REVIEW

Importance of crosstalk between the microbiota and the neuroimmune system for tissue homeostasis

Kunyu Li, Kevin Ly, Sunali Mehta & Antony Braithwaite
Department of Pathology, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

Abstract
The principal function of inflammation is cellular defence against ‘danger signals’ such as tissue injury and pathogen infection to maintain the homeostasis of the organism. The initiation and progression of inflammation are not autonomous as there is substantial evidence that inflammation is known to be strongly influenced by ‘neuroimmune crosstalk’, involving the production and expression of soluble signalling molecules that interact with cell surface receptors. In addition, microbiota have been found to be involved in the development and function of the nervous and immune systems and play an important role in health and disease. Herein, we provide an outline of the mechanisms of neuroimmune communication in the regulation of inflammation and immune response and then provide evidence for the involvement of microbiota in the development and functions of the host nervous and immune systems. It appears that the nervous and immune systems in multicellular organisms have co-evolved with the microbiota, such that all components are in communication to maximise the ability of the organism to adapt to a wide range of environmental stresses to maintain or restore tissue homeostasis.

Keywords: dysbiosis, immune cells, immune system, inflammation, microbiota, nervous system, neuroimmune regulation, neurons, quorum sensing, signalling molecules

INTRODUCTION
The immune system is a built-in defence system in complex organisms that exists to protect the host from health threats such as tissue injury, pathogen infection and tumorigenesis. During immune defence, the biological process of inflammation is responsible for initiating an immune response. This involves the production and secretion of inflammatory cytokines and chemokines, which, together with the expression of cell surface receptors, form signalling cascades that integrate both innate and adaptive immune cells into the immune response. It was originally thought that the cells in the immune system are solely responsible for facilitating inflammation and immune responses. However, there are clear regulatory links with the nervous system that show the immune system is not autonomous, but functions in close association with the nervous system. It is now clear that these two systems are intimately connected and reciprocally influence the function of each other, and this constitutes the neuroimmune network. Anatomically, nerves and immune cells are connected throughout the human body. Mechanistically, nerve cells and
immune cells produce soluble factors that communicate through their cognate receptors to regulate immune processes such as inflammation. Indeed, the central nervous system (CNS) has been suggested to be a virtual secondary lymphoid organ that is involved in the regulation of immune responses throughout the human body. Communication between neurons and immune cells in the regulation of inflammation contributes not only to cellular defence, but also to inflammatory-associated pathology. As a result of restrictive entry of immune cells into the brain, brain cells other than the neurons, such as microglia and astrocytes, also act as a first line of defence to control inflammation and immune responses in both CNS and peripheral tissues. In addition to communication between different cells within the organism, interspecies communication between the microbiota and host brain cells, neurons and immune cells occurs, and can have an impact on health and disease. Herein, we briefly summarise the involvement of neurons and immune cells in the regulation of inflammation, as well as the involvement of microbiota in the development of the nerve and immune systems. We then focus on recent findings on the contribution of microbiota in the regulation of cellular defence.

**ROLE OF IMMUNE CELLS AND NEURONS IN INFLAMMATION AND CELLULAR DEFENCE**

**The initiation of immune responses**

All living organisms are constantly exposed to environmental threats and potential invasion by harmful substances. To protect against these dangers, mammalian hosts operate a surveillance mechanism that is commonly known as immunosurveillance. It is a monitoring process of the immune system to detect pathogen invasion and neoplastically transformed cells and destroy them to enhance the survival of the host. This task is performed by the joint action of the two arms of the immune system: the innate and the adaptive. Innate immunity is the first line of defence against pathogen invasion, and innate immune cells react immediately upon detection of ‘danger’ in an antigen non-specific manner. Adaptive immunity is the second line of defence that requires the help of innate immune cells for activation and adaptive immune cells react to their targets in an antigen-specific manner. The family of pathogen-associated molecular patterns (PAMPs) that are derived from microbes and damage-associated molecular patterns (DAMPs) derived from host cells are the main categories of ‘danger’ molecules that initiate innate immune responses and inflammation. Upon pathogen invasion or tissue damage, these molecules are released and detected by pattern recognition receptors (PRRs) that are expressed by innate surveillance immune cells. Toll-like receptors (TLRs) are a class of PRRs that sense the presence of conserved microbial molecular patterns for early immune recognition of a pathogen. The binding of PAMPs or DAMPs to TLRs on innate immune cells such as macrophages initiates infectious or non-infectious acute inflammatory responses, respectively. These events result in intracellular cascades such as the Nuclear factor-kappa B (NF-κB) pathway to initiate the transcription of both pro- and anti-inflammatory cytokines. This leads to subsequent activation and recruitment of adaptive lymphocytes to the site of inflammation, where cytokines such as IFN-γ, IL-10 or TGF-β are released to clear the infection and/or to settle down inflammation and initiate tissue repair (Figure 1). When acute inflammation fails to settle, it can progress to prolonged, low-level inflammation resulting in chronic conditions such as autoimmune diseases and cancer. Therefore, the level and the process of inflammation are tightly regulated to avoid inflammation-associated pathology.

**The neuronal communications**

The nervous system regulates numerous physiological responses, including movement, digestion, body temperature, stress and secretion of various enzymes and hormones. All these responses are regulated by communication between neurons of different parts of the nervous system, with the central nervous system (CNS) in the brain and the peripheral nervous system (PNS) that connects the CNS to every part of the body through the spinal cord. Neurons communicate with each other to send messages to and from the brain and spinal cord to various parts of the body by both electrical and chemical signals involving a range of soluble molecules that interact with cell surface receptors. The signalling process initiates as dendrites, which receive external stimuli followed by the cell body generating an electrical
signal (action potential) that propagates along the axon to the nerve terminal. This results in the release of chemical signalling molecules as neuronal messengers, such as neurotransmitters, to regulate the responses of target cells such as neurons, muscles and immune cells (Figure 2a).

Cells of the nerve system participate in immune surveillance and cellular defence at different levels and regions via both neural and non-neural communicating pathways. These include the blood-brain barrier (BBB) pathway, the neuroendocrine pathways and the microbiota–gut–brain (MGB) axis, in which soluble molecules such as neurotransmitters, hormones and cytokines are the main communication tools.

**Neuroimmune regulation of inflammation and cellular defence**

Research in the area of neuroimmunology has revealed that neurological signalling utilising soluble molecules is involved in the communication between neurons and immune cells, which regulates inflammation and immune responses. Neurons have been found to express various cytokine and chemokine receptors such as the IL-6 receptor and CXCR4 that allow them to receive proinflammatory stimuli from immune cells. Treatment with TNF-α and IL-1β has been shown to evoke a neural response in mouse vagus nerve cells in a dose-dependent manner. Indeed, these proinflammatory cytokines were found to be more effective than LPS, norepinephrine, and nerve growth factor for activating primary neurons in cultures. In addition to immune cells, human and mouse neurons express TLRs that enable them to directly detect danger signals. Expression of TLR-7 by mouse airway neurons was also found to be increased after stimulation with neuropeptide substance P and contributes to airway inflammation and immune defence. Activation of sensory neurons through either cytokine or PAMPs/DAMPs leads to the production of neuronal signalling molecules, including neurotransmitters (reviewed in Pinho-Ribeiro et al. ; Figure 2b). In addition, neurons are also capable of producing cytokines to regulate inflammation. This has been observed where stimulation of P2X purinoceptor 7
receptors (P2X7Rs) on the neural membrane trigger
the release of multiple cytokines by mouse neurons
and provide neuroprotection.31

Similar to neurons, many subsets of immune
cells have been found to express receptors for
various neurotransmitters as well as being
capable of producing neurotransmitters upon
activation.32,33 Serotonin, which is a multi-
functional neurotransmitter, has been found to
drive both proinflammatory34 and anti-
inflammatory35,36 responses through serotonin
receptors expressed on mouse immune cells such
as T cells. Gamma-aminobutyric acid (GABA),
which is a neurotransmitter in the brain and
pancreatic islets, has been found to inhibit the
release of inflammatory cytokines by human
peripheral blood mononuclear cells (PBMC) and
CD4+ T cells by blocking calcium signalling and
NF-κB activity.37,38 Treatment with GABA or
GABAergic drugs in mouse bone marrow-derived
macrophages (BMDM) inhibited the production of
proinflammatory cytokines TNF-α and IL-6 but
enhanced antimicrobial responses of BMDM
through intracellular calcium release and
autophagy.39 Recent studies by two independent
groups have both reported that mouse T cell-
derived acetylcholine promotes immune
infiltration and the production of
proinflammatory cytokines at the site of
pathogen invasion to clear the infection.40,41

Therefore, signalling through neurotransmitters
and their receptors can lead to either pro- or
anti-inflammatory responses, depending on the
local stimuli and the target cells they are acting
on (reviewed in Hodo et al.).42

Overall, cells of the immune and nervous
systems communicate with each other through a
common language using soluble molecules and
cell surface receptors. Such signalling
processes allows the integration of neurological and
immunological signals to detect pathogen
invasion, regulate inflammation and orchestrate
tissue homeostasis.33,43,44

**MICROBIOTA ARE INVOLVED IN THE
DEVELOPMENT OF THE NERVOUS AND
IMMUNE SYSTEMS AND MODULATION
OF INFLAMMATION**

It was originally considered that the foetal and
perinatal immune systems develop in a relatively
sterile environment where microbial and maternal
immune cells have restricted entry. However, the
human placenta and amniotic fluid have been
found to harbour a unique microbiome, which
shares features of microbiota detected in the
infant meconium and might contribute to the
initiation of microbiota colonisation in the
gut.45,46 In addition, a recent human study
discovered the presence of several types of

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**Figure 2.** Signal transduction in neurons: (a) a schematic of a neuron and (b) neuronal activations of immune cells. The sensory neuronal cells express PPRs, which detect the presence of danger. This leads to activation of the sensory neurons and subsequent production of neurotransmitters and no cytokines, which in turn regulate inflammation and activation of immune cells.
bacteria in the foetal gut, skin, placenta and lungs in the 2nd trimester of gestation. These bacteria were found to be able to induce activation of memory T cells isolated from the foetal mesenteric lymph node, suggesting their contribution in priming the foetal immune cells during early human development. It is now clear that microbial encounters occur in at least three stages of early mammalian life: in utero during pregnancy, microbes acquired at the time of delivery, and microbes established postnatally by the acquisition of maternal and environmental bacteria. The early life exposures to microbiota imprint long-lasting changes in the offspring’s nervous and immune systems that affect the health and risk of diseases throughout life. The enteric nervous system (ENS), which is part of the autonomic nervous system (ANS), is a unique nervous system that largely functions independently from but does communicate with the CNS. Innervation of the gut by a network of ENS provides a unique opportunity for gut microbiota to form a multidirectional communication axis with the local neurons, immune cells and also cells of the brain. This forms the microbiota-gut-brain (MGB) axis, which drives a variety of processes including intestinal barrier function, blood-brain barrier (BBB) function and neuroimmune crosstalk to regulate not only brain health but also the development and function of the host defence systems (reviewed in Bistoletti et al. and others).

Microbiota are important for the development of the nervous and immune system

The importance of microbiota in the development and health of the brain and CNS has been clearly shown in mice lacking gut microbiota, where development of anxiolytic-like behaviour and neurodegenerative disease was observed. Compared to specific pathogen-free mice, germ-free mice were found to have altered expression of genes involved in signalling mechanisms that affect motor control and anxiety behaviour. Mice transplanted with gut microbiota from patients with neurobehavioral disorders also showed altered brain structure and anxious behaviour. Studies in obese and non-obese individuals also found that alterations in microbial composition affect brain microstructure and cognitive function. Maternal probiotic administration of mice with Lactobacillus acidophilus and Bifidobacterium infantis has been shown to promote neuronal and oligodendrocyte progenitor cell development in the offspring. At the molecular level, the microbiota has been found to not only regulate the production, transportation and functioning of neurotransmitters but are also capable of producing neurotransmitters to regulate the development of the brain and CNS. Bifidobacteria, which are a group of commensal bacteria in the gut, have been found to harbour the gene and enzymatic machinery to generate neurotransmitters such as GABA and tyrosine. Altering the composition of the gut microbiota with a high-sugar and high-fat diet altered neurotransmitter metabolism and affected brain function. Although the precise molecular mechanisms of microbiota interaction with host cells are largely unknown, there is growing evidence that the microbiota interact with host cells and affect their development and function through microbial-derived soluble molecules (reviewed in Silva et al. and Wall et al.).

Short-chain fatty acids (SCFAs) are the one of the most studied metabolites produced by the gut microbiota through fermentation of dietary fibre and indigestible polysaccharides. Microbial-derived SCFAs has been found to promote the production of serotonin by host cells. This contributes to the maintenance of the neuroanatomy and maturation of the enteric nervous system (ENS). Mice fed with a diet containing a low level of SCFAs during gestation have been found to have impaired neurocognitive functions of the offspring. Germ-free mice and mice deficient for SCFA receptors have both been found to display global defects in the maturation and function of microglial cells, leading to impaired cellular defence in the CNS. In another mouse study, microbial metabolites other than SCFAs derived from spore-forming gut bacteria were also found to serve as signalling molecules to regulate the biosynthesis of serotonin, contributing to gastrointestinal motility and platelet function.

To endow the newborn with the ability to mount an immune response against pathogen invasion after birth, mammalian immunity starts to develop during the prenatal period of life and continues to evolve throughout the lifetime of the individual. Maternal microbiota and early life microbiota exposure during birth and through breast milk have been found to influence the
lineage development and the education of the hematopoietic cells, as well as functional responses of immune cells in the newborn.\textsuperscript{49,80} The effects of microbiota on immune cells have also been found to occur via their metabolites. Mucosal-associated invariant T cells (MAIT) are gut resident innate immune cells that play an important role in gut inflammation and defence against pathogen infection. Bacterial riboflavin-derived antigen, 5-OP-RU, was found to be able to travel from mucosal surfaces to the thymus and be taken up by the major histocompatibility complex class I-related protein (MR1) to promote the generation of MAIT.\textsuperscript{81,82} Consequently, early life exposure to microbial riboflavin can regulate the development of and also interact with MAIT cells, to promote gut immunity and homeostasis.\textsuperscript{83} The SCFA butyrate, a major gut metabolite, has also been found to facilitate either the differentiation of T regulatory cells or effector T helper-1 cells under different conditions, suggesting that the influence of gut microbiota on the differentiation of immune cells is subjected to the local environment.\textsuperscript{84}

**Microbiota communicate with host cells to modulate inflammation**

In addition to the development of the nervous and immune systems, microbiota influence the ability of neurons, brain and immune cells to regulate inflammation.\textsuperscript{85} Astrocytes are a subtype of glial cells that have a wide range of functions within the CNS, including structural support in the brain, uptake and release of neurotransmitters, defence against oxidative stress, tissue repair and maintenance of the BBB.\textsuperscript{86-88} They have also been reported to regulate inflammation and contribute to a range of neurodegenerative diseases, such as Alzheimer’s and Parkinson’s diseases.\textsuperscript{89} A recent study in germ-free mice showed that microbiota are required for a subset of LAMP1\textsuperscript{+}TRAIL\textsuperscript{+} astrocytes to fight inflammation in a mouse model of autoimmune encephalomyelitis (EAE). Using specific gene knockout mice, these astrocytes were found to limit inflammation in the CNS by inducing apoptosis of inflammatory T cells through binding of TRAIL to death receptor 5 (DR5) expressed on T cells.\textsuperscript{90} More importantly, the expression of TRAIL on astrocytes was dependent on the production of IFN-\(\gamma\) by meningeal natural killer cells (NK), which were induced by the microbiota.\textsuperscript{90} This study identifies a previously unknown mechanism of how microbiota modulate the production of proinflammatory cytokines by brain ‘immune cells’ to support brain health.

Another mechanism of microbiota interaction with the CNS is through the BBB, where they can alter BBB integrity, change BBB transport rates and induce the release of neuroimmune substances from the barrier cells (reviewed in Logsdon et al.).\textsuperscript{91} The microbiota have also been found to protect against inflammation in the neonatal brain by regulating BBB function and preventing IL-1\(\beta\)-induced microglia and astrocyte activation through NF-\(\kappa\)B/\(\kappa\)B signalling in the developing brain.\textsuperscript{67}

Aryl hydrocarbon receptor (AhR) is a transcription factor found in virtually all neurons and some subsets of immune cells. It is involved in the development of nervous and immune systems, acts as a biosensor in intestinal neural signalling to regulate intestinal immunity and regulates the onset and progression of inflammation.\textsuperscript{92-97} The microbiota have been found to induce neural expression of AhR, which enable the neurons to sense and respond to the luminal environment by upregulating neuron-specific effector mechanisms.\textsuperscript{96} The effects of microbiota on AhR have been found to occur via SCFAs where they upregulate AhR signalling to limit intestinal inflammation by mediating IL-10 and IL-22 production.\textsuperscript{98} An interdependent relationship has been found between the microbiota and AhR signalling in regulating inflammation. Mice fed with a diet lacking AhR ligands that drive AhR signalling\textsuperscript{99} were found to have alterations of the gut microbiota correlating with reduced IgA levels.\textsuperscript{100} Mice fed with AhR ligands-free diet also had enhanced susceptibility to dextran sodium sulphate (DSS) induced colitis that correlated with alterations in the microbiome.\textsuperscript{99}

In addition to their indirect effects on immune responses, microbiota and their derivatives can also affect immune cells directly to modulate inflammation. CD4\textsuperscript{+}CD8\textsuperscript{+} double-negative T cells (DNTs), which are important players in autoimmune disease, were found to be dramatically increased in both the brain and peripheral blood of stroke patients and a mouse model of neuroinflammation.\textsuperscript{101} SCFAs derived from intestinal bacteria of patients with Alzheimer’s disease were recently found to activate intestinal NLRP3 inflammasome, leading to upregulation of proinflammatory cytokine
production by intestinal DNTs. In addition, bacterial N-formylated peptides and the pore-forming toxin α-haemolysin have also been shown to induce calcium influx and an action potential, which directly activate sensory neurons to modulate inflammation and immune infiltration.

Microbiota dysbiosis is associated with neuroimmune dysregulation of inflammation

A highly diverse gut microbial community has beneficial effects on brain health, the function of the nervous immune system and cellular defence against pathogen infection. Under normal physiological conditions, gut commensal microbes establish a mutualism, or symbiosis with the host that allows better nutrient supply, improved metabolic attributes such as vitamins and fatty acids, and defence against invasion by pathogenic microorganisms. However, in some instances, the symbiotic relationship is impaired leading to dysbiosis. Dysbiosis is characterised by disruption to microbial homeostasis, reduced microbial diversity and loss of beneficial bacteria. It is associated with a range of diseases and complications, including inflammation-induced autoimmunity,109 autoimmune diseases,110-113 impaired immune response to vaccination and viral infection,114,115 and defective brain function and brain inflammation.116,117

Multiple factors are known to lead to microbial dysbiosis, and antibiotic usage is the most studied. Experimental evidence suggests that antibiotic use during pregnancy, infancy and childhood dramatically alters the composition of the gut microbiota, leading to dysbiosis that correlates with long-lasting health complications. Administration of antibiotics transiently alters the microbial composition and affect central levels of brain-derived neurotrophic factors and behaviour in mice. In a recent study, altering the microbial composition by antibiotics was found to decrease the levels of serotonin and dopamine in the hypothalamus and the circulation of piglets. Decreased bacteria-derived SCFAs by antibiotic usage also affect the ability of the gut microbiota to control intestinal inflammation and alter the immune response and neuronal signalling in the gut. The pathogenic mechanisms caused by microbial dysbiosis are associated with alterations of intestinal permeability, BBB function and metabolic pathways of several neurotransmitters affecting neuroimmune regulation of inflammation. Moreover, infection by SARS-CoV-2 was reported to alter the composition of gut microbiota and promote intestinal and systemic inflammation leading to BBB damage. These in turn are associated with activation of microglia and astrocytes to promote the degeneration of neurons and inflammation in the brain. Therefore, dysbiosis caused by either antibiotic or pathogen infection sets up a feedback circle to further promote dysbiosis and inflammation.

Neurological stress and microbial dysbiosis are associated with and contribute to neuroimmune dysregulation of inflammation

The HPA axis is a neuroendocrine mechanism that mediates a stress response to control physiological and immunological responses. Although stress is very common, not all stresses are associated with neuroinflammation/pathology and the nuances that link one to the other are still inconclusive. While short-term stress can enhance immunoprotection, chronic stress is known to suppress protective immune responses and exacerbate inflammation to promote pathological immune responses. In a mouse study, chronic stress was found to stimulate the release of neuron-derived damage signals, which attract and activate microglia to eliminate the ‘distressed’ neurons. This caused destruction of the connection between the distressed neuron with other neurons, leading to loss of connectivity between brain cells and hence functional complications and brain pathology. Norepinephrine, which acts both as a stress hormone and neurotransmitter, has been found to compromise immune responses by attenuating the production of IFN-γ and augmenting IL-10 production in vitro, in mice and humans after LPS challenge. Stress hormones such as glucocorticoid have been shown to promote cancer progression by suppressing the production of anti-tumor IFN-γ and inducing immune dysfunction. In addition to direct immunomodulatory effects through stress hormones, stress can also lead to neuroimmune dysregulation of inflammation through microbial dysbiosis. Both animal and human research on the effects of different stress
paradigms have found that chronic stress and early life stress affect the structure and function of the gut microbiota, which in turn affects immunoregulatory responses and the microbiota–gut–brain axis.¹⁴²–¹⁴⁵ A study in an experimental model of psychological stress also showed that stress-induced microbial dysbiosis was associated with compromised intestinal and BBB function in rodents.¹³⁸ The association between neurological stress and dysbiosis has also been demonstrated in a mouse study in which maternal stress altered the vaginal microbiome, which in turn affected the microbial composition in the neonatal gut.¹⁴⁶ This corresponded with changes in metabolite profiles and disruption of amino acid profiles, which affected neonatal brain development and increased risk of neurological disorders.¹⁴⁶,¹⁴⁷ Early life stress has been shown to increase plasma corticosterone that was associated with an increase in intestinal permeability of the immature gut in 10-day-old rat pups.¹⁴⁸ Furthermore, chronic stress also enhanced the expansion of inflammation-promoting bacteria, leading to dysbiosis, compromised function of the mucosal barrier and facilitating inflammation as shown in a mouse model of DSS-induced colitis.¹⁴⁹

Besides neurological stress, gut inflammation in various contexts, including pathogen infection,¹⁵⁰ chemical treatment¹⁵¹ and defective immunity,¹⁵² has also been found to drive bacterial dysbiosis as the inflamed gut is particularly conducive to the blooms of pathogenic but not to symbiotic microbes.¹⁵³ Gut microbiota isolated from mice that had brain inflammation can also alter brain functional connectivity when transplanted into germ-free mice.¹⁵⁴ For example, Akkermansia muciniphila (A. muciniphila), which is a species of human intestinal mucin-degrading bacterium, has been shown to have anti-inflammation effects¹⁵⁵,¹⁵⁶ and alters gut barrier function.¹⁵⁷ In a recent study, expansion of A. muciniphila in the gut was shown to upregulate the T regulatory cell response to ameliorate neuroinflammation in an experimental mouse model of autoimmune encephalomyelitis (EAE).¹⁵⁸ Collectively, these findings suggest that inflammation, chronic stress and microbial dysbiosis are closely associated and interplay with each other to influence the outcome of neuroimmune regulation.¹²⁷ Therefore, the health of the gut and brain is interlinked, as intestinal inflammatory disorders and many disorders of the central nervous system (CNS) are often accompanied by each other, which are all related to the dysregulation of inflammation and compromised immune mechanisms.¹⁵⁹,¹⁶⁰

**The utilisation of host neuronal factors by pathogens to affect immune defence**

The microbiota can sense changes in the host environment to adjust their responses to the host to benefit their growth. Access to iron is important for bacterial survival and growth during infection. Therefore, sequestering iron is one of the strategies utilised by mammalian hosts to prevent the growth of pathogens.¹⁶¹ However, pathogenic Escherichia coli O157:H7 and Salmonella enterica serovar Typhimurium have been found to express genes that allow them to respond to catecholamines and norepinephrine to increase iron acquisition to enhance pathogen survival.¹⁶² These neurotransmitters also act as chemoattractants to increase mobility and upregulate the expression of genes that are associated with bacterial colonisation and virulence.¹⁶² Some pathogens have been reported to hijack the host regulatory mechanisms to facilitate their survival and infection. Staphylococcus aureus (S. aureus) has also been shown to be able to modulate inflammation by inducing calcium flux and action potentials in the host, which activates the sensory neurons to modulate an inflammatory response.¹⁰³ Streptococcus pyogenes are also able to directly activate nociceptors (a type of sensory neurons) by releasing streptomycin S.¹⁶³ Activation of nociceptor leads to the release of neuropeptide calcitonin gene-related peptide (CGRP) to inhibit the recruitment of neutrophils and phagocytic killing of S. pyogenes.¹⁶³ These findings suggest that pathogenic microorganisms promote their survival by evading the host defence systems.

**THE CONTRIBUTION OF MICROBIAL QUORUM SENSING IN CELLULAR DEFENCE**

**Interspecies communication via QS**

The ability of the microbiota to regulate their growth in response to environmental cues is largely because of a fundamental microbial system, the Quorum sensing (QS), which is a cell–cell communication process that bacteria use to monitor local population density.¹⁶⁴ It relies on
the production and detection of group-level response to chemical signalling molecules called autoinducers. As bacteria reproduce, an increase in the concentration of autoinducers allows bacteria to detect and respond to cell population density and nutrient deprivation in the environment by altering the programme of gene expression. QS has been found to regulate a variety of physiological functions in bacteria, including symbiosis, virulence, antibiotic production, sporulation and formation of biofilm/bacterial colonies. Thus, communication via the production of QS molecules allows individual bacteria within the community to share information, coordinate and carry out colony-wide activities to enhance the survival and fitness of the community.

Although receptor specificity is required for cooperation within the species, multiple QS receptors have been found to display a wide range of reactivities to both self and non-self-derived QS signals. This indicates that QS is also involved in the crosstalk between different microbial communities to regulate survival, competition and cooperation (Figure 3a). QS can regulate interspecies communication to shape the balance of the microbial community and influence the ability of opportunistic pathogens to cause infection. A study on S. aureus showed that the expression of genes by other Staphylococcal species under the control of the QS system exerts an inhibitory effect on the density and virulence of S. aureus. In another animal study, increased production of QS signalling molecule autoinducer 2 (AI-2) by Escherichia coli (E. coli) was found to counterbalance antibiotic-induced microbial dysbiosis. This favored the expansion of Firmicutes phylum, which is important for many gut functions and promoted recovery of gut homeostasis after antibiotic treatment. The findings of these studies suggest that interspecies communication using QS is required to maintain microbiota–host symbiosis and homeostasis.

The interplay between microbial QS and their mammalian host

Bacterial QS has also been found to modulate the functions of human neural and immune cells via a range of QS molecular targets that are expressed on the host cells. (Figure 3a). In a mouse study, three chemically diverse QS oligopeptides were found to be able to cross the BBB and influx into the mouse brain. QS molecules can also activate microglial cells to produce IL-6 and TNF-α in vitro in an NF-κB-dependent manner. In an in vitro transwell model, AI-2 was found to activate NF-κB-mediated inflammatory pathways followed by upregulation of negative feedback elements that might serve to temper the inflammatory response for immune tolerance to commensal microbes. In addition, colonisation of mice by commensal human gut bacteria was found to promote AI-2 production upon Vibrio cholerae invasion to protect the host from the pathogen infection.

While QS signals from commensal microbiota support gut homeostasis and immunity, those from pathogens can promote infection by manipulating the host immune system (Figure 3b). QS peptides PapRIV produced by Bacillus cereus species have been found to be able to cross the gastrointestinal tract and the BBB and reach the brain to activate the production of proinflammatory cytokines by microglia leading to neurotoxic effects. QS infection of macrophages by Group A Streptococcus was also found to inhibit their activation and production of proinflammatory cytokines through QS signalling. The QS molecule N-3O-dodecanoylhomoserine lactone (3O-C12) produced by Pseudomonas aeruginosa (P. aeruginosa) is able to modulate immune responses through multiple mechanisms. These include enhancing infiltration of immune cells and inflammatory responses, induce the release of reactive oxygen species (ROS) and promote apoptosis of neutrophils. Interestingly, serotonin has been found to activate bacterial QS to enhance the virulence of P. aeruginosa both in vitro and in an animal host. It is possible that QS is the control centre that allows pathogenic organisms to hijack the host components to enhance their survival and infection. Indeed, S. aureus was recently found to be able to produce neuromodulatory mediators leading to a biphasic response in extrinsic sensory afferent nerves, increased membrane permeability in cultured sensory neurons and altered intestinal motility and secretion. Genetic manipulation revealed that the production of these neuromodulatory mediators by S. aureus was initiated by two key QS-regulated classes of pore-forming toxins that mediate excitation and inhibition of extrinsic sensory nerves. The findings of this study suggest the potential roles
of bacterial QS molecules in the modulation of MGB communication to influence intestinal inflammation and pathogen infection.

To counterattack the immunomodulatory effect of microbes, host cells can also fight back by secreting signalling molecules that mimic QS molecules. Studies in zebrafish, mice and human cells showed that host AhR acts as a sensor to qualitatively and quantitatively detect *P. aeruginosa* QS molecules to regulate the scale and

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**Figure 3.** Quorum sensing signalling contributes to tissue homeostasis and pathology. (a) In response to pathogen invasion, commensal bacteria produce QS molecules. Signalling from these QS molecules inhibit the growth of pathogenic organisms, modulate immune responses and induce expansion of commensal bacteria to counterbalance dysbiosis and restore homeostasis of the gut microbial community. (b) QS molecules produced by pathogenic bacterial can modulate inflammation by targeting multiple host cells. They alter the gut permeability and cross the BBB to induce activate neurons and other brain cells such as microglia cells to upregulate the production of inflammatory cytokines. QS molecules can also bind to receptors on immune cells to induce secretion of proinflammatory mediators, induce apoptosis of neutrophils and inhibit macrophage activation. These events further promote pathogen infection, dysbiosis and inflammation, leading to tissue pathology.
intensity of host defence mechanisms. In addition, mouse mast cells were recently found to be able to detect 24 QS molecules derived from Gram-negative bacteria via G protein-coupled receptor Mrgprb2 to promote host defence against pathogen invasion. In response to bacteria or tight-junction disruption, or when cultured in PBS only, mammalian epithelia are also capable of producing an AI-2 mimic to activate QS. Decreased production of an AI-2 mimic by epithelial cells in the absence of bacterial derived pore-forming toxins suggests that sensing ‘danger’ is necessary for the host to defend against pathogen invasion. However, the consequence of QS activation was not investigated in this study. Nevertheless, the findings of this study suggest that the production of bacterial QS mimics by mammalian cells might foster cross-kingdom signalling to promote host-bacterial symbioses.

Thus, QS signals from commensal microbiota facilitate symbiosis, which is beneficial for host homeostasis and immunity, whereas QS from pathogenic organisms might represent a master control centre that regulates pathogen invasion. Through QS, microbiota influence the host immune response, MGB axis and development of inflammatory disorders.

CONCLUSION

Extensive research in the area of neuron–immune interaction has changed our view as to how the immune system functions. It is now clear that immune system is intimately linked with the nervous system in which each system is in constant communication with the other. This occurs through the sharing of secreted molecules and their respective receptors including both cytokines and neurotransmitters. It is also clear that this neuroimmune signalling is modulated by the gut microbiota which also involves secreted molecules, mostly bacterial metabolites such as SCFAs, highlighting a conserved mechanism of intercellular communication across evolution. This constant communication involving feedback and feedforward loops enables ongoing surveillance of the external and internal environments of the host organism to ensure physiological homeostasis and mutualism. Based on the same principle of enhancing the survival and fitness of the community/organisms, we also propose that neuroimmune communication is a strategy that multicellular organisms have adopted from bacterial quorum sensing to enhance the adaptability of the host. However, neurological stress, inflammation and dysbiosis can alter the symbiotic relationship, leading to dysregulation of the host defence mechanisms and tissue pathology. The involvement of microbiota in the development of the nervous and immune systems since the prenatal stage suggests that microbial dysbiosis could be the initiator that leads to dysregulation of inflammation via the neuroimmune network. Indeed, a ‘stressed gut’, which is associated with microbial dysbiosis, has been found to cause a ‘stressed mind’, leading to many health complications. Thus, maintaining a healthy gut microbiome appears to be the key for maintaining the health of the brain and immune system: enhancing immune defence and minimising inflammatory disorders. For instance, probiotics have been widely used to improve gut health and immune functions in both animals and humans. Psychobiotics, which are microbes with the ability to produce ‘mind-altering’ neurotransmitters, have also been suggested to be used as a potential therapeutic strategy in the prevention and/or treatment of certain neurological conditions and neuroimmune dysregulation. In the final analysis, the interplay between pathogen and their host might potentially influence the co-evolution of the host and the microbiota to affect the outcome of human health. Research on the molecular interactions between host- and microbial-derived soluble/signalling factors might also identify potential targets to treat pathogen infections, inflammation, as well as enhance host immune defence to other health threats.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.
AUTHOR CONTRIBUTION

Kunyu Li: Writing – original draft. Kevin Ly: Writing – review & editing. Sunali Mehta: Writing – review & editing. Antony Braithwaite: Writing – review & editing.

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Graphical Abstract

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Inflammation is an indispensable process that is required to initiate cellular defense and maintain homeostasis. The process of inflammation is tightly regulated by the immune system and beyond to ensure the survival benefit of the host and also limit pathology. This manuscript is about how microbiota contributes to the development and function of nerves and immune systems to regulate inflammation and immune response.