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

Correspondence

K Li, Department of Pathology, Dunedin School of Medicine, University of Otago, Hercus Building, 58 Hanover Street, PO Box 56, Dunedin 9012 New Zealand.
E-mail: kunyu.li@otago.ac.nz

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.[1] 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.[2]

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.[3-9] 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.[10] 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.[11] 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.[12] 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.[13] The signalling process initiates as dendrites, which receive external stimuli followed by the cell body generating an electrical
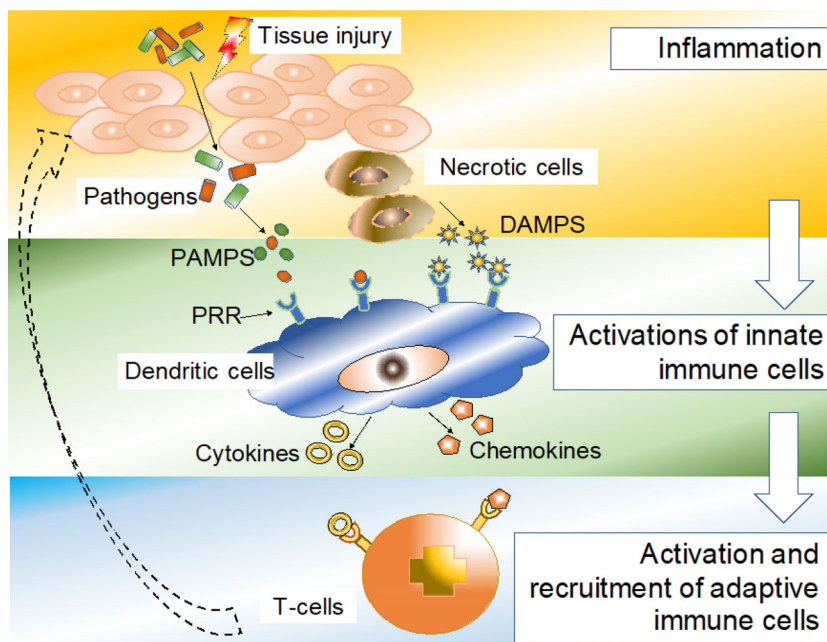
Figure 1. Signalling transduction and activation of an immune response upon detections of danger signals. Upon tissue injury or infection, PAMPs or DAMPs bind to PRRs on resident innate immune cells such as dendritic cells (DCs). This leads to the activation of DCs, and subsequent expression of inflammatory cytokines and chemokines, and migration to the local draining lymph nodes (LNs), where they also present antigen and co-stimulation signal to induce T-cell activation. The chemokines produced by innate cells at the site of inflammation serve as a signal to recruit more immune cells, including T cells in the local draining LNs. The cytokines produced by DC either on the site of inflammation or the local LNs serve as the third signal to further amplify the function of T cells to clear the infection following by settling down of inflammation and initiation of tissue repair.

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,[14] 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.[15] These include the blood-brain barrier (BBB) pathway,[16] the neuroendocrine pathways[17] and the microbiota–gut–brain (MGB) axis,[18] in which soluble molecules such as neurotransmitters, hormones and cytokines are the main communication tools.[1,19]

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.[20-22] 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.[23] Indeed, these proinflammatory cytokines were found to be more effective than LPS, norepinephrine, and nerve growth factor for activating primary neurons in cultures.[24] In addition to immune cells, human and mouse neurons express TLRs[25,26] that enable them to directly detect danger signals.[27,28] 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.[29] 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.[30]; Figure 2b). In addition, neurons are also capable of producing cytokines to regulate inflammation. This has been observed where stimulation of P2X purinoceptor 7
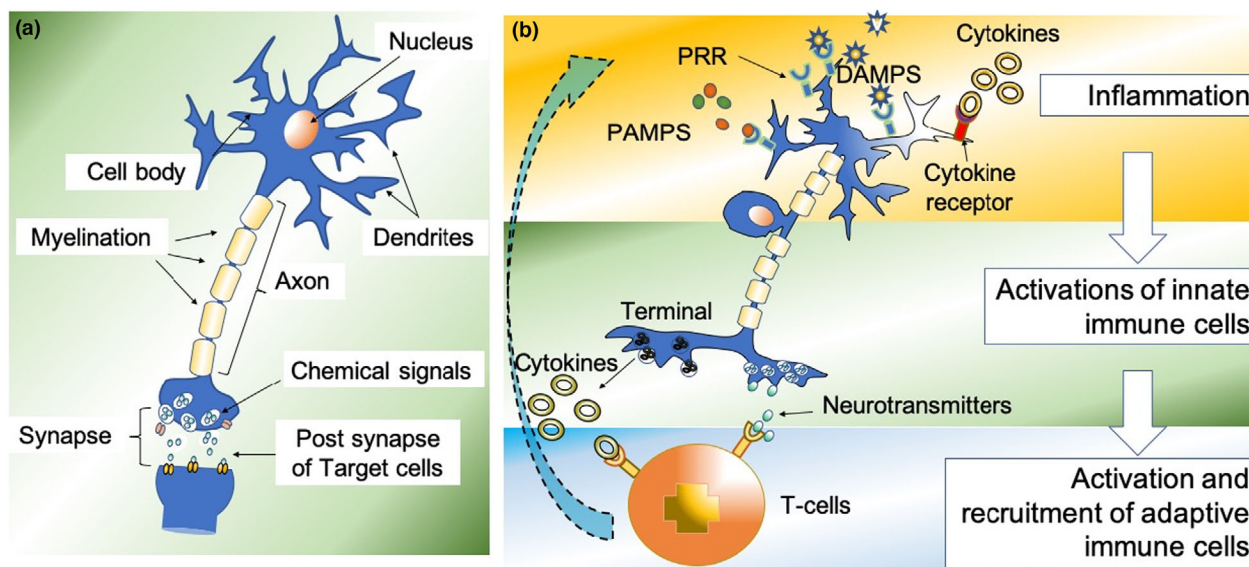
Figure 2. Signal transduction in neurons: **(a)** a schematic of a neuron and **(b)** neuronal activations of immune cells. The sensory neuronal cells express PPRs, which detect the presence of danger. This leads to activation of the sensory neurons and subsequence production of neurotransmitters and no cytokines, which in turn regulate inflammation and activation of immune cells.

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 multifunctional neurotransmitter, has been found to drive both proinflammatory[34] and anti-inflammatory[35,36] 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

bacteria in the foetal gut, skin, placenta and lungs in the 2nd trimester of gestation.[47] 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.[47] 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.[48-50] 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.[51-55] 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.[56] 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[57] but also the development and function of the host defence systems (reviewed in Bistoletti *et al.*[18] and others).[58-60]

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.[61-63] 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.[64] Mice transplanted with gut microbiota from patients with neurobehavioral disorders also showed altered brain structure and anxious behaviour.[65] Studies in obese and non-obese individuals also found that alterations in microbial composition affect brain microstructure and cognitive function.[66] 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.[67] 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.[68,69] *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.[70] Altering the composition of the gut microbiota with a high-sugar and high-fat diet altered neurotransmitter metabolism and affected brain function.[71] 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.*[72] and Wall *et al.*).[73]

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.[74] This contributes to the maintenance of the neuroanatomy and maturation of the enteric nervous system (ENS).[75] Mice fed with a diet containing a low level of SCFAs during gestation have been found to have impaired neurocognitive functions of the offspring.[76] 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.[77] 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.[78]

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.[79] 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.[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.[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.[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.[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.[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.[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.[89] A recent study in germ-free mice showed that microbiota are required for a subset of LAMP1$^+$TRAIL$^+$ 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.[90] More importantly, the expression of TRAIL on astrocytes was dependent on the production of IFN-γ by meningeal natural killer cells (NK), which were induced by the microbiota.[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*.).[91] The microbiota have also been found to protect against inflammation in the neonatal brain by regulating BBB function and preventing IL-1β-induced microglia and astrocyte activation through NF-κB/IκB signalling in the developing brain.[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.[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.[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.[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[99] were found to have alterations of the gut microbiota correlating with reduced IgA levels.[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.[99]

In addition to their indirect effects on immune responses, microbiota and their derivatives can also affect immune cells directly to modulate inflammation. CD4$^-$/CD8$^-$ 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.[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.[102] 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.[103]

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.[104,105] 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.[106-108] 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 pathology,[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.[118] Administration of antibiotics transiently alters the microbial composition and affect central levels of brain-derived neurotrophic factors and behaviour in mice.[119] 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.[120] 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.[121-124] 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.[125-128] 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.[129] These in turn are associated with activation of microglia and astrocytes to promote the degeneration of neurons and inflammation in the brain.[130-132] 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.[133-135] 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.[136] 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.[137] Stress hormones such as glucocorticoid have been shown to promote cancer progression by suppressing the production of anti-tumor IFN-γ and inducing immune dyfunction.[138-141]

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 treatment[151] 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 effects[155,156] 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.[165] 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.[165,166] 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.[167-171] 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.[172]

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.[173] 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.[174,175] 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*.[176] 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.[177] This favored the expansion of *Firmicutes phylum*, which is important for many gut functions and promoted recovery of gut homeostasis after antibiotic treatment.[177] 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[178,179] (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.[180] QS molecules can also activate microglial cells to produce IL-6 and TNF-α *in vitro* in an NF-κB-dependent manner.[161] 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.[181] 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.[182]

While QS signals from commensal microbiota support gut homeostasis and immunity, those from pathogens can promote infection by manipulating the host immune system[178] (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.[179] *In vitro* infection of macrophages by Group A *Streptococcus* was also found to inhibit their activation and production of proinflammatory cytokines through QS signalling.[183] The QS molecule N-3O-dodecanoyl-homoserine 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.[184-188] Interestingly, serotonin has been found to activate bacterial QS to enhance the virulence of *P. aeruginosa* both *in vitro* and in an animal host.[189] 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.[190] 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.[190] The findings of this study suggest the potential roles
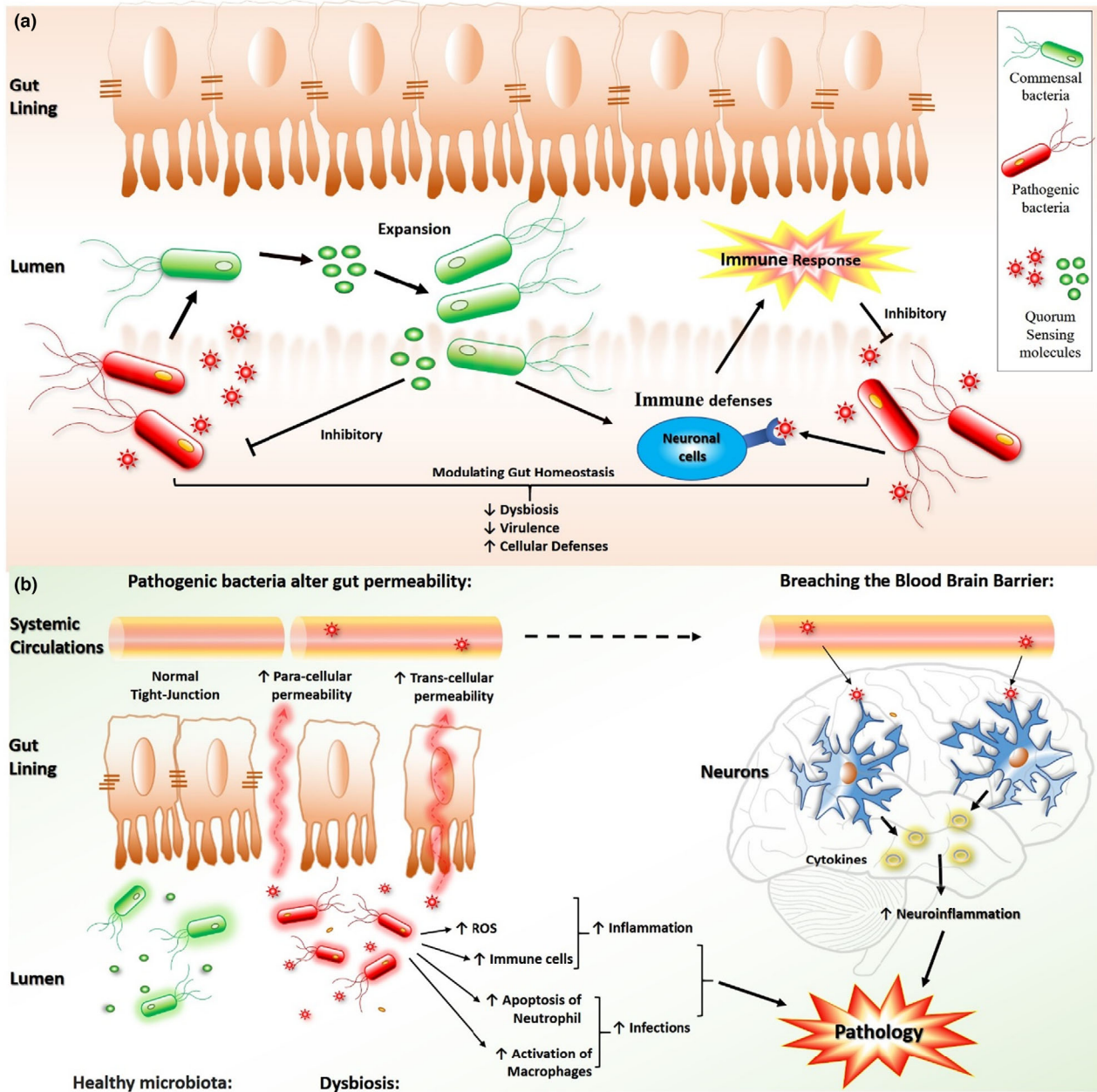
Figure 3. Quorum sensing signalling contributes to tissue homeostasis and pathology. **(a)** In response to pathogen invasion, commensal bacteria produce QS molecules. Signalling from these QS molecules inhibit the growth of pathogenic organisms, modulate immune responses and induce expansion of commensal 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.

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

intensity of host defence mechanisms.[191] 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.[192] 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.[193] 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.[193] 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.[178,194,195,196]

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.[197] 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.[198,199] For instance, probiotics have been widely used to improve gut health and immune functions in both animals and humans.[200,201] 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.[202] 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.

ACKNOWLEDGMENTS

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.

REFERENCES

1. Dantzer R. Neuroimmune interactions: from the brain to the immune system and vice versa. *Physiol Rev* 2018; **98**: 477–504.
2. Negi N, Das BK. CNS: not an immunoprivilaged site anymore but a virtual secondary lymphoid organ. *Int Rev Immunol* 2018; **37**: 57–68.
3. Xu S, Lu J, Shao A, Zhang JH, Zhang J. Glial cells: role of the immune response in ischemic stroke. *Front Immunol* 2020; **11**: 294.
4. Williams K Jr, Ulvestad E, Cragg L, Blain M, Antel JP. Induction of primary T cell responses by human glial cells. *J Neurosci Res* 1993; **36**: 382–390.
5. Antel JP, Becher B, Ludwin SK, Prat A, Quintana FJ. Glial cells as regulators of neuroimmune interactions in the central nervous system. *J Immunol* 2020; **204**: 251–255.
6. Chhatbar C, Prinz M. The roles of microglia in viral encephalitis: from sensome to therapeutic targeting. *Cell Mol Immunol* 2021; **18**: 250–258.
7. Wyatt-Johnson SK, Brutkiewicz RR. The Complexity of microglial interactions with innate and adaptive immune cells in Alzheimer's disease. *Front Aging Neurosci* 2020; **12**: 592359.
8. Olson JK, Miller SD. Microglia initiate central nervous system innate and adaptive immune responses through multiple TLRs. *J Immunol* 2004; **173**: 3916–3924.
9. Ibiza S, García-Cassani B, Ribeiro H *et al*. Glial-cell-derived neuroregulators control type 3 innate lymphoid cells and gut defence. *Nature* 2016; **535**: 440–443.
10. Paape MJ, Shafer-Weaver K, Capuco AV, Van Oostveldt K, Burvenich C. Immune surveillance of mammary tissue by phagocytic cells. *Adv Exp Med Biol* 2000; **480**: 259–277.
11. Ramadan A, Land WG, Paczesny S. Editorial: danger signals triggering immune response and inflammation. *Front Immunol* 2017; **8**: 979.
12. Mueller C. Danger-associated molecular patterns and inflammatory bowel disease: is there a connection? *Dig Dis* 2012; **30**(Suppl 3): 40–46.
13. Lovinger DM. Communication networks in the brain: neurons, receptors, neurotransmitters, and alcohol. *Alcohol Res Health* 2008; **31**: 196–214.
14. Franco R, Pacheco R, Lluis C, Ahern GP, O'Connell PJ. The emergence of neurotransmitters as immune modulators. *Trends Immunol* 2007; **28**: 400–407.
15. Eskandari F, Webster JI, Sternberg EM. Neural immune pathways and their connection to inflammatory diseases. *Arthritis Res Ther* 2003; **5**: 251–265.
16. Marchetti L, Engelhardt B. Immune cell trafficking across the blood-brain barrier in the absence and presence of neuroinflammation. *Vasc Biol* 2020; **2**: H1–H18.
17. Savino W, Silva PO, Besedovsky H. Network of bidirectional interactions between the neuroendocrine and immune systems. Preface. *Ann NY Acad Sci* 2009; **1153**: xi.
18. Bistoletti M, Bosi A, Banfi D, Giaroni C, Baj A. The microbiota-gut-brain axis: focus on the fundamental communication pathways. *Prog Mol Biol Transl Sci* 2020; **176**: 43–110.
19. ThyagaRajan S, Priyanka HP. Bidirectional communication between the neuroendocrine system and the immune system: relevance to health and diseases. *Ann Neurosci* 2012; **19**: 40–46.
20. Sawada M, Itoh Y, Suzumura A, Marunouchi T. Expression of cytokine receptors in cultured neuronal and glial cells. *Neurosci Lett* 1993; **160**: 131–134.
21. Tran PB, Banisadr G, Ren D, Chenn A, Miller RJ. Chemokine receptor expression by neural progenitor cells in neurogenic regions of mouse brain. *J Comp Neurol* 2007; **500**: 1007–1033.
22. Salvador AF, de Lima KA, Kipnis J. Neuromodulation by the immune system: a focus on cytokines. *Nat Rev Immunol* 2021; **21**: 526–541.
23. Zanos TP, Silverman HA, Levy T *et al*. Identification of cytokine-specific sensory neural signals by decoding murine vagus nerve activity. *Proc Natl Acad Sci USA* 2018; **115**: e4843–E4852.
24. Listwak SJ, Rathore P, Herkenham M. Minimal NF-κB activity in neurons. *Neuroscience* 2013; **250**: 282–299.
25. Frederiksen HR, Haukedal H, Freude K. Cell type specific expression of toll-like receptors in human brains and implications in Alzheimer's disease. *BioMed Res Int* 2019; **2019**: 1–18.
26. Kaul D, Habbel P, Derkow K *et al*. Expression of Toll-like receptors in the developing brain. *PLoS One* 2012; **7**: e37767.
27. Donnelly CR, Chen O, Ji RR. How do sensory neurons sense danger signals? *Trends Neurosci* 2020; **43**: 822–838.
28. Park CK, Xu ZZ, Berta T *et al*. Extracellular microRNAs activate nociceptor neurons to elicit pain via TLR7 and TRPA1. *Neuron* 2014; **82**: 47–54.
29. Larsson O, Tengroth L, Xu Y *et al*. Substance P represents a novel first-line defense mechanism in the nose. *J Allergy Clin Immunol* 2018; **141**: 128–136 e123.
30. Pinho-Ribeiro FA, Verri WA Jr, Chiu IM. Nociceptor sensory neuron-immune interactions in pain and inflammation. *Trends Immunol* 2017; **38**: 5–19.
31. Lim JC, Lu W, Beckel JM, Mitchell CH. Neuronal release of cytokine IL-3 triggered by mechanosensitive autostimulation of the P2X7 receptor is neuroprotective. *Front Cell Neurosci* 2016; **10**: 270.
32. Rosenberg KM, Singh NJ. Mouse T cells express a neurotransmitter-receptor signature that is quantitatively modulated in a subset- and activation-dependent manner. *Brain Behav Immun* 2019; **80**: 275–285.
33. Kerage D, Sloan EK, Mattarollo SR, McCombe PA. Interaction of neurotransmitters and neurochemicals with lymphocytes. *J Neuroimmunol* 2019; **332**: 99–111.
34. Wan M, Ding L, Wang D, Han J, Gao P. Serotonin: a potent immune cell modulator in autoimmune diseases. *Front Immunol* 2020; **11**: 186.

35. Domínguez-Soto Á, Usategui A, Casas-Engel ML *et al*. Serotonin drives the acquisition of a profibrotic and anti-inflammatory gene profile through the 5-HT7R-PKA signaling axis. *Sci Rep* 2017; **7**: 14761.

36. Nau F Jr, Yu B, Martin D, Nichols CD. Serotonin 5-HT2A receptor activation blocks TNF-α mediated inflammation *in vivo*. *PLoS One* 2013; **8**: e75426.

37. Datusalia AK, Sharma SS. NF-κB inhibition resolves cognitive deficits in experimental type 2 diabetes mellitus through CREB and Glutamate/GABA neurotransmitters pathway. *Curr Neurovasc Res* 2016; **13**: 22–32.

38. Bhandage AK, Jin Z, Korol SV *et al*. GABA regulates release of inflammatory cytokines from peripheral blood mononuclear cells and CD4⁺ T cells and is immunosuppressive in Type 1 diabetes. *EBioMedicine* 2018; **30**: 283–294.

39. Kim JK, Kim YS, Lee HM *et al*. GABAergic signaling linked to autophagy enhances host protection against intracellular bacterial infections. *Nat Commun* 2018; **9**: 4184.

40. Cox MA, Duncan GS, Lin GHY *et al*. Choline acetyltransferase-expressing T cells are required to control chronic viral infection. *Science* 2019; **363**: 639–644.

41. Ramirez VT, Godinez DR, Brust-Mascher I *et al*. T-cell derived acetylcholine aids host defenses during enteric bacterial infection with *Citrobacter rodentium*. *PLoS Pathog* 2019; **15**: e1007719.

42. Hodo TW, de Aquino MTP, Shimamoto A, Shanker A. Critical neurotransmitters in the neuroimmune network. *Front Immunol* 2020; **11**: 1869.

43. Qiu Y, Peng Y, Wang J. Immunoregulatory role of neurotransmitters. *Adv Neuroimmunol* 1996; **6**: 223–231.

44. Levite M. Neurotransmitters activate T-cells and elicit crucial functions via neurotransmitter receptors. *Curr Opin Pharmacol* 2008; **8**: 460–471.

45. Aagaard K, Ma J, Antony KM *et al*. The placenta harbors a unique microbiome. *Sci Transl Med* 2014; **6**: 237ra265.

46. Collado MC, Rautava S, Aakko J, Isolauri E, Salminen S. Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. *Sci Rep* 2016; **6**: 23129.

47. Mishra A, Lai GC, Yao LJ *et al*. Microbial exposure during early human development primes fetal immune cells. *Cell* 2021; **184**: 3394–3409.e20.

48. Younge N, McCann JR, Ballard J *et al*. Fetal exposure to the maternal microbiota in humans and mice. *JCI Insight* 2019; **4**: e127806.

49. Kalbermatter C, Fernandez Trigo N, Christensen S, Ganal-Vonarburg SC. Maternal microbiota, early life colonization and breast milk drive immune development in the newborn. *Front Immunol* 2021; **12**: 683022.

50. Pronovost GN, Hsiao EY. Perinatal interactions between the microbiome, immunity, and neurodevelopment. *Immunity* 2019; **50**: 18–36.

51. Jain N. The early life education of the immune system: moms, microbes and (missed) opportunities. *Gut Microbes* 2020; **12**: 1824564.

52. Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. *Cell Host Microbe* 2015; **17**: 565–576.

53. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. *Cell Res* 2020; **30**: 492–506.

54. Ma Q, Xing C, Long W *et al*. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. *J Neuroinflammation* 2019; **16**: 53.

55. Al Nabhani Z, Eberl G. Imprinting of the immune system by the microbiota early in life. *Mucosal Immunol* 2020; **13**: 183–189.

56. Furness JB, Callaghan BP, Rivera LR, Cho HJ. The enteric nervous system and gastrointestinal innervation: integrated local and central control. *Adv Exp Med Biol* 2014; **817**: 39–71.

57. Rao M, Gershon MD. The bowel and beyond: the enteric nervous system in neurological disorders. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 517–528.

58. Muller PA, Matheis F, Schneeberger M *et al*. Microbiota-modulated CART⁺ enteric neurons autonomously regulate blood glucose. *Science* 2020; **370**: 314–321.

59. O'Connor KM, Lucking EF, Cryan JF, O'Halloran KD. Bugs, breathing and blood pressure: microbiota-gut-brain axis signalling in cardiorespiratory control in health and disease. *J Physiol* 2020; **598**: 4159–4179.

60. Schächtle MA, Rosshart SP. The microbiota-gut-brain axis in health and disease and its implications for translational research. *Front Cell Neurosci* 2021; **15**: 698172.

61. Pan JX, Deng FL, Zeng BH *et al*. Absence of gut microbiota during early life affects anxiolytic behaviors and monoamine neurotransmitters system in the hippocampal of mice. *J Neurol Sci* 2019; **400**: 160–168.

62. Luczynski P, McVey Neufeld KA, Oriach CS *et al*. Growing up in a bubble: using germ-free animals to assess the influence of the gut microbiota on brain and behavior. *Int J Neuropsychopharmacol* 2016; **19**: pyw020.

63. Huang F, Wu X. Brain neurotransmitter modulation by gut microbiota in anxiety and depression. *Front Cell Dev Biol* 2021; **9**: 649103.

64. Diaz Heijtz R, Wang S, Anuar F *et al*. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci USA* 2011; **108**: 3047–3052.

65. Tengeler AC, Dam SA, Wiesmann M *et al*. Gut microbiota from persons with attention-deficit/hyperactivity disorder affects the brain in mice. *Microbiome* 2020; **8**: 44.

66. Fernandez-Real JM, Serino M, Blasco G *et al*. Gut microbiota interacts with brain microstructure and function. *J Clin Endocrinol Metab* 2015; **100**: 4505–4513.

67. Lu J, Lu L, Yu Y, Baranowski J, Claud EC. Maternal administration of probiotics promotes brain development and protects offspring's brain from postnatal inflammatory insults in C57/BL6J mice. *Sci Rep* 2020; **10**: 8178.

68. Strandwitz P. Neurotransmitter modulation by the gut microbiota. *Brain Res* 2018; **1693**: 128–133.

69. Chen Y, Xu J, Chen Y. Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders. *Nutrients* 2021; **13**: 2099.

70. Luck B, Horvath TD, Engevik KA *et al*. Neurotransmitter Profiles are altered in the gut and brain of mice mono-associated with bifidobacterium dentium. *Biomolecules* 2021; **11**: 1091.

71. Guo Y, Zhu X, Zeng M *et al*. A diet high in sugar and fat influences neurotransmitter metabolism and then affects brain function by altering the gut microbiota. *Transl Psychiatry* 2021; **11**: 328.

72. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. *Front Endocrinol (Lausanne)* 2020; **11**: 25.

73. Wall R, Cryan JF, Ross RP *et al*. Bacterial neuroactive compounds produced by psychobiotics. *Adv Exp Med Biol* 2014; **817**: 221–239.

74. Reigstad CS, Salmonson CE, Rainey JF 3rd *et al*. Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. *FASEB J* 2015; **29**: 1395–1403.

75. De Vadder F, Grasset E, Mannerås Holm L *et al*. Gut microbiota regulates maturation of the adult enteric nervous system via enteric serotonin networks. *Proc Natl Acad Sci USA* 2018; **115**: 6458–6463.

76. Yu L, Zhong X, He Y, Shi Y. Butyrate, but not propionate, reverses maternal diet-induced neurocognitive deficits in offspring. *Pharmacol Res* 2020; **160**: 105082.

77. Erny D, Hrabě de Angelis AL, Jaitin D *et al*. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci* 2015; **18**: 965–977.

78. Yano JM, Yu K, Donaldson GP *et al*. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. *Cell* 2015; **161**: 264–276.

79. Dietert RR, Piepenbrink MS. The managed immune system: protecting the womb to delay the tomb. *Hum Exp Toxicol* 2008; **27**: 129–134.

80. Yu Q, Jia A, Li Y, Bi Y, Liu G. Microbiota regulate the development and function of the immune cells. *Int Rev Immunol* 2018; **37**: 79–89.

81. Legoux F, Bellet D, Daviaud C *et al*. Microbial metabolites control the thymic development of mucosal-associated invariant T cells. *Science* 2019; **366**: 494–499.

82. Matsuoka T, Motozono C, Hattori A *et al*. The effects of 5-OP-RU stereochemistry on its stability and MAIT-MR1 axis. *ChemBioChem* 2021; **22**: 672–678.

83. Constantinides MG, Link VM, Tamoutounour S *et al*. MAIT cells are imprinted by the microbiota in early life and promote tissue repair. *Science* 2019; **366**: eaax6624.

84. Kespohl M, Vachharajani N, Luu M *et al*. The microbial metabolite butyrate induces expression of Th1-associated factors in CD4$^+$ T cells. *Front Immunol* 2017; **8**: 1036.

85. Blander JM, Longman RS, Iliev ID, Sonnenberg GF, Artis D. Regulation of inflammation by microbiota interactions with the host. *Nat Immunol* 2017; **18**: 851–860.

86. Kim Y, Park J, Choi YK. The role of astrocytes in the central nervous system focused on BK channel and heme oxygenase metabolites: a review. *Antioxidants (Basel)* 2019; **8**: 121.

87. Heithoff BP, George KK, Phares AN *et al*. Astrocytes are necessary for blood-brain barrier maintenance in the adult mouse brain. *Glia* 2021; **69**: 436–472.

88. Kirischuk S, Héja L, Kardos J, Billups B. Astrocyte sodium signaling and the regulation of neurotransmission. *Glia* 2016; **64**: 1655–1666.

89. Li K, Li J, Zheng J, Qin S. Reactive astrocytes in neurodegenerative diseases. *Aging Dis* 2019; **10**: 664–675.

90. Sanmarco LM, Wheeler MA, Gutiérrez-Vázquez C *et al*. Gut-licensed IFNγ^+ NK cells drive LAMP1$^+$TRAIL$^+$ anti-inflammatory astrocytes. *Nature* 2021; **590**: 473–479.

91. Logsdon AF, Erickson MA, Rhea EM, Salameh TS, Banks WA. Gut reactions: How the blood-brain barrier connects the microbiome and the brain. *Exp Biol Med (Maywood)* 2018; **243**: 159–165.

92. Guarnieri T, Abruzzo PM, Bolotta A. More than a cell biosensor: aryl hydrocarbon receptor at the intersection of physiology and inflammation. *Am J Physiol Cell Physiol* 2020; **318**: C1078–C1082.

93. Pernomian L, Duarte-Silva M, de Barros Cardoso CR. The aryl hydrocarbon receptor (AHR) as a potential target for the control of intestinal inflammation: insights from an immune and bacteria sensor receptor. *Clin Rev Allergy Immunol* 2020; **59**: 382–390.

94. Nehmar R, Fauconnier L, Alves-Filho J *et al*. Aryl hydrocarbon receptor (AhR)-dependent Il-22 expression by type 3 innate lymphoid cells control of acute joint inflammation. *J Cell Mol Med* 2021; **25**: 4721–4731.

95. Michaudel C, Bataille F, Maillet I *et al*. Ozone-induced aryl hydrocarbon receptor activation controls lung inflammation via interleukin-22 modulation. *Front Immunol* 2020; **11**: 144.

96. Obata Y, Castaño Á, Boeing S *et al*. Neuronal programming by microbiota regulates intestinal physiology. *Nature* 2020; **578**: 284–289.

97. Schiering C, Wincent E, Metidji A *et al*. Feedback control of AHR signalling regulates intestinal immunity. *Nature* 2017; **542**: 242–245.

98. Yang W, Yu T, Huang X *et al*. Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity. *Nat Commun* 2020; **11**: 4457.

99. Schanz O, Chijiiwa R, Cengiz SC *et al*. Dietary AhR ligands regulate AhRR expression in intestinal immune cells and intestinal microbiota composition. *Int J Mol Sci* 2020; **21**: 3189.

100. Brawner KM, Yeramilli VA, Duck LW *et al*. Depletion of dietary aryl hydrocarbon receptor ligands alters microbiota composition and function. *Sci Rep* 2019; **9**: 14724.

101. Meng H, Zhao H, Cao X *et al*. Double-negative T cells remarkably promote neuroinflammation after ischemic stroke. *Proc Natl Acad Sci USA* 2019; **116**: 5558–5563.

102. Ruan S, Zhai L, Wu S, Zhang C, Guan Q. SCFAs promote intestinal double-negative T cells to regulate the inflammatory response mediated by NLRP3 inflammasome. *Aging (Albany NY)* 2021; **13**: 21470–21482.

103. Chiu IM, Heesters BA, Ghasemlou N *et al*. Bacteria activate sensory neurons that modulate pain and inflammation. *Nature* 2013; **501**: 52–57.

104. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. *Nature* 2012; **489**: 220–230.

105. Heiman ML, Greenway FL. A healthy gastrointestinal microbiome is dependent on dietary diversity. *Mol Metab* 2016; **5**: 317–320.

106. Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. *Science* 2005; **307**: 1915–1920.

107. Mohajeri MH, Brummer RJM, Rastall RA *et al*. The role of the microbiome for human health: from basic science to clinical applications. *Eur J Nutr* 2018; **57**: 1–14.

108. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. *BMJ* 2018; **361**: k2179.

109. Sochocka M, Donskow-Łysoniewska K, Diniz BS *et al*. The gut microbiome alterations and inflammation-driven pathogenesis of Alzheimer's disease-a critical review. *Mol Neurobiol* 2019; **56**: 1841–1851.

110. Russell SL, Gold MJ, Hartmann M *et al*. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep* 2012; **13**: 440–447.

111. Love BL, Mann JR, Hardin JW *et al*. Antibiotic prescription and food allergy in young children. *Allergy Asthma Clin Immunol* 2016; **12**: 41.

112. Metzler S, Frei R, Schmaußer-Hechfellner E *et al*. Association between antibiotic treatment during pregnancy and infancy and the development of allergic diseases. *Pediatr Allergy Immunol* 2019; **30**: 423–433.

113. Nguyen LH, Örtqvist AK, Cao Y *et al*. Antibiotic use and the development of inflammatory bowel disease: a national case-control study in Sweden. *Lancet Gastroenterol Hepatol* 2020; **5**: 986–995.

114. Lynn MA, Tumes DJ, Choo JM *et al*. Early-life antibiotic-driven dysbiosis leads to dysregulated vaccine immune responses in mice. *Cell Host Microbe* 2018; **23**: 653–660.e5.

115. Carrillo-Salinas FJ, Mestre L, Mecha M *et al*. Gut dysbiosis and neuroimmune responses to brain infection with Theiler's murine encephalomyelitis virus. *Sci Rep* 2017; **7**: 44377.

116. Sun MF, Shen YQ. Dysbiosis of gut microbiota and microbial metabolites in Parkinson's Disease. *Ageing Res Rev* 2018; **45**: 53–61.

117. Jiang C, Li G, Huang P, Liu Z, Zhao B. The gut microbiota and Alzheimer's disease. *J Alzheimers Dis* 2017; **58**: 1–15.

118. Neuman H, Forsythe P, Uzan A, Avni O, Koren O. Antibiotics in early life: dysbiosis and the damage done. *FEMS Microbiol Rev* 2018; **42**: 489–499.

119. Bercik P, Denou E, Collins J *et al*. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology* 2011; **141**: 599–609.

120. Gao K, Pi Y, Mu CL *et al*. Antibiotics-induced modulation of large intestinal microbiota altered aromatic amino acid profile and expression of neurotransmitters in the hypothalamus of piglets. *J Neurochem* 2018; **146**: 219–234.

121. Hosseinkhani F, Heinken A, Thiele I *et al*. The contribution of gut bacterial metabolites in the human immune signaling pathway of non-communicable diseases. *Gut Microbes* 2021; **13**: 1–22.

122. Robson MJ, Quinlan MA, Blakely RD. Immune system activation and depression: roles of serotonin in the central nervous system and periphery. *ACS Chem Neurosci* 2017; **8**: 932–942.

123. Banskota S, Regmi SC, Gautam J *et al*. Serotonin disturbs colon epithelial tolerance of commensal *E. coli* by increasing NOX2-derived superoxide. *Free Radic Biol Med* 2017; **106**: 196–207.

124. Regmi SC, Park SY, Ku SK, Kim JA. Serotonin regulates innate immune responses of colon epithelial cells through Nox2-derived reactive oxygen species. *Free Radic Biol Med* 2014; **69**: 377–389.

125. Spielman LJ, Gibson DL, Klegeris A. Unhealthy gut, unhealthy brain: The role of the intestinal microbiota in neurodegenerative diseases. *Neurochem Int* 2018; **120**: 149–163.

126. Rutsch A, Kantsjö JB, Ronchi F. The Gut-brain axis: how microbiota and host inflammasome influence brain physiology and pathology. *Front Immunol* 2020; **11**: 604179.

127. Rogers GB, Keating DJ, Young RL *et al*. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Mol Psychiatry* 2016; **21**: 738–748.

128. Zhu Y, Huan F, Wang J *et al*. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine Induced Parkinson's disease in mouse: potential association between neurotransmitter disturbance and gut microbiota dysbiosis. *ACS Chem Neurosci* 2020; **11**: 3366–3376.

129. Yeoh YK, Zuo T, Lui GC *et al*. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut* 2021; **70**: 698–706.

130. Serra D, Almeida LM, Dinis TCP. The impact of chronic intestinal inflammation on brain disorders: the microbiota-gut-brain axis. *Mol Neurobiol* 2019; **56**: 6941–6951.

131. Manosso LM, Arent CO, Borba LA *et al*. Microbiota-gut-brain communication in the SARS-CoV-2 infection. *Cells* 2021; **10**: 1993.

132. Poloni TE, Medici V, Moretti M *et al*. COVID-19-related neuropathology and microglial activation in elderly with and without dementia. *Brain Pathol* 2021; **31**: e12997.

133. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. *NeuroImmunoModulation* 2009; **16**: 300–317.

134. Viswanathan K, Dhabhar FS. Stress-induced enhancement of leukocyte trafficking into sites of surgery or immune activation. *Proc Natl Acad Sci USA* 2005; **102**: 5808–5813.

135. Dhabhar FS. Effects of stress on immune function: the good, the bad, and the beautiful. *Immunol Res* 2014; **58**: 193–210.

136. de Pablos RM, Herrera AJ, Espinosa-Oliva AM *et al*. Chronic stress enhances microglia activation and exacerbates death of nigral dopaminergic neurons under conditions of inflammation. *J Neuroinflammation* 2014; **11**: 34.

137. Stolk RF, van der Pasch E, Naumann F *et al*. Norepinephrine dysregulates the immune response and compromises host defense during sepsis. *Am J Respir Crit Care Med* 2020; **202**: 830–842.

138. Yang H, Xia L, Chen J *et al*. Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity. *Nat Med* 2019; **25**: 1428–1441.

139. Curtin NM, Boyle NT, Mills KH, Connor TJ. Psychological stress suppresses innate IFN-gamma production via glucocorticoid receptor activation: reversal by the anxiolytic chlordiazepoxide. *Brain Behav Immun* 2009; **23**: 535–547.

140. Obradović MMS, Hamelin B, Manevski N *et al*. Glucocorticoids promote breast cancer metastasis. *Nature* 2019; **567**: 540–544.

141. Zhang L, Pan J, Chen W, Jiang J, Huang J. Chronic stress-induced immune dysregulation in cancer: implications for initiation, progression, metastasis, and treatment. *Am J Cancer Res* 2020; **10**: 1294–1307.

142. Hantsoo L, Zemel BS. Stress gets into the belly: Early life stress and the gut microbiome. *Behav Brain Res* 2021; **414**: 113474.

143. Bharwani A, Mian MF, Foster JA *et al*. Structural & functional consequences of chronic psychosocial stress on the microbiome & host. *Psychoneuroendocrinology* 2016; **63**: 217–227.

144. Gur TL, Bailey MT. Effects of stress on commensal microbes and immune system activity. *Adv Exp Med Biol* 2016; **874**: 289–300.

145. Geng S, Yang L, Cheng F *et al*. Gut microbiota are associated with psychological stress-induced defections in intestinal and blood-brain barriers. *Front Microbiol* 2019; **10**: 3067.

146. Jašarević E, Howerton CL, Howard CD, Bale TL. Alterations in the vaginal microbiome by maternal stress are associated with metabolic reprogramming of the offspring gut and brain. *Endocrinology* 2015; **156**: 3265–3276.

147. Babenko O, Kovalchuk I, Metz GA. Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. *Neurosci Biobehav Rev* 2015; **48**: 70–91.

148. Moussaoui N, Braniste V, Ait-Belgnaoui A *et al*. Changes in intestinal glucocorticoid sensitivity in early life shape the risk of epithelial barrier defect in maternal-deprived rats. *PLoS One* 2014; **9**: e88382.

149. Gao X, Cao Q, Cheng Y *et al*. Chronic stress promotes colitis by disturbing the gut microbiota and triggering immune system response. *Proc Natl Acad Sci USA* 2018; **115**: e2960–e2969.

150. Lupp C, Robertson ML, Wickham ME *et al*. Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of Enterobacteriaceae. *Cell Host Microbe* 2007; **2**: 119–129.

151. Zeng MY, Cisalpino D, Varadarajan S *et al*. Gut microbiota-induced immunoglobulin G controls systemic infection by symbiotic bacteria and pathogens. *Immunity* 2016; **44**: 647–658.

152. Carvalho FA, Koren O, Goodrich JK *et al*. Transient inability to manage proteobacteria promotes chronic gut inflammation in TLR5-deficient mice. *Cell Host Microbe* 2012; **12**: 139–152.

153. Zeng MY, Inohara N, Nuñez G. Mechanisms of inflammation-driven bacterial dysbiosis in the gut. *Mucosal Immunol* 2017; **10**: 18–26.

154. Wang H, Ren S, Lv H, Cao L. Gut microbiota from mice with cerebral ischemia-reperfusion injury affects the brain in healthy mice. *Aging (Albany NY)* 2021; **13**: 10058–10074.

155. Li J, Lin S, Vanhoutte PM, Woo CW, Xu A. *Akkermansia muciniphila* protects against atherosclerosis by preventing metabolic endotoxemia-induced inflammation in Apoe$^{-/-}$ mice. *Circulation* 2016; **133**: 2434–2446.

156. Raftar SKA, Ashrafian F, Abdollahiyan S *et al*. The anti-inflammatory effects of *Akkermansia muciniphila* and its derivates in HFD/CCL4-induced murine model of liver injury. *Sci Rep* 2022; **12**: 2453.

157. Chelakkot C, Choi Y, Kim DK *et al*. *Akkermansia muciniphila*-derived extracellular vesicles influence gut permeability through the regulation of tight junctions. *Exp Mol Med* 2018; **50**: e450.

158. Liu S, Rezende RM, Moreira TG *et al*. Oral administration of miR-30d from Feces of MS patients suppresses MS-like symptoms in mice by expanding *Akkermansia muciniphila*. *Cell Host Microbe* 2019; **26**: 779–794.e8.

159. Zois CD, Katsanos KH, Kosmidou M, Tsianos EV. Neurologic manifestations in inflammatory bowel diseases: current knowledge and novel insights. *J Crohns Colitis* 2010; **4**: 115–124.

160. Morís G. Inflammatory bowel disease: an increased risk factor for neurologic complications. *World J Gastroenterol* 2014; **20**: 1228–1237.

161. Parrow NL, Fleming RE, Minnick MF. Sequestration and scavenging of iron in infection. *Infect Immun* 2013; **81**: 3503–3514.

162. Bearson BL. Molecular profiling: catecholamine modulation of gene expression in *Escherichia coli* O157:H7 and *Salmonella enterica* Serovar Typhimurium. *Adv Exp Med Biol* 2016; **874**: 167–182.

163. Pinho-Ribeiro FA, Baddal B, Haarsma R *et al*. Blocking neuronal signaling to immune cells treats Streptococcal invasive infection. *Cell* 2018; **173**: 1083–1097.e22.

164. Waters CM, Bassler BL. Quorum sensing: cell-to-cell communication in bacteria. *Annu Rev Cell Dev Biol* 2005; **21**: 319–346.

165. Papenfort K, Bassler BL. Quorum sensing signal-response systems in Gram-negative bacteria. *Nat Rev Microbiol* 2016; **14**: 576–588.

166. Zhao K, Zhou X, Li W, Zhang X, Yue B. Nutrient reduction induced stringent responses promote bacterial quorum-sensing divergence for population fitness. *Sci Rep* 2016; **6**: 34925.

167. Miller MB, Bassler BL. Quorum sensing in bacteria. *Annu Rev Microbiol* 2001; **55**: 165–199.

168. Singh R, Ray P. Quorum sensing-mediated regulation of staphylococcal virulence and antibiotic resistance. *Future Microbiol* 2014; **9**: 669–681.

169. Rajkumari J, Borkotoky S, Murali A *et al*. Attenuation of quorum sensing controlled virulence factors and biofilm formation in *Pseudomonas aeruginosa* by pentacyclic triterpenes, betulin and betulinic acid. *Microb Pathog* 2018; **118**: 48–60.

170. Wu L, Luo Y. Bacterial quorum-sensing systems and their role in intestinal bacteria-host crosstalk. *Front Microbiol* 2021; **12**: 611413.

171. Bivar Xavier K. Bacterial interspecies quorum sensing in the mammalian gut microbiota. *C R Biol* 2018; **341**: 297–299.

172. Bassler BL. How bacteria talk to each other: regulation of gene expression by quorum sensing. *Curr Opin Microbiol* 1999; **2**: 582–587.

173. Wellington S, Greenberg EP. Quorum sensing signal selectivity and the potential for interspecies cross talk. *MBio* 2019; **10**: e00146-19.

174. Xue J, Chi L, Tu P *et al*. Detection of gut microbiota and pathogen produced N-acyl homoserine in host circulation and tissues. *NPJ Biofilms Microbiomes* 2021; **7**: 53.

175. Sperandio V, Torres AG, Jarvis B, Nataro JP, Kaper JB. Bacteria-host communication: the language of hormones. *Proc Natl Acad Sci USA* 2003; **100**: 8951–8956.

176. Canovas J, Baldry M, Bojer MS *et al*. Cross-talk between *Staphylococcus aureus* and other staphylococcal species via the agr quorum sensing system. *Front Microbiol* 2016; **7**: 1733.

177. Thompson JA, Oliveira RA, Djukovic A, Ubeda C, Xavier KB. Manipulation of the quorum sensing signal AI-2 affects the antibiotic-treated gut microbiota. *Cell Rep* 2015; **10**: 1861–1871.

178. Krasulova K, Illes P. Intestinal interplay of quorum sensing molecules and human receptors. *Biochimie* 2021; **189**: 108–119.

179. Janssens Y, Debunne N, De Spiegeleer A *et al*. PapRIV, a BV-2 microglial cell activating quorum sensing peptide. *Sci Rep* 2021; **11**: 10723.

180. Wynendaele E, Verbeke F, Stalmans S *et al*. Quorum sensing peptides selectively penetrate the blood-brain barrier. *PLoS One* 2015; **10**: e0142071.

181. Zargar A, Quan DN, Carter KK *et al*. Bacterial secretions of nonpathogenic *Escherichia coli* elicit inflammatory pathways: a closer investigation of interkingdom signaling. *MBio* 2015; **6**: e00025.

182. Hsiao A, Ahmed AM, Subramanian S *et al*. Members of the human gut microbiota involved in recovery from *Vibrio cholerae* infection. *Nature* 2014; **515**: 423–426.

183. Rahbari KM, Chang JC, Federle MJ. A Streptococcus quorum sensing system enables suppression of innate immunity. *MBio* 2021; **12**: e03400-20.

184. Shiner EK, Terentyev D, Bryan A *et al*. *Pseudomonas aeruginosa* autoinducer modulates host cell responses through calcium signalling. *Cell Microbiol* 2006; **8**: 1601–1610.

185. Smith RS, Harris SG, Phipps R, Iglewski B. The *Pseudomonas aeruginosa* quorum-sensing molecule N-(3-oxododecanoyl)homoserine lactone contributes to virulence and induces inflammation *in vivo*. *J Bacteriol* 2002; **184**: 1132–1139.

186. Yadav VK, Singh PK, Kalia M *et al*. *Pseudomonas aeruginosa* quorum sensing molecule N-3-oxo-dodecanoyl-l-homoserine lactone activates human platelets through intracellular calcium-mediated ROS generation. *Int J Med Microbiol* 2018; **308**: 858–864.

187. Singh PK, Yadav VK, Kalia M *et al*. *Pseudomonas aeruginosa* quorum-sensing molecule N-(3-oxo-dodecanoyl)-L-homoserine lactone triggers mitochondrial dysfunction and apoptosis in neutrophils through calcium signaling. *Med Microbiol Immunol* 2019; **208**: 855–868.

188. Glucksam-Galnoy Y, Sananes R, Silberstein N *et al*. The bacterial quorum-sensing signal molecule N-3-oxo-dodecanoyl-L-homoserine lactone reciprocally modulates pro- and anti-inflammatory cytokines in activated macrophages. *J Immunol* 2013; **191**: 337–344.

189. Knecht LD, O'Connor G, Mittal R *et al*. Serotonin activates bacterial quorum sensing and enhances the virulence of *Pseudomonas aeruginosa* in the host. *EBioMedicine* 2016; **9**: 161–169.

190. Uhlig F, Grundy L, Garcia-Caraballo S *et al*. Identification of a quorum sensing-dependent communication pathway mediating bacteria-gut-brain cross talk. *iScience* 2020; **23**: 101695.

191. Moura-Alves P, Puyskens A, Stinn A *et al*. Host monitoring of quorum sensing during *Pseudomonas aeruginosa* infection. *Science* 2019; **366**: eaaw1629.

192. Pundir P, Liu R, Vasavda C *et al*. A connective tissue mast-cell-specific receptor detects bacterial quorum-sensing molecules and mediates antibacterial immunity. *Cell Host Microbe* 2019; **26**: 114–122.e8.

193. Ismail AS, Valastyan JS, Bassler BL. A host-produced autoinducer-2 mimic activates bacterial quorum sensing. *Cell Host Microbe* 2016; **19**: 470–480.

194. De Spiegeleer B, Verbeke F, D'Hondt M *et al*. The quorum sensing peptides PhrG, CSP and EDF promote angiogenesis and invasion of breast cancer cells *in vitro*. *PLoS One* 2015; **10**: e0119471.

195. Castillo-Juárez I, Maeda T, Mandujano-Tinoco EA *et al*. Role of quorum sensing in bacterial infections. *World J Clin Cases* 2015; **3**: 575–598.

196. Coquant G, Grill JP, Seksik P. Impact of N-Acyl-Homoserine lactones, quorum sensing molecules, on gut immunity. *Front Immunol* 2020; **11**: 1827.

197. Petra AI, Panagiotidou S, Hatziagelaki E *et al*. Gut-microbiota-brain axis and its effect on neuropsychiatric disorders with suspected immune dysregulation. *Clin Ther* 2015; **37**: 984–995.

198. Zhu F, Li C, Chu F, Tian X, Zhu J. Target dysbiosis of gut microbes as a future therapeutic manipulation in Alzheimer's disease. *Front Aging Neurosci* 2020; **12**: 544235.

199. Ding RX, Goh WR, Wu RN *et al*. Revisit gut microbiota and its impact on human health and disease. *J Food Drug Anal* 2019; **27**: 623–631.

200. Ding S, Yan W, Ma Y, Fang J. The impact of probiotics on gut health via alternation of immune status of monogastric animals. *Anim Nutr* 2021; **7**: 24–30.

201. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. *Therap Adv Gastroenterol* 2013; **6**: 39–51.

202. Bermúdez-Humarán LG, Salinas E, Ortiz GG *et al*. From probiotics to psychobiotics: live beneficial bacteria which act on the brain-gut axis. *Nutrients* 2019; **11**: 890.

Graphical Abstract

The contents of this page will be used as part of the graphical abstract
of html only. It will not be published as part of main.
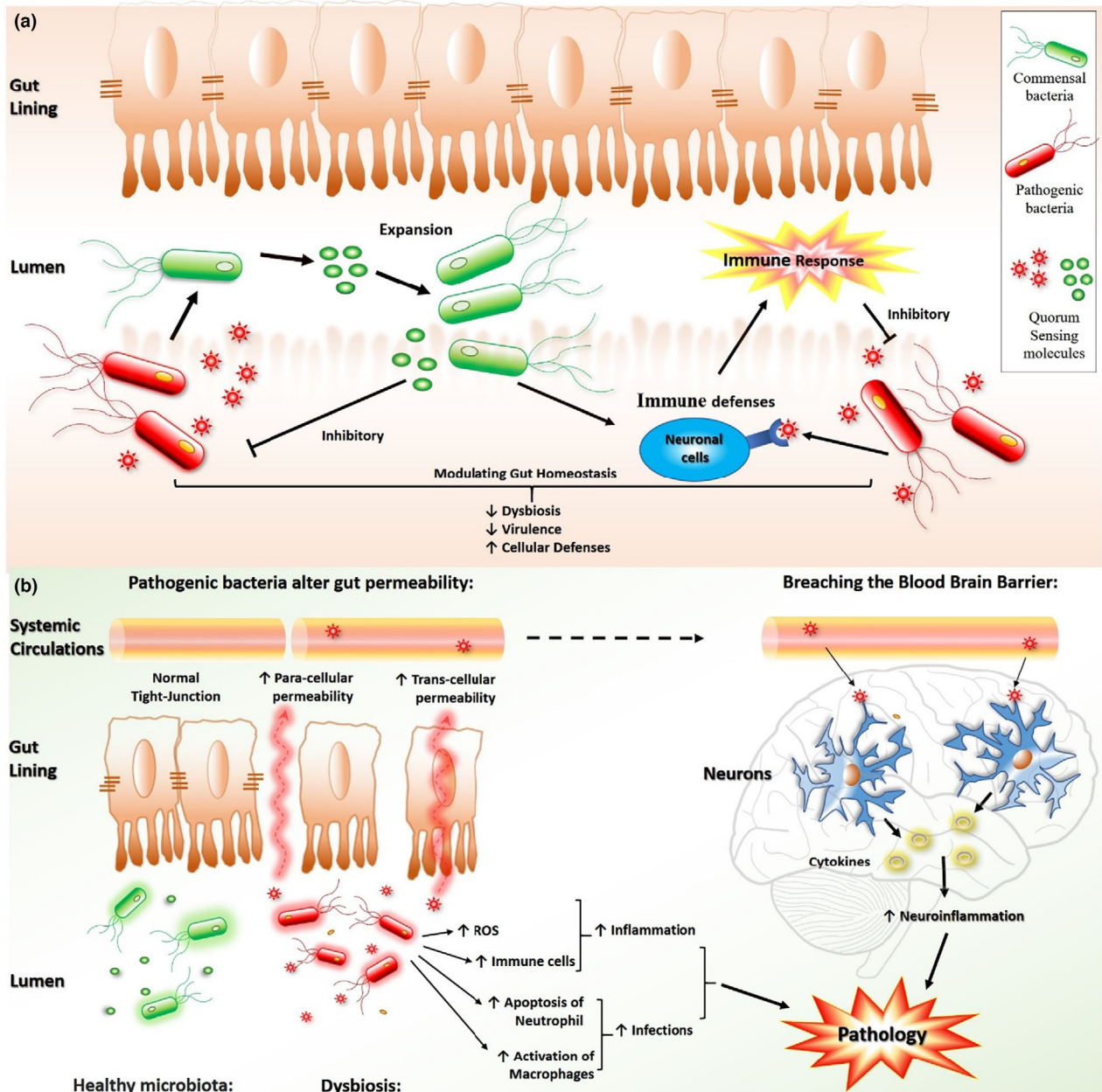
Inflammation is an indispensable process that is required to initiate cellular defense and maintain homeostasis. The process of inflammation is tightly regulated by the immune system and beyond to ensure the survival benefit of the host and also limit pathology. This manuscript is about how microbiota contributes to the development and function of nerves and immune systems to regulate inflammation and immune response.