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Role of neurons in the control of immune defense

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Studies in recent years have strengthened the notion that neural mechanisms are involved in the control of immune responses. From initial studies that highlighted the vagus nerve control of inflammatory responses in vertebrates, many advances have been made, including the dissection of specific neural circuits that are involved in controlling immunity. Part of this has been facilitated by the use of a tractable model animal, *Caenorhabditis elegans*, in which individual neurons involved in sensing pathogens and controlling the immune response have been identified. Importantly, some of the underlying mechanisms involved in the neural control of immune pathways appear to be present in evolutionarily diverse species. This review focuses on some major developments in vertebrates and *C. elegans*, and how these discoveries may lead to advances in understanding neural-immune connections that govern inflammatory responses.

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Introduction

The mechanisms by which individual cells sense and respond to pathogens vary, but in general, cell-autonomous innate immune responses involve surface-displayed receptors, which recognize microbial-associated molecular patterns and/or damage associated molecular patterns to activate innate immune signaling pathways. However, cells do not operate in isolation and are in direct and indirect contact with a variety of other cells in the body. Paracrine signals from neighboring cells and cytokines in the circulation alter the physiology of cells involved in the innate immune response. It also appears that neuroendocrine signals from the nervous system have the potential to alter different cellular pathways in response to pathogen infection.

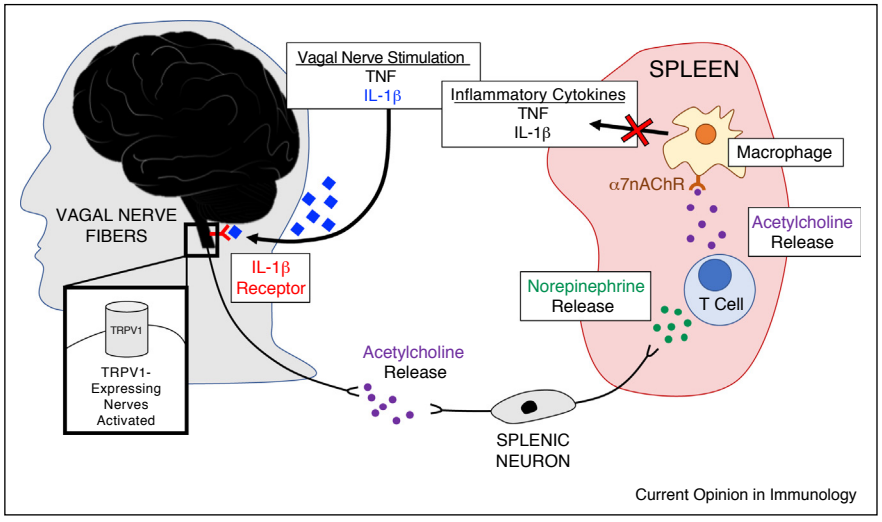
In recent years, the connection between the immune and the nervous systems to orchestrate appropriate immune responses has become more apparent, and it appears that a cross-talk between the two systems is evolutionarily conserved [1]. Neuropeptide receptors are present in immune cells, and cytokine receptors are present in neurons. Neurons in the central nervous system produce cytokines and cells of the immune system produce neuropeptides [1–3]. It has been shown that cytokines can regulate diverse physiological processes, including sleep cycles, neuroendocrine function, neuronal development, and responsiveness of the autonomic nervous system [1]. Neuropeptides and neuronal signaling are able to control inflammation and innate immune responses [4]. Herein, we describe recent evidence for non-cell-autonomous control of immune responses by the nervous system.

Vagus nerve stimulation of the immune system

A seminal study by Borovikova *et al.* demonstrated that vagus nerve stimulation suppresses inflammation [5], solidifying earlier observations that there is communication between the immune and the nervous system. The nervous system senses inflammation in peripheral tissues by the binding of IL-1β ligand to the IL-1β receptor on some or all sensory vagal fibers expressing TRPV1, a ligand-gated non-selective calcium-permeable ion channel [6•]. This results in the activation of vagal neurons and the subsequent signaling for a downstream anti-inflammatory pathway, deemed the vagal nerve reflex [7••]. The vagal nerve reflex was originally discovered when the vagus nerve was directly stimulated *in vivo* during lethal endotoxemia in rats. This stimulation inhibited the production of tumor necrosis factor (TNFα) and ultimately prevented the development of systemic shock [8]. Vagus nerve stimulation results in the release of the principle vagal neurotransmitter, acetylcholine, which activates adrenergic splenic neurons to produce and secrete norepinephrine [8]. Norepinephrine binds and activates lymphocytes, specifically splenic T cells. These splenic T cells then produce acetylcholine, which was demonstrated *in vitro* to attenuate the release of inflammatory cytokines from macrophages activated by endotoxin (lipopolysaccharide) [5]. Mice devoid of T cells (nude mice) are unable to reduce TNFα levels upon vagal nerve stimulation. Subsequent work showed that vagus nerve suppression of the inflammatory response requires the α-7 nicotinic acetylcholine receptor-dependent pathway in splenic macrophages [9].

These observations, outlined in Figure 1, were consistent with reports that showed cells from both the nervous and

Figure 1



The Vagus Nerve Controls Inflammatory Responses.
Electrical vagal nerve stimulation was shown to prevent death and systemic shock in mice and humans. During endotoxemia, inflammatory cytokines are elevated systemically, including TNF and IL-1b. These cytokines are able to activate vagal nerve fibers expressing TRPV1, which triggers the release of acetylcholine. It was shown that electrical vagal nerve stimulation also resulted in the production of acetylcholine, which signals via splenic neurons. These splenic neurons release norepinephrine, which stimulates T cell release of acetylcholine. Acetylcholine binds to a7AChR (a-7 nicotinic acetylcholine receptor) on splenic macrophages to block the release of TNF and IL-1b.

the immune systems expressed ligands and receptors from the other. Although these neural-immune pathways have been dissected primarily *in vitro* and *in vivo* in murine models, vagal stimulation through pharmacological agents, such as CNI-1493, has been used to inhibit TNFα synthesis in humans. CNI-1493 has undergone phase 1 and phase 2 clinical trials for the treatment of inflammatory diseases, including Crohn's Disease [10,11].

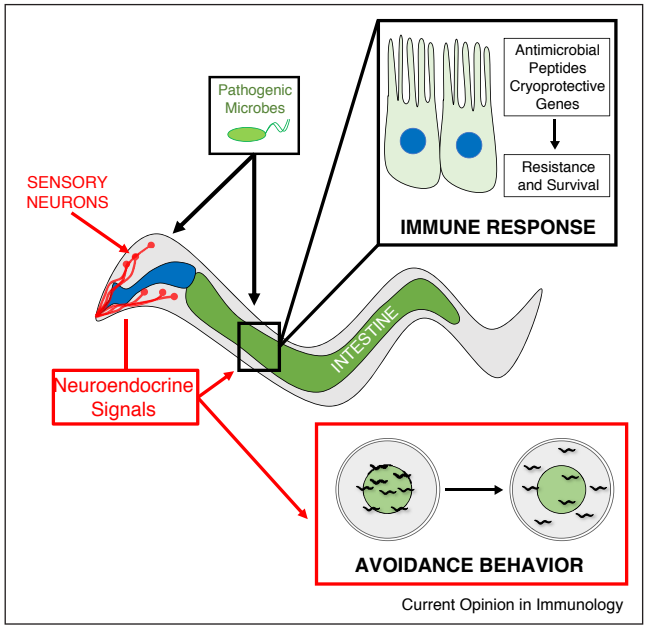
Lessons from *Caenorhabditis elegans*, a simple model system

The aforementioned studies in mammalian systems indicate that the nervous system senses and regulates the immune system to maintain immunological homeostasis. However, understanding the functions of individual neurons in this process is challenging because of the complexity and size of the nervous system of humans and most model animals. The adult human brain contains approximately 86 billion neurons, with some estimates higher. With current technology, it is difficult to imagine scientists thoroughly dissecting neural-immune signaling at the neuronal, single cell level in vertebrates. The complex systems present in vertebrates and shortcomings in current technology create a barrier for understanding neural-immune connections in higher-order organisms. With advances in understanding the nervous systems of vertebrates and the development of genetic tools, dissecting neural circuits and individual neurons that control immune responses in higher-order organisms will become possible. Other model organisms may currently provide better alternatives to understanding these neural-immune connections.

Some of the first pieces of evidence showing that specific neurons are capable of controlling innate immune pathways came from studies performed in the nematode, *C. elegans*. The soil-dwelling bacterivore serves as a model organism for understanding the functions of individual neurons and their roles in the immune response (Figure 2). *C. elegans* has a simple, well-defined nervous system containing only 302 neurons, and the synaptic connectivity of each neuron has been mapped. In addition, the innate immune system of *C. elegans* resembles some aspects of the human innate immune system, allowing for the study of conserved mechanisms of neural-immune signaling.

One of the initial studies linking specific neurons to immune responses in *C. elegans* demonstrated that NPR-1, a neuronally expressed G-protein coupled receptor (GPCR) is required for immune responses to a variety of pathogens. *C. elegans* mutants in *npr-1* show enhanced susceptibility to *Pseudomonas aeruginosa*, *Salmonella enterica*, and *Enterococcus faecalis*. To identify the specific neurons that coordinate neural-immune regulation, genetic ablation of sensory neurons expressing *npr-1*, AQR, PQR, and URX, was performed. This ablation resulted in increased survival during infection with *P. aeruginosa* and rescued the enhanced susceptibility of *npr-1* mutants, suggesting that *npr-1* plays an inhibitory role in the immune response [12]. Further characterization

Figure 2



Neural-Immune Connections in *C. elegans*.
The nematode, *C. elegans*, has a simple, well-defined nervous system which includes sensory neurons located in the head of the animal. Pathogenic microbes activate and/or regulate innate immune pathways that increase resistance and survival. Additionally, neurons are able to sense the presence of pathogenic microbes to signal for avoidance behavior, or the movement of the animals away from pathogens (marked green in the figure).

showed that *npr-1* downregulates innate immune genes, partially via post-translational control of the p38 mitogen-activated protein kinase, PMK-1, as well as other PMK-1 independent pathways [12]. The GPCR, NPR-1, was also shown to play a role in pathogen avoidance behavior [12,13], which will be discussed in more detail below.

Neurotransmitters and neuropeptides

A variety of neurotransmitters and neuropeptides have been identified to play a role in the control of immune pathways in both humans and *C. elegans*. Herein, some of the neuropeptides and neurotransmitters that regulate immune defense during infection in both *C. elegans* and higher organisms will be described. Several of these findings have been briefly summarized in Table 1.

Neuromedin U in mammals

Mast cells are at the interface between the neuroendocrine system and the immune system because these cells can be activated by neuropeptides. In addition, chemical mediators, such as serotonin and histamine, produced by mast cells can activate neural cells. Neuromedin U (NMU) is a neuropeptide produced by the central nervous system, that binds receptors NMU-R1 (expressed in peripheral tissues) and NMU-R2 (expressed on nerve cells only) [14••]. NMU-R1/2 are GPCRs that mobilize intracellular calcium when activated. NMU was known to have roles in regulating smooth muscle contractions in the uterus, reducing food intake and weight, regulating stress responses, and modifying ion transport.

It was recently shown that NMU stimulates the secretion of cytokines in mouse group 2 lymphoid cells and that these type 2 cytokines (IL-4, IL-5, IL-9, and IL-13) activate and mobilize mast cells. NMU-deficient mice were unable to activate mast cells [15]. Group 2 lymphoid cells, expressing NMU-R1, in the gastrointestinal tract co-localize with cholinergic neurons that express NMU [14••,16••]. These enteric neurons can sense and respond to helminth infection. Enteric neuron, neurosphere-derived neuronal organoids, when stimulated with alarmin IL-33 or with *Nippostrongylus brasiliensis* excretory and secretory products, induced neuron-derived expression of NMU. Moreover, supernatants from the

Table 1

Identified roles for neurotransmitters in mice and humans. Neurotransmitters that have been identified in *C. elegans* have also been implicated in the control of inflammatory responses in vertebrates. The roles of selected neurotransmitters are discussed and referenced in Table 1

Neurotransmitter	Role in immune response control	References
Serotonin	Serotonin activates innate immune cells, increases immune cell trafficking, regulates chemotaxis and proliferation.	[48,49]
	Serotonin levels are increased in the intestinal mucosa during inflammatory diseases. Reduction in serotonin levels reduces severity of intestinal inflammation and downregulates inflammatory cytokines.	[50–53]
Dopamine	Macrophages express receptors for dopamine and are able to produce dopamine. Dopamine decreases TNFα production and upregulates IL-6 and IL-10 production.	[54,55]
	Receptors are present on neutrophils. Dopamine inhibits superoxide production, increases adhesion molecule expression, influences cell migration and phagocytic activity.	[54,56–59]
Acetylcholine	Prevents tumor necrosis factor production in macrophages.	[5]

stimulated neuronal organoids applied to group 2 lymphoid cells resulted in type 2 cytokine production [14••].

In vitro NMU stimulation of these group 2 lymphoid cells resulted in an influx of Ca2+, which activates the calcium-dependent serine/threonine phosphatase (calcineurin), leading to NFAT nuclear translocation [14••]. NMU administration increased secretion of type 2 cytokines, activation of the group 2 lymphoid cells, and proliferation [14••,16••]. *In vivo* administration of NMU resulted in potent type 2 cytokine response [14••,16••]. During infection, NMU enhanced expulsion of the gastrointestinal nematode *N. brasiliensis* and NMU-R1 deficient mice had a higher burden of pathogen than WT. These studies outline a specific pathway in which enteric neurons sense and respond to *N. brasiliensis* infection, to then regulate the local immune response.

Octopamine

Sellegounder *et al.* recently reported that octopamine, a neurotransmitter closely related to norepinephrine, functions in immune regulation in *C. elegans* [17•]. Under steady state conditions, RIC neurons produce octopamine, which serves as the endogenous ligand for OCTR-1, a neuronally expressed GPCR. OCTR-1 functions in sensory neurons ASH and ASI to suppress innate immune responses in non-neural [18••,19,20]. Octopamine signaling suppresses unwanted innate immune responses by preventing infection triggered protein synthesis and the unfolded protein response, resulting in immunological homeostasis [17•]. In the presence of pathogenic bacteria, RIC neurons are deactivated, decreasing octopamine production and allowing for enhanced innate immunity [17•]. It is hypothesized that the octopamine-OCTR-1 pathway functions to suppress excessive responses to infection and to restore protein homeostasis after infection [19].

Acetylcholine

Acetylcholine is released from the nervous system in *C. elegans*. The neurotransmitter functions in a neuroendocrine fashion to activate muscarinic receptors in intestinal epithelial cells, leading to increased expression of Wnt and Frizzled in the intestinal epithelium. The activation of the canonical Wnt pathway increases the expression of host defense genes, such as C-type lectin (clec-60) and lysozymes [21••].

Dopamine

The immune inhibitory function of dopamine in *C. elegans* originates in CEP neurons and requires active DOP-4 (dopamine receptor) in downstream ASG neurons. Using pharmacological techniques, it was shown that the PMK-1/p38 mitogen-activated protein kinase signaling pathway can be activated by chlorpromazine, a phenothiazine antipsychotic drug. The drug signals through DOP-4 to enhance host resistance against bacterial infections [22•].

Serotonin

Serotonin, produced and secreted by chemosensory neurons in *C. elegans*, was also found to modulate the immune response, possibly in response to changes in the availability and/or quality of food. Serotonin released by the chemosensory ADF neuron binds to serotonin receptors SER-1 and SER-7. This directly or indirectly activates G-protein, GOA-1 (Gαo) in rectal epithelial cells, resulting in the suppression of the immune response to *Microbacterium nematophilum* [23].

Neuronal control of pathogen avoidance responses

Behavioral responses are complementary to other forms of immune defenses, such as immunological resistance and tolerance. Avoidance behavior has been demonstrated in a range of animals, including nematodes [24–32,33••,34,35••,36–38,39•], crustaceans [40], mice [41], bonobos (pygmy chimpanzee) [42•], and humans. All of these animals are able to sense and respond to environmental cues of pathogenic contamination.

Panulirus argu, the Caribbean spiny lobster, can be infected by the lethal *P. argus* virus 1. This species of lobster shows avoidance behavior toward infected individuals, and are able to determine that others are infected before visual signs of disease are present [40]. Bonobos are able to sense and avoid olfactory cues linked to infection and contamination (such as feces or soil). These pygmy chimpanzees prefer food items lacking contaminants and actively move away from areas with contamination [42•]. In humans, avoidance behavior is frequently classified as disgust and although little is known about the neural circuitry that controls this phenomenon, it was recently shown that serotonin may play a role. Serotonin levels were elevated during the induction of vomiting and are possibly involved in the development of learned aversion to contamination [43].

The mechanisms, by which these avoidance behaviors are controlled are not well known in vertebrates, but some of the specific neuronal signaling pathways that govern avoidance behavior in mice have been mapped. For example, the vomeronasal circuit was previously described to mediate male sexual preference, female sexual behavior, and predator avoidance. It was recently demonstrated that the vomeronasal organ also senses olfactory cues emitted by parasitized or infected conspecifics [41]. Mice typically spend more time investigating healthy individuals in comparison to sick, and this was found to be dependent on specific signaling molecules present in infected individuals' urine. To better understand the mechanisms, by which mice use the vomeronasal organ to sense and avoid contamination, four neuronally expressed formyl-peptide GPCRs were studied for their role in sensing disease-related ligands. Expression of these GPCRs *in vitro* in non-neuronal cells conferred sensitivity to pathogen and inflammation related compounds [44].

In *C. elegans*, several neural networks that control avoidance behavior and learned avoidance behavior have been mapped. Interestingly, certain cues are sensed by *C. elegans* and trigger both a molecular innate immune response and avoidance behavior. The GPCR receptor, OCTR-1 functions in at least ASH and ASI neurons to control immunity [18••]. While ASI neurons are required for pathogen avoidance behavior, ASH neurons coordinate an immune response that consists of the activation of microbial-killing and cellular-homeostatic pathways [18••,20]. This provides an example of the integration of multiple sensory stimuli that result in a global immune response that involves the activation of both immune-related pathways and pathogen avoidance. Yet to be answered is the timing of each of these responses and if these two distinct responses occur at the same time.

Other neuronal pathways potentially involved in sensing bacterial metabolites have been identified in *C. elegans*. *P. aeruginosa* metabolites, phenazine-1-carboxamide, and pyochelin, were shown to activate G-protein signaling in ASJ neurons, leading to expression of *daf-7* by ASJ neurons. Secreted DAF-7 binds to the TGF-β receptors in adjacent interneurons to activate the canonical TGF-β signaling pathway, promoting the avoidance of *P. aeruginosa* [24]. *C. elegans* is also able to avoid *P. aeruginosa* by detecting nitric oxide produced by the bacteria. Both the presence and removal of nitric oxide stimulates intracellular calcium increases in ASJ neurons. These changes (transients) in calcium are mediated by the redox sensing protein, TRX-1/thioredoxin, which switches between trans-nitrosylation activity and de-nitrosylation activity to promote the ON and OFF calcium transients respectively [45•].

In addition to the roles of neuropeptides in controlling the molecular immune response to pathogens, neuropeptides have been demonstrated to signal for avoidance behavior in *C. elegans*. INS-6, an insulin-like neuropeptide expressed in ASI neurons, promotes aversive behavior by blocking *ins-7* expression in URX neurons [30]. This circuit was further dissected to show that INS-11, a neuropeptide expressed in the intestine is increased upon infection. This results in the downregulation of *ins-6*, ultimately decreasing aversive behavior, possibly fine-tuning the avoidance of contaminated and non-contaminated food sources. INS-11 was also shown to regulate serotonin and insulin-like signaling in neurons to control avoidance behavior [35••].

Conclusions

We have presented recent and some landmark studies that provide evidence of the roles of neural signals in the control of immune response to pathogens. The neural tractability of *C. elegans* permitted the identification of specific neurons that control immune pathways. Some of these pathways, particularly those in which neurotransmitters control immune responses, appear to be evolutionarily conserved and thus could be further explored in higher organisms. Advances in technology have led to the mapping of the complete volume of the adult *Drosophila melanogaster* brain [46] and over 300 neurons were traced in a brain wiring map in mice [47]. Using these tools, with other technologies that have made studying individual neurons possible in higher order organisms, the identification of specific neurons and signaling pathways that govern neural-immune control is foreseeable. It was recently predicted that the next revolution in immunology would come by integrating the neural circuits that regulate innate and adaptive immunity, including the mechanisms by which the nervous system senses microbes, to ultimately fine-tune the immune response [1]. One of the benefits of understanding these neural-immune connections is that they can be employed to control excess inflammation and/or stimulate proper immune responses during infection and inflammatory diseases. Some of the compounds that alter neuronal-immune signaling are being used to treat human diseases, in which excess inflammation causes damage.

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Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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