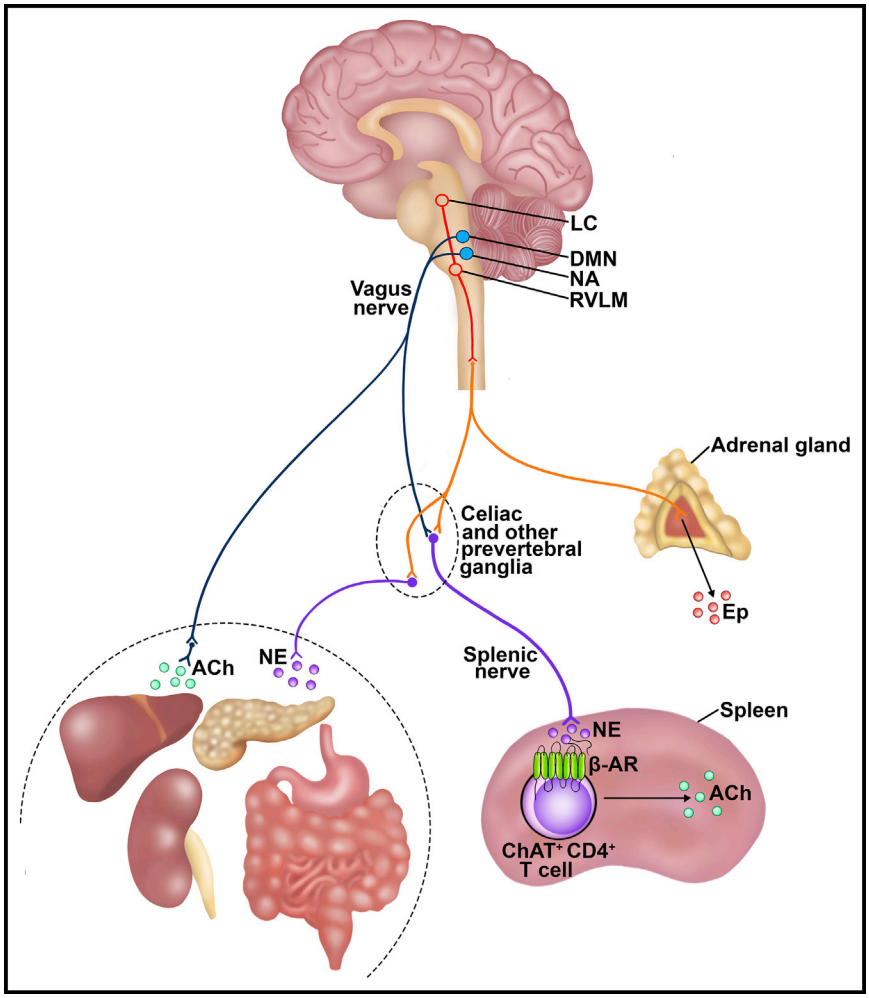

Figure 3. Anatomy of Efferent Autonomic Neurons with a Role in Immune Regulation

Efferent vagus nerve neurons originate in the dorsal motor nucleus of the vagus (DMN) and nucleus ambiguus (NA) in the brainstem medulla oblongata. These preganglionic cholinergic neurons give projections to visceral organs in the thoracic and abdominal cavity, including the lungs, heart, liver, gastrointestinal tract, kidneys, and pancreas. They interact with postganglionic vagal neurons in proximity to or within the innervated organs, and these neurons predominantly release acetylcholine. Vagus nerve preganglionic neurons also terminate in the celiac ganglia and the superior mesenteric ganglion, where the splenic nerve originates. Splenic nerve catecholaminergic neurons release norepinephrine (NE) in the spleen. NE interacts with β adrenergic receptors on choline acetyltransferase $(ChAT)^+CD4^+$ T cells and causes the release of acetylcholine. The locus coeruleus (LC) and the rostroventrolateral medula (RVLM) are brain regions associated with sympathetic control. The RVLM gives descending projections to sympathetic neurons in the spinal cord. Sympathetic preganglionic (cholinergic) fibers project to paravertebral (not shown) and prevertebral ganglia, including the celiac ganglia. Postganglionic fibers predominantly release NE in the innervated visceral organs. Postganglionic fibers from paravertebral ganglia innervate the lungs and the heart (not shown). Postganglionic fibers from perivertebral ganglia innervate the liver, gastrointestinal tract, kidneys, pancreas, and other visceral organs. Sympathetic preganglionic fibers also innervate the adrenal medulla and stimulate the secretion of epinephrine (Ep) from chromaffin cells.

2014; Figure 4). An important role for this pathway has been indicated in controlling inflammation in the viscera, which is directly innervated by the vagus nerve, in several inflammatory conditions (Pavlov, 2008; Tracey, 2007). Electrical vagus nerve stimulation suppresses hepatic, cardiac, and circulating TNF levels, and vagotomy abrogates these effects during murine endotoxemia (Borovikova et al., 2000; Bernik et al., 2002). Vagus nerve stimulation also suppresses the inflammatory cascade triggered by NF-κB activation in the liver, decreases hepatic and serum TNF, and improves survival in a model of hemorrhagic shock; vagotomy abolishes these effects (Guarini et al., 2003). Vagotomy or pharmacological blockade of nAChRs enhances the severity of murine pancreatitis and increases IL-6 levels, whereas treatment with an α7nAChR agonist (GTS-21) substantially alleviates pancreatitis (van Westerloo et al., 2006). Vagus nerve stimulation alleviates surgery-induced inflammation and postoperative ileus by activating STAT3 in intestinal macrophages (de Jonge et al., 2005). STAT3 phosphorylation by the tyrosine kinase Jak2 recruited to the α7nAChR is an underlying intracellular mechanism in this model (de Jonge et al., 2005). A protective role of α7nAChR-mediated cholinergic signaling along the vagus nerve in IBD has also been indicated in studies using vagotomy and pharmacological interventions and murine models of colitis (Ghia et al., 2006; Ghia et al., 2007). Vagus nerve stimulation alleviates inflammation and exerts significant protection against renal ischemia and reperfusion injury in mice (Inoue et al., 2016). Interestingly, the anti-inflammatory effect requires α7nAChR-mediated signaling in the spleen (Inoue et al., 2016).

Resolution of inflammation is an active process in terminating inflammatory responses. It is mediated by pro-resolving molecules, including resolvins, protectins, lipoxins, and maresins (Serhan et al., 2015; Serhan, 2014). Restraining leukocyte infiltration and enhancing neutrophil and macrophage phagocytosis of necrotic cells are important events in inflammation resolution, which ultimately leads to the reestablishment of homeostasis. Dysregulation in pro-resolving mediator signaling is associated with unresolved chronic inflammation, which drives pathology in a myriad of diseases (Serhan, 2014; Nathan and Ding, 2010). Recent findings indicate that inflammation resolution is regulated by neural signaling along the vagus nerve (Mirakaj et al., 2014; Dalli et al., 2017). Experiments with vagotomy (unilateral cervical) in a mouse model of zymosan-induced peritonitis revealed that vagus nerve signals control lung and abdominal tissue expression of netrin-1, an axonal guidance molecule that was rediscovered as a pro-resolving mediator in the innate immune system (Mirakaj et al., 2014). A synergistic interaction between netrin-1 and pro-resolving lipid mediators, including protectin D1 and RvD5, promotes inflammatory resolution (Mirakaj et al., 2014).

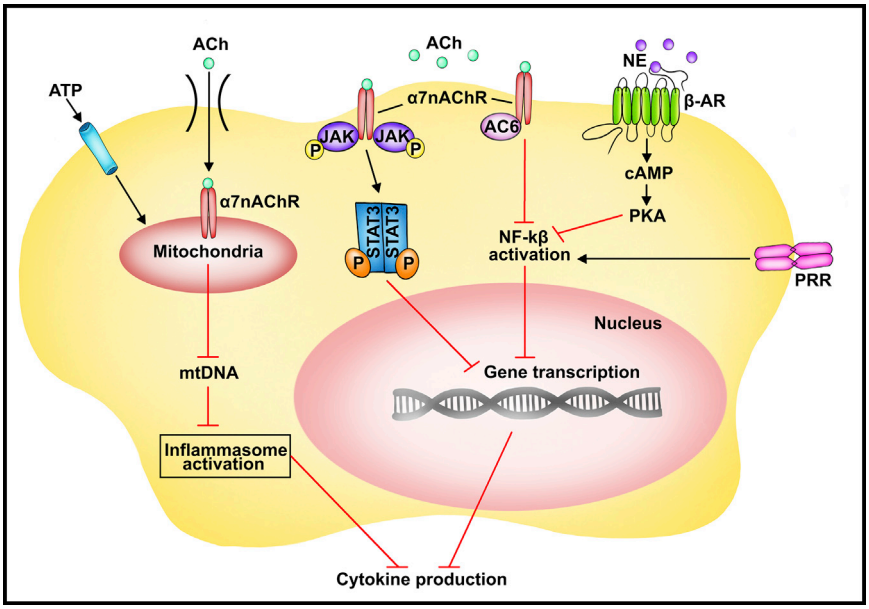

Figure 4. Molecular Mechanisms of Acetylcholine- and Catecholamine-Mediated Regulation of Cytokine Release

Norepinephrine binding to β adrenergic receptors on macrophages and other immune cells triggers intracellular signaling, including activation of intracellular cyclic AMP (cAMP) and protein kinase A (PKA). This activation results in inhibition of NF-κB activation and attenuation of pro-inflammatory cytokine production. Acetylcholine (ACh) interacts with the α7 nicotinic ACh receptor (α7nAChR) expressed on macrophages and other immune cells. This interaction triggers intracellular signaling involving activation of adenylyl cyclase 6 (AC6), which leads to inhibition of NF-κB activity and suppressed production of TNF and other pro-inflammatory cytokines. Through another mechanism, ACh binding to α7nAChR leads to interaction between α7nAChR and JAK2, which results in phosphorylation of STAT3. Phosphorylated STAT3 dimers translocate to the nucleus to induce suppression of pro-inflammatory cytokines. In addition, activation of immune cells with extracellular ATP leads to a rapid influx of ACh into the cytoplasm. Cytoplasmic ACh attenuates mitochondrial DNA release via mitochondrial α7nAChR and subsequently inhibits inflammasome activation and IL-1β cytokine release.

Vagotomy lowers acetylcholine and netrin-1 levels and increases TNF, IL-1β, IL-6, and other cytokines and chemokines and enhances the leukocyte presence in inflammatory exudates (Mirakaj et al., 2014). A very recent study demonstrated the effect of vagus nerve signaling on the resolution of peritoneal inflammation during bacterial infection (Dalli et al., 2017). Unilateral cervical vagotomy significantly decreases levels of peritoneal pro-resolving mediators, including protectin conjugates in tissue regeneration 1 (PCTR1), and elevates levels of eicosanoids. Vagotomy also results in dysregulated peritoneal innate immune responses, including alterations in peritoneal leukocyte composition and macrophage phenotype. This is indicated by a significant reduction in the number of type 3 innate lymphoid cells (ILC3s) and an increased number of F4/80^{+}CD11b^{+} peritoneal macrophages. Acetylcholine significantly upregulates the PCTR biosynthetic pathway in ILC3s (Dalli et al., 2017). *E.coli* inoculation in mice with vagotomy results in significantly lower *E.coli* phagocytosis by exudate leukocytes and higher bacterial counts. Intriguingly, administration of PCTR1 or ILC3s to mice with vagotomy restores the resolution process and enhances the host responses to *E.coli* infection (Dalli et al., 2017). These findings demonstrating the role of efferent vagus nerve cholinergic signaling in the resolution of inflammation, together with its function in limiting excessive pro-inflammatory responses, suggest that the vagus nerve could provide a neural conduit of integration of inflammatory stages and processes.

Sympathetic neurons residing in the thoracic and lumbar parts of the spinal cord give preganglionic projections to paravertebral or prevertebral ganglia (Elenkov et al., 2000; Jänig, 2014). These neurons release acetylcholine, which mediates ganglionic neurotransmission. Postganglionic fibers releasing predominantly norepinephrine and some quantities of other catecholamines and neuropeptide Y in turn innervate the blood vessels, lymphoid tissue and organs, bone marrow, joints, spleen, lungs and airways, gastrointestinal tract, liver, kidneys, and other visceral organs (Elenkov et al., 2000; Jänig, 2014; Figure 3). Sympathetic preganglionic fibers also innervate the adrenal medulla and stimulate the secretion of epinephrine and, to a lesser extent, other catecholamines (norepinephrine and dopamine) from chromaffin cells (Figure 3). These molecules are released in the circulation and exert their physiological effects by acting as hormones. Catecholamines are important regulators of cardiovascular, pulmonary, and gastrointestinal function, hematopoiesis, and numerous metabolic processes (Elenkov et al., 2000). Catecholamines regulate a myriad of innate and adaptive immune responses, which have been described in detail elsewhere (Elenkov et al., 2000; Sternberg, 2006). Norepinephrine released from catecholaminergic axon terminals can interact with adrenergic receptors on immune cells in a synapse-like fashion or after diffusion through the parenchyma of the innervated tissue (Elenkov et al., 2000; Pavlov and Tracey, 2004; Sternberg, 2006; Marino and Cosentino, 2013). Catecholamines can exert anti- or pro-inflammatory effects depending on the context, the involved receptor on the immune cell, and the cell type (Sternberg, 2006; Marino and Cosentino, 2013). For instance, norepinephrine and epinephrine inhibit pro-inflammatory and stimulate anti-inflammatory cytokine production through activation of β_2 adrenoceptors (Elenkov et al., 2000; Sternberg, 2006; Figure 4). In contrast, norepinephrine acting on α_2 adrenoceptors on monocytes and macrophages promotes the synthesis of TNF and other cytokines (Miksa et al., 2009; Grisanti et al., 2011; Sternberg, 2006). Adrenergic receptors are G-protein-coupled receptors linked to specific intracellular cascades. Norepinephrine can interact with β_2 adrenergic receptors on macrophages, neutrophils, dendritic cells, T cells, B cells, and mast cells (Sternberg, 2006). This interaction triggers downstream signaling, including increased cyclic AMP and protein kinase A, which suppresses NF-kB nuclear translocation and inhibits the synthesis of TNF and other pro-inflammatory cytokines (Sternberg, 2006; Figure 4). Dopamine activates a multitude of

dopamine receptors expressed on T cells, which results in altered cell migration and cytokine release (Besser et al., 2005).

Recent studies have substantially extended the scope of catecholaminergic immunomodulatory regulation and have suggested new approaches to controlling immune dysregulation. Catecholaminergic activation of lymphocyte β_2 adrenergic receptors was shown to result in the retention of lymphocytes within lymph nodes and reduced lymphocyte recruitment to peripheral tissues (Nakai et al., 2014). This catecholaminergic signaling is physically and functionally linked with chemokine CXCR4 receptors in T cells and CCR7 in B cells (Nakai et al., 2014). This regulation could have an important role in preventing T-cell-mediated tissue damage (Nakai et al., 2014; Tracey, 2014). Recent observations have highlighted a neural catecholaminergic mechanism in the regulation of gut immunity (Gabanyi et al., 2016). In this study, the authors used advanced transcriptional profiling and imaging to show that lamina propria macrophages and muscularis macrophages possess specific inflammatory programming. Lamina propria macrophages have a pro-inflammatory profile with a potential role in immune responses in the case of damage to the epithelial barrier (Gabanyi et al., 2016). Muscularis macrophages, localized deeper in the gut wall, have an anti-inflammatory, tissue-protective phenotype (Gabanyi et al., 2016). Interestingly, the presence of pathogenic *Salmonella* in the bowel enhances this tissue-protective phenotype of muscularis macrophages through a neural mechanism. This regulation requires extrinsic, catecholaminergic innervations and is mediated through β_2 adrenergic receptors on muscularis macrophages. A viable tissue-protective function of resident macrophages is an essential feature of immune responses to pathogens (Medzhitov et al., 2012). Therefore, catecholaminergic potentiation of the tissue-protective macrophage function in the intestinal muscularis could be critical during local inflammatory damage caused by environmental perturbations (Gabanyi et al., 2016). Post-stroke immunosuppression and the associated increased susceptibility to infection are well-documented phenomena with deleterious consequences (Prass et al., 2003; Meisel et al., 2005). Studies have implicated neural catecholaminergic signaling in post-stroke immune dysregulation (Prass et al., 2003; Meisel et al., 2005). Recent specific insight was provided by observations that catecholaminergic innervations of the liver have an important mediating role (Wong et al., 2011). In a mouse model of stroke, catecholaminergic signaling on hepatic invariant natural killer (NK) T cells resulted in a shift from pro-inflammatory T helper 1 (Th1)-type cytokine production to anti-inflammatory Th2-type cytokine production. This is directly associated with IL-10-mediated immunosuppression and promotes bacterial infection (Wong et al., 2011). Administration of the β-adrenergic receptor blocker propranolol or chemical disruption of hepatic catecholaminergic innervations significantly reduced bacterial infections (Wong et al., 2011). A recent study provided insight into brain control of sympathetic immunomodulatory activity (Ben-Shaanan et al., 2016). Chemogenetic stimulation of dopamine receptors in the ventral tegmental area enhances phagocytic activity of dendritic cells and macrophages, as well as monocyte and macrophage bactericidal properties, and alleviates bacterial load in the liver in response to *E. coli* exposure (Ben-Shaanan et al., 2016). Chemical disruption of catecholaminergic neurons in the periphery abrogates these effects, demonstrating a role of catecholaminergic signaling in enhancing peripheral immune antibacterial responses after selective brain modulation (Ben-Shaanan et al., 2016).

Inflammation is importantly involved in cancer development and progression (Grivennikov et al., 2010). Tumor-associated macrophages, T cells and other immune cells, and cytokines and other inflammatory products are active constituents of the tumor microenvironment, angiogenesis modulation, and tumor progression and metastases (Grivennikov et al., 2010; Lin and Karin, 2007). Both catecholaminergic and vagus nerve signals have been implicated in the regulation of cancer-related inflammation (Cole et al., 2015). Catecholaminergic signaling has been shown to stimulate macrophage infiltration in the solid-tumor microenvironment, inflammation, angiogenesis, and epithelial-mesenchymal transition and to promote metastasis (Cole et al., 2015). A very recent study demonstrated the role of the vagus nerve in controlling pancreatic cancer in a murine model induced by orthotopic implantation (in the pancreas) of tumor cells (Partecke et al., 2017). Subdiaphragmatic vagotomy results in increased tumor growth and worsened survival associated with higher tumor TNF levels and an increased number of tumor-associated macrophages (Partecke et al., 2017). Tumor cell implantation in TNF-knockout mice results in significantly longer survival, and vagotomy has no significant effect in these mice. These findings suggest that the vagus nerve has a tonic tumor-growth-suppressive function mediated through an effect on tumor-associated macrophages and TNF (Partecke et al., 2017). However, vagotomy suppress the development of gastric cancer through a cholinergic muscarinic receptor (M3 mAChR)-dependent mechanism (Zhao et al., 2014), which suggests a differential organ-specific effect. Vagotomy in experimental 4THMpc breast carcinoma exacerbates the metastatic process (Erin et al., 2008; Erin et al., 2013). Bilateral subdiaphragmatic vagotomy enhances experimental carcinogen-induced pancreatic cancer (Ogawa et al., 1991) and gastric cancer (Tatsuta et al., 1985; Tatsuta et al., 1988). Vagotomy performed clinically for treating ulcers has been related to an increased risk of gastric, colorectal, biliary tract, and lung cancers (Caygill et al., 1987; Houghton and Leaper, 1987). Cancer-related inflammation has been actively studied as a potential therapeutic target, and further insight into neural regulatory mechanisms is of interest for new therapeutic approaches.

Reflexes in Neuro-immune Communication

Reflexes play a major role in the regulation of physiological homeostasis and in pathophysiological scenarios (Abboud and Thames, 2011; Dampney, 2016; Abboud and Thames, 2011; Travagli et al., 2006; Mazzone and Undem, 2016). Reflexes can be as simple as the axon reflex, which involves peripheral terminals of sensory neurons. In the axon reflex, action potentials generated upon activation of peripheral axon terminals of sensory neurons propagate in an orthodromic fashion (in a peripheral-to-central direction) and then are diverted to other terminal branches of the same axon in an antidromic manner (against the peripheral-to-central direction) (Yaprak, 2008; Dubin and Patapoutian, 2010; Mazzone and Undem, 2016). The resultant release of peptides and other substances has a local effect on other neuronal terminals, endothelial cells, and smooth muscle cells (Dubin and Patapoutian, 2010; Talbot et al., 2016). Thus,

in addition to monitoring alterations in the local microenvironment, peripheral axonal terminals of sensory neurons are active reflexive regulators of this microenvironment. Axon reflexes play a role in the regulation of skin blood flow and vasodilation in response to heat (Houghton et al., 2006; Nieuwenhoff et al., 2016; Yaprak, 2008), in asthma (Barnes, 1986), and in other physiological and pathophysiological conditions (Mazzone and Undem, 2016). Both spinal and vagal sensory neurons are involved in the axon reflex regulation (Talbot et al., 2016; Mazzone and Undem, 2016).

Reflexes, composed of afferent and efferent circuits, and CNS integrative and regulatory centers mediate peripheral-CNS interaction and nervous system control of somatic and visceral function (Abboud and Thames, 2011; Dampney, 2016; Abboud and Thames, 2011; Travagli et al., 2006). Signaling through vagal afferents to the brain plays a role in the generation of important physiological reflexes. Vagal afferents expressing markers of nociceptors, including TRPV1 and TRPA1, respond to chemical, mechanical, or thermal stimuli in the lung and airways to initiate protective reflexes, such as coughing (Mazzone and Undem, 2016). The vagus nerve has an important role in the baroreflex and the regulation of gastrointestinal motility and secretion, feeding behavior, and glucose homeostasis (Pavlov and Tracey, 2012; Mayer, 2011; Dampney, 2016; Abboud and Thames, 2011). Activation of sensory DRGs to the spinal cord is associated with a reflexive output through spinal thoracic and lumbar nerves. Recent advances in studying neuro-immune communication have indicated that reflexes play an important role in neural control of immunity and inflammation (Andersson and Tracey, 2012; Pavlov and Tracey, 2017; Chavan and Tracey, 2017; Talbot et al., 2016). These reflexes can be protective but also detrimental.

Axon reflexes mediate communication between immune cells and the peripheral axons of sensory neurons. This communication might have anti-inflammatory and protective aspects, but in other cases, it could promote immune derangements and deleterious inflammation (Chiu et al., 2013; Talbot et al., 2015; Talbot et al., 2016). Sensory neurons in the mouse hind paw are activated by the pathogen *Staphylococcus aureus* (Chiu et al., 2012). *S. aureus* directly activates sensory neurons via the release of *N*-formyl peptides and the pore-forming toxin α-hemolysin, which induce calcium flux and action potentials mediating pain sensation (Figure 2). This activation occurs in parallel with pathogen-induced innate and adaptive immune cell activation, but it does not require these processes because genetic ablation of TLR2 and MyD88 and the absence of NK cells, T cells, and B cells do not alter it. In an antidromic fashion, sensory neurons release CGRP, galanin, and somatostatin, which interact with their receptors expressed on neutrophils, monocytes, and macrophages and suppress *S. aureus*-induced innate immune activation (Chiu et al., 2013). Genetic ablation of $Na_v1.8$-lineage neurons, which include nociceptors, abrogates the pain associated with *S. aureus* infection and increases local inflammation, tissue TNF levels, and lymphadenopathy, indicating a tonic anti-inflammatory function of nociceptors (Chiu et al., 2013). *S aureus* is a major cause of wound and surgical infections, and this and further insight into the nociceptor axon-reflex regulation of immune responses to this pathogen is of therapeutic interest. Sensory neurons and immune cells might communicate in amplifying immunopathology; neuro-immune interactions within axon reflexes are important components of ''neurogenic inflammation'' in asthma and other conditions (Talbot et al., 2016; Chiu et al., 2012). In a mouse model of ovalbumin-induced allergic inflammation and bronchial hyper-responsiveness, capsaicin activation of lung nociceptors stimulated the release of VIP and other neuropeptides and increased immune cell infiltration (Talbot et al., 2015). Silencing of nociceptors or genetic ablation of $Na_v1.8^+$ nociceptors decreases immune cell infiltration and bronchial hyper-responsiveness. An important mediator in this inflammatory loop is IL-5. This cytokine directly activates pulmonary nociceptors and causes the release of VIP, which in turn acts on ILC2s and $CD4^+$ T cells, leading to increased cytokine production and inflammation (Talbot et al., 2015). Localized specific pharmacological silencing of TRP-mediated signaling in neuroreceptors interrupts these interactions and abolishes inflammation (Talbot et al., 2015). These observations reveal the importance and mechanisms of an axon-reflex signaling loop in the modulation of adaptive immune responses in the lung (Talbot et al., 2015). They suggest that selective interruption of this communication between immune cells and sensory neurons could be a new approach in the treatment of allergic airway inflammation (Talbot et al., 2015; Talbot et al., 2016). Other studies have also provided important mechanistic insight into the role of sensory neurons in airway inflammation and hyperreactivity (Caceres et al., 2009; Tränkner et al., 2014). In addition to $Na_v1.8^+$, TRPA1 was identified as a key molecule in the interactions between immune cells and chemosensory neurons in the airways in that it drives asthmatic airway inflammation in the murine ovalbumin model of asthma (Caceres et al., 2009). Neuro-immune communication and a specific role for TRPA1 and cutaneous sensory nerve release of CGRP and SP have been implicated in exacerbating inflammation in dermatitis (Liu et al., 2013; Ward et al., 2012).

Upon immune challenge, antigens are transported and processed in local lymph nodes and presented to the lymphocytes to mount an antigen-specific response. A key step in developing a dynamic antigen-specific response is the regulation of antigen transport through the lymphatic system. Lymphoid organs are directly innervated by a dense plexus of neural fibers. A recent study identified a neural reflex circuit that modulates the lymphatic antigen trafficking in immunized animals (Hanes et al., 2016). Antigen re-exposure in immunized animals activates $TRPV1^-Na_v1.8^+$ neurons. Local neuronal activation in the mouse hind paw results in restricted antigen transport within the lymphatic network. Direct stimulation of the local neural plexus innervating these lymph nodes recapitulates the antigen restriction in a naive mouse in the absence of prior immunization. In contrast, blocking neural activation restores antigen trafficking in the immunized animals. FcR is required for mediating antigen-specific restriction in the immunized animals, as indicated in FcR-knockout mice. These observations indicate that antigen-specific activation of nociceptors via FcR contributes to antigen restriction and transport. The lymphatic system mediates dissemination of pathogens and tumor cells. In this context, these findings suggest that a critical step in the spread of pathogenic bacteria or micrometastases is under neural reflex control, which can be modulated for therapeutic benefit (Hanes et al., 2016).

Vagus-nerve-based reflexes importantly regulate immune function and inflammation (Tracey, 2002; Chavan and Tracey, 2017; Pavlov and Tracey, 2017). An important observation suggesting a reflexive regulation was that administration of IL-1β into the rat hepatic portal system increased afferent vagus nerve activity but also resulted in increased efferent vagus nerve and splenic nerve activity (Niijima, 1996). As described in the previous section, signals transmitted through efferent vagus nerve fibers suppress the release of TNF and other pro-inflammatory cytokines (Borovikova et al., 2000; Figures 3 and 4). Neuronal interaction between vagal afferents and vagal efferents takes place within the brainstem DVC (Berthoud and Neuhuber, 2000; Niijima, 1996). These findings led to the concept of the inflammatory reflex, which controls peripheral cytokine levels and inflammation (Tracey, 2002; Tracey, 2010). Functional signals along the efferent vagus nerve to the splenic nerve, which increase the release of acetylcholine by a subset of T lymphocytes, constitute the efferent arm of this inflammatory reflex (Rosas-Ballina et al., 2008; Rosas-Ballina et al., 2011). Catecholaminergic neurons of the splenic nerve are in close proximity to T lymphocytes containing functional choline acetyltransferase (ChAT), an enzyme that synthesizes acetylcholine (Rosas-Ballina et al., 2011). Vagus nerve stimulation via catecholaminergic, β adrenergic receptor signaling on ChAT-expressing T cells increases acetylcholine levels in the spleen (Rosas-Ballina et al., 2011). T cell deficiency (in nude mice) abolishes the anti-inflammatory effect of vagus nerve stimulation, and the adoptive transfer of ChAT-expressing T cells into nude mice restores this effect, demonstrating the important role of these acetylcholine-producing cells in the circuit (Rosas-Ballina et al., 2011). Acetylcholine, released from ChAT-expressing T cells under vagus nerve control, interacts with a α7nAChR to suppress pro-inflammatory cytokine production. Insight into the inflammatory reflex revealed new aspects of neural regulation of immunity; the efferent arm of this reflex is neither parasympathetic nor sympathetic, and immune cells such as T cells are not the final recipient; instead, they are mediators of neural signaling (Rosas-Ballina et al., 2011). These findings and further insight into other immunoregulatory reflexes (Torres-Rosas et al., 2014; Song et al., 2012; Arima et al., 2012) indicated that the classical vagus (parasympathetic) and sympathetic neuronal designations cannot be precisely used to describe the variety of structural components of these circuits (Pavlov and Tracey, 2017). Further molecular characterization of neurons and neurotransmitters involved will contribute to their better characterization. The functional cooperation between the efferent vagus nerve and the splenic nerve in the inflammatory reflex can be mediated by neural interaction in the celiac plexus ganglia. This is consistent with studies demonstrating that (1) efferent vagus nerve fibers innervate the celiac ganglia and the superior mesenteric ganglion (Berthoud and Powley, 1993; Berthoud and Powley, 1996) and (2) the celiac ganglia and the superior mesenteric ganglion are the sources of spleen-projecting catecholaminergic fibers (Bellinger et al., 1989; Nance and Burns, 1989; Li et al., 2010). The discovery of the inflammatory reflex generated a great deal of interest in studying the axis between the vagus nerve and splenic nerve in the regulation of immune function in a variety of conditions, including antibody secretion following exposure of B cells to blood-borne antigen and modulating cell trafficking and splenic lymphoid architecture (Mina-Osorio et al., 2012), IBD (Ji et al., 2014; Munyaka et al., 2014), renal ischemia and reperfusion injury (Inoue et al., 2016), and T cell activation and egression from the spleen in experimental hypertension (Carnevale et al., 2016). In addition, research initially performed to further characterize T-ChAT cells led to the important discovery that a specific subset of these cells mediate blood-pressure regulation (Olofsson et al., 2016). Although it is known that acetylcholine causes vasodilation and results in decreased blood pressure, blood-vessel innervations are almost exclusively catecholaminergic, and the origin of acetylcholine-associated causes of endothelium-derived relaxation has remained enigmatic for a long time. Importantly, selective ablation of ChAT expression in $CD4^+$ T cells in mice results in a hypertensive phenotype that can be reversed by direct infusion of Jurkat T cells overexpressing ChAT (Olofsson et al., 2016). This observation indicates the homeostatic role of $ChAT^+CD4^+$ T cells in vasorelaxation and regulation of blood pressure. T cells have been shown to play a role in atherosclerosis and chronic vascular inflammation to mediate chronic hypertension. These current findings (Olofsson et al., 2016) suggest that dysregulation of $ChAT^+CD4^+$ T cells could also contribute to the development of a hypertensive phenotype. Acetylcholine-producing $CD4^+$ T cells in the spleen, and possibly other tissues, are regulated by neural signals traveling in the vagus and splenic nerves (Rosas-Ballina et al., 2011), which provides a regulatory mechanism that can be therapeutically explored.

Other reflexes involving the vagus nerve have also been identified (Andersson and Tracey, 2012; Pavlov and Tracey, 2017; Chavan and Tracey, 2017). For instance, somatosensory activation by electroacupuncture triggers brain mAChR-mediated signaling, which is linked with efferent vagus nerve activity and catecholaminergic signaling to the spleen (Song et al., 2012). This neural circuit suppresses pro-inflammatory cytokines and improves survival in murine endotoxemia (Song et al., 2012). Stimulation of sciatic nerve activity by electroacupuncture activates efferent vagus nerve signaling to the adrenal medulla and subsequently increases dopamine secretion, leading to suppression of the systemic inflammatory response by a D1-receptor-mediated mechanism and improved survival in murine sepsis (Torres-Rosas et al., 2014). Reflex regulation via afferent and efferent vagus nerve fibers of the inflammatory tumor microenvironment has also been proposed (Gidron et al., 2005; Ondicova and Mravec, 2010).

In addition to stimulation of efferent vagus nerve signaling, activation of afferent vagus nerve signals results in anti-inflammatory output (Olofsson et al., 2015; Inoue et al., 2016). This effect was observed even in the presence of blocked neurotransmission via the contralateral vagus nerve (Inoue et al., 2016). These observations indicate that in addition to efferent signaling within the inflammatory reflex to the spleen, brain-derived pathways, including spinal neurons projecting to celiac ganglia, might be activated upon electrical stimulation of the vagus nerve (Pavlov and Tracey, 2017). This is consistent with findings that brain networks among the DVC, rostroventrolateral medulla, locus coeruleus, and paraventricular nucleus of the hypothalamus integrate efferent vagus nerve signaling, sympathetic regulation, and the hypothalamo-pituitary-adrenal axis, another important immunoregulatory and anti-inflammatory physiological mechanism

(Elenkov et al., 2000; Mayer, 2011; Pavlov et al., 2003; Pavlov and Tracey, 2017; Webster et al., 2002; Chrousos, 1995). Reciprocal projections between these brain areas and forebrain regions of the limbic system constitute an extended brain network for controlling peripheral autonomic and hormonal regulation (Benarroch, 1993; Shipley, 1982; Dampney, 2016; Pavlov and Tracey, 2017). Brain mechanisms can be explored for the control of peripheral immunomodulatory pathways and inflammation. For instance, brain cholinergic mAChR-mediated mechanisms have been implicated in the regulation of inflammation in endotoxemia, sepsis, IBD, and other inflammatory conditions through activation of the inflammatory reflex (Pavlov et al., 2006; Pavlov et al., 2009; Ji et al., 2014; Munyaka et al., 2014; Lee et al., 2010; Guarini et al., 2004). Recently, a role for C1 neurons residing in the brainstem medullar reticular formation in regulating inflammatory responses in a mouse kidney ischemia and reperfusion injury was demonstrated via activation of spinal sympathetic neurons (Abe et al., 2017). Brain dopaminergic signaling was shown to activate immune responses to bacterial infection through catecholaminergic peripheral modulation (Ben-Shaanan et al., 2016).

Abrupt impairment of the normal physiological neural interactions between the brain and spinal cord occurs in spinal cord injury. Cervical or upper thoracic spinal cord injury results in a loss of brainstem control over spinal autonomic function, a condition known as autonomic dysreflexia (Zhang et al., 2013). The pathophysiological manifestations of this condition include eliciting spinal reflexes triggered by activation of somatosensory and visceral spinal afferents as a result of constriction of splanchnic vasculature and activation of spinal sympathetic neuronal activity, which can cause severe hypertension (Zhang et al., 2013). These potentially life-threatening autonomic reflexes and increased catecholaminergic output from postganglionic fibers cause major immune dysregulation and immunosuppression (Brommer et al., 2016; Ueno et al., 2016; Lucin et al., 2007). Activated catecholaminergic signaling to the spleen in high-level spinal cord injury (at thoracic level 3) has been specifically attributed to lymphocyte apoptosis, impaired antibody production, and concomitant immunosuppression (Lucin et al., 2007; Lucin et al., 2009). This immunosuppression in high-level thoracic spinal cord injury was shown to be caused by increased spinal neuronal activation below the lesion in mice and linked to increased infectious complications (indicated by the occurrence of pneumonia) in mice and humans (Brommer et al., 2016). A recent study provided an important insight into the mechanisms of immunosuppression after spinal cord injury. The increased catecholaminergic signaling to the spleen in mice with high-level spinal cord injury was associated with neuronal plasticity within spinal autonomic networks below the levels of the injury as a major driver of a reflex circuitry (Ueno et al., 2016). This reflex is triggered by activation of primary sensory neurons, which interact with interneurons and preganglionic sympathetic neurons in the spinal cord (Ueno et al., 2016). Chemogenetic silencing of glutamatergic excitatory neurons within this aberrant intraspinal network interrupts this reflex, prevents splenic atrophy, and restores the total numbers of splenocytes, including helper $CD4^+$ and cytotoxic $CD8^+$ T cells and $B220^+$ B cells (Ueno et al., 2016). Mechanistic insight into the neurocircuitry involved in immune dysregulation after spinal cord injury could indicate new treatment options for post-spinal-cord-injury visceral derangements based on neuromodulation (Wong et al., 2011; Ueno et al., 2016; Meisel et al., 2005). In this respect, an interesting option is related to the vagus nerve, which is not directly affected by spinal cord injury (Herrity et al., 2015). A recent study indicated the occurrence of neurochemical plasticity in vagal afferents after spinal cord injury in rats, suggesting an effect of the condition on sensory vagus neurons implicated in visceral homeostasis. Whether vagus nerve afferent or efferent signaling can be explored for therapeutic benefit in spinal cord injury remains an interesting open question.

Multiple sclerosis (MS) is an autoimmune disease characterized by neuronal demyelination in the CNS and has limited treatment options (Steinman, 2014). Autoreactive pathogenic $CD4^+$ T cells are importantly involved in the processes of neuronal demyelination in the CNS. In mice with experimental autoimmune encephalomyelitis, an animal model of MS, the dorsal blood vessels of the fifth lumbar cord of the spine were identified as a major gateway for pathogenic $CD4^+$ T cells to enter the CNS (Arima et al., 2012). This access of autoreactive T cells to the CNS was found to be regulated by a neural circuit termed the gateway reflex (Arima et al., 2012; Sabharwal et al., 2014). Communication between DRG sensory neurons with peripheral axonal endings in the soleus muscles and sympathetic catecholaminergic neurons was identified within reflex circuitry (Arima et al., 2012; Sabharwal et al., 2014). Soleus muscle contraction activates this neuronal communication, leading to the release of catecholamines, which stimulate an IL-6 amplifier mechanism that upregulates expression of the chemokine CCL20 in the L5 dorsal blood vessels (Arima et al., 2012). This stimulation results in increased T cell entry into the CNS. Interestingly, suspending mice by their tails to limit soleus muscle simulation by gravity interrupts this reflex communication, reduces localized chemokine expression, and limits the pathological process (Arima et al., 2012). Improved understanding of the neural mechanisms regulating the entry of autoreactive pathogenic T cells into the CNS could be therapeutically explored in future treatments (Sabharwal et al., 2014).

Emerging Clinical Perspectives

Mechanistic insights into neuro-immune communication and neural circuits regulating immunity have been therapeutically explored in preclinical models and recently in human clinical trials. In addition to vagus nerve stimulation, several lines of pharmacological modalities (including α7nAChR agonists, centrally acting acetylcholinesterase inhibitors and mAChR agonists, and β_2 adrenoreceptor agonists) have been explored in preclinical settings of inflammatory and autoimmune disorders (van Westerloo et al., 2006; Parrish et al., 2008; Pavlov et al., 2007; Hanes et al., 2015; Rosas-Ballina et al., 2015; Yeboah et al., 2008; Terrando et al., 2015; Pavlov et al., 2009; Marino and Cosentino, 2013; Ji et al., 2014; Munyaka et al., 2014). Pharmacological approaches that target the inflammatory reflex have been studied in subjects with obesity-driven disorders. In addition, implantable bioelectronic devices that activate the inflammatory reflex are being studied in diseases that were historically treated with drugs or biological agents. These treatments take advantage of the neural circuitry to deliver anti-inflammatory signals to target organs. Results from some of these clinical trials were recently reported, and others are ongoing or in early planning stages.

Metabolic syndrome is an obesity-driven condition of epidemic proportions that increases the risk of cardiovascular disease, type 2 diabetes, and other diseases (Eckel et al., 2005). Chronic low-grade inflammation in the metabolic syndrome is linked to insulin resistance and other metabolic derangements (Cornier et al., 2008). Galantamine, a centrally acting acetylcholinesterase inhibitor in clinical use (in the treatment of Alzheimer's disease), is a brain activator of the inflammatory reflex (Pavlov et al., 2009; Ji et al., 2014) with anti-inflammatory properties in an animal model of obesity and metabolic syndrome (Satapathy et al., 2011). Galantamine is currently being tested in a randomized, double-blind, placebo-controlled clinical trial in patients with the disorder (ClinicalTrials.gov: NCT02283242).

Rheumatoid arthritis is a chronic inflammatory and autoimmune disease that affects more than 1.3 million people in the US alone, and tens of billions of dollars are spent on the treatment annually. Recent clinical studies carried out in 17 patients with rheumatoid arthritis demonstrated the efficacy of electrical vagus nerve stimulation by an implantable bioelectronic device in attenuating disease severity (Koopman et al., 2016). The therapeutic efficacy of this neuromodulation was shown in two cohorts of patients. The first cohort of seven patients was in the early disease stage and unresponsive to methotrexate; these patients had not previously received a biological TNF antagonist or had failed treatment with TNF antagonists because of drug toxicity. The second cohort included patients who had failed methotrexate therapy and treatment with at least two biological agents with different mechanisms of action (e.g., anti-TNF, anti-IL-6 receptor, anti-CD20 antibodies, and/or T cell costimulation inhibitor; Koopman et al., 2016). Vagus nerve stimulation, one to four times per day, significantly inhibited TNF production. Moreover, this treatment conferred significant improvement in disease severity, and retraction of the electrical stimulation worsened the disease (Koopman et al., 2016).

IBD, including Crohn's disease and ulcerative colitis, affects as many as 1.6 million people in the US alone, significantly worsens a patient's quality of life, and is associated with a high financial burden. Current treatments for IBD are mainly biological and have significant side effects. Previous clinical studies have established that vagus nerve tone is attenuated in patients with Crohn's disease and that electrical vagus nerve stimulation can be applied to restore it. In a recent pilot study, seven patients with mild to active Crohn's disease were subjected to vagus nerve stimulation and followed for 6 months (Bonaz et al., 2016). Chronic stimulation induced a disease remission at 6 months in the majority of the patients. Vagus nerve stimulation improved biological parameters (C-reactive protein and/or fecal calprotectin) and perceived abdominal pain. In addition, vagus nerve tone was improved after the stimulation.

These first promising results of vagus nerve stimulation in rheumatoid arthritis and IBD suggest that bioelectronic devices for the modulation of neural circuitries can be an efficient alternative to drug treatments. Emerging technological and conceptual advances in the growing field of bioelectronic medicine can be used to provide treatments of many diseases and conditions with limited treatment options, as recently demonstrated in paralysis (Tracey, 2015; Bouton et al., 2016).

Concluding Remarks

Neuro-immune communication is an exciting area of research that bridges disciplines and addresses questions of great physiological importance and clinical relevance. Here, we have described mechanisms of this communication by focusing on the functional role of sensory neurons in conditions of pathogen invasion, tissue injury, and autoimmune derangements and the importance of efferent autonomic nerves in the regulation of inflammatory and autoimmune alterations. An integral part of the substantial progress in studying neuro-immune communication for the last 20 years has been the conceptual view that neuronal circuits organized in a reflexive manner regulate immunity. These neural circuits have an important protective role but could be detrimental in cases of massive homeostatic failure, such as spinal cord injury. Molecular mechanisms at the interface between the neural and immune components in these circuitries have been explored via pharmacological approaches and electrical neuromodulation for therapeutic benefit in numerous inflammatory conditions. This preclinical research has recently resulted in clinical studies exploiting neuromodulation in inflammatory and autoimmune diseases. Future research taking advantage of the latest technologies for genetic molecular mapping, imaging, and optogenetic and chemogenetic modulation will characterize in greater detail the specificity of neuro-immune communication. These advances will contribute to the continuous progress in our basic understanding of neuro-immune regulatory mechanisms and will allow precise targeting for therapeutic benefit.

ACKNOWLEDGMENTS

This work was supported by the following grants from the NIH National Institute of General Medical Sciences: R01GM089807 (to V.A.P. and K.J.T.) and 1 R35 GM118182-01 (to K.J.T.).

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