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Competing interests statement

The authors declare no competing financial interests.

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SCIENCE AND SOCIETY

Reciprocal regulation of the neural and innate immune systems

Michael R. Irwin and Steven W. Cole

Abstract | Innate immune responses are regulated by microorganisms and cell death, as well as by a third class of stress signal from the nervous and endocrine systems. The innate immune system also feeds back, through the production of cytokines, to regulate the function of the central nervous system (CNS), and this has effects on behaviour. These signals provide an extrinsic regulatory circuit that links physiological, social and environmental conditions, as perceived by the CNS, with transcriptional 'decision-making' in leukocytes. CNS-mediated regulation of innate immune responses optimizes total organism fitness and provides new opportunities for therapeutic control of chronic infectious, inflammatory and neuropsychiatric diseases.

Immune responses are mediated by the activation of immune response genes that encode regulatory and effector molecules, such as cytokines, antimicrobial peptides, antibodies and cytolytic molecules. Transcriptional activation in innate immune cells is triggered by two types of signal from the body's internal environment: pathogen-associated molecular patterns (PAMPs) and 'danger signals' derived from host cell stress or death¹. A growing body of research shows that a third class of stimulus, in the form of neural and endocrine signals that result from macroenvironmental sensing, also plays a significant role in modulating immune responses². In addition, immune mediators such as cytokines feed back to the brain to regulate neural and endocrine activity³. The resulting neuro-immune circuit coordinates immune responses with other physiological processes — such as fight-or-flight stress responses — to maximize the overall fitness of the organism within

complex environments that bear multiple threats. Such threats can be microbial, physiological (such as trauma and sleep loss) or social-ecological (such as predation, conspecific violence and interpersonal loss) in nature⁴.

The neuro-immune circuit was initially discovered in the context of adaptive immune responses², but recent findings suggest that this circuit originates with the innate immune system^{5,6}. This article highlights emerging biological themes on the reciprocal regulation of immune response gene expression and central nervous system (CNS) function. We map the molecular signalling pathways involved in this reciprocal regulation, discuss their implications for social influences on disease⁷ and highlight new therapeutic approaches for inflammatory diseases and psychiatric syndromes such as major depression, insomnia and fatigue³. In addition, we discuss the evolutionary basis for the emergence of a third, CNS-derived signal that controls immune responses⁶.

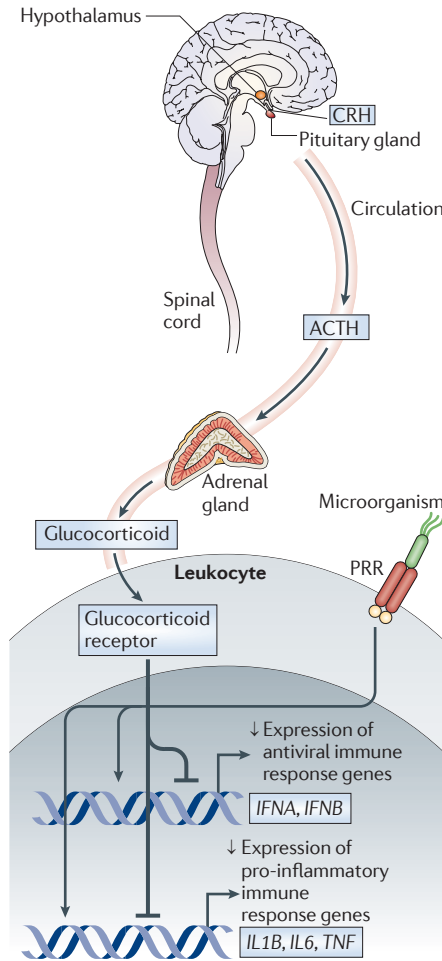
Immune response gene regulation

Functional genomics studies have identified two broad gene expression programmes that can be induced in myeloid lineage cells by different types of microbial stimulus⁸. Extracellular pathogens, such as bacteria, activate a pro-inflammatory gene programme characterized by the expression of genes such as interleukin-1 β (*IL1B*), *IL6* and tumour necrosis factor (*TNF*) via transcription factors including nuclear factor- κ B (NF- κ B) and activator protein 1 (AP1). Intracellular pathogens, such as viruses, elicit a distinct antiviral gene programme that involves the induction of type I interferon (IFN) genes via transcription factors such as interferon regulatory factors (IRFs). These two gene expression programmes mediate fundamentally different effector responses^{8,9}, but they have in common a substantial energetic cost and the potential for collateral damage (for example, septic shock, autoimmunity, fibrosis and the promotion of inflammation-associated diseases such as atherosclerosis, diabetes, neurodegeneration and neoplasia)¹⁰. To mitigate these autotoxic risks, an additional layer of regulation exists for the key genes mediating pro-inflammatory and antiviral responses. One type of licensing signal is mediated by 'danger' and requires the presence of signals that are induced by host cell stress, necrosis or apoptosis to generate high-level immune response gene transcription¹. A second, macroenvironmental licensing signal allows the CNS to integrate information regarding general physiological conditions and the extra-organismal perceived environment to regulate immune response gene expression programmes via hormones and neurotransmitters² (FIG. 1).

The neural environment

The primary physiological role of the CNS is to perceive external physical and social conditions (the environment, broadly speaking), assess their implications for organismal well-being (fitness) and modulate the activity of internal physiological processes to optimally adapt to those external conditions⁴. In response to the perception of a threatening environment (for example, the appearance of a predator or hostile conspecifics), the CNS signals for adaptive changes in physiological function (for example, fight-or-flight stress responses). This signalling occurs via the release of neuroeffector molecules (such as noradrenaline) from nerves of the sympathetic nervous system (SNS) or of

a Hypothalamic-pituitary-adrenal axis



b Sympathetic nervous system

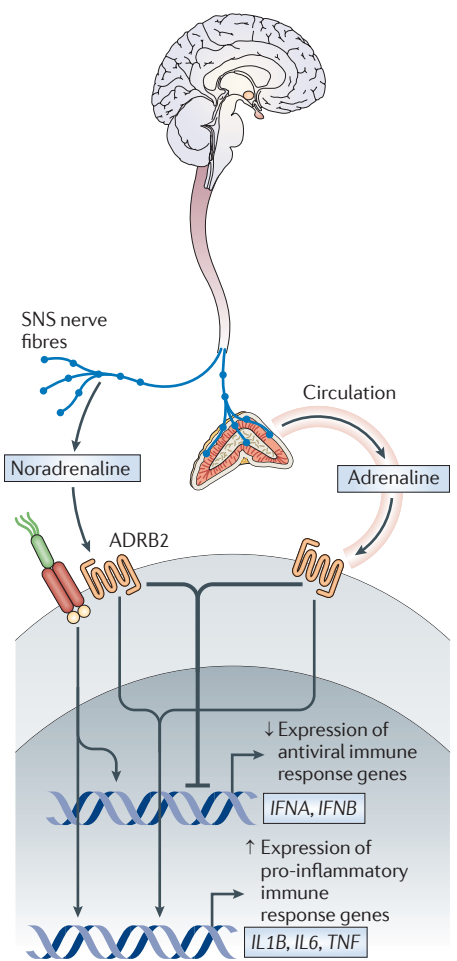


Figure 1 | CNS regulation of innate immune response gene programmes. **a** | The hypothalamic-pituitary-adrenal (HPA) axis distributes glucocorticoid hormones through the blood to regulate gene expression in virtually every cell of the body. Hormone activation of the glucocorticoid receptor in leukocytes results in profound suppression of both pro-inflammatory gene networks (for example, NF- κ B-mediated transcription of pro-inflammatory cytokine genes, such as *IL1B*, *IL6* and *TNF*) and antiviral gene programmes (for example, IRF-mediated transcription of type I interferon (IFN) genes, such as *IFNA* and *IFNB*). Activation of cytokine receptors in the hypothalamus triggers the production of glucocorticoids by the HPA axis. This constitutes the body's primary systemic mechanism for negative feedback control of pro-inflammatory gene expression triggered by microbial pattern recognition receptors (PRRs). **b** | During fight-or-flight responses and acute injury, nerve fibres from the sympathetic nervous system (SNS) release the neurotransmitter noradrenaline into primary and secondary lymphoid organs, all other major organ systems (including the vasculature and perivascular tissues) and many peripheral tissues in which pro-inflammatory reactions occur. SNS nerve fibres can also stimulate the adrenal glands to release stored adrenaline into the systemic circulation. Both of these neuromediators regulate vascular function and stimulate leukocyte adrenergic receptors (for example, ADRB2) to activate transcription factors such as CREB and GATA family factors. SNS-induced transcriptional alterations can modulate haematopoiesis, redeploy leukocytes between tissue and blood, and repress IRF-mediated antiviral immune response gene programmes while enhancing many NF- κ B-mediated pro-inflammatory programmes. ACTH, adrenocorticotropic hormone; ADRB2, β 2-adrenergic receptor; CRH, corticotropin-releasing hormone; IL, interleukin; IRF, interferon regulatory factor; NF- κ B, nuclear factor- κ B; TNF, tumour necrosis factor.

glucocorticoids from the hypothalamic-pituitary-adrenal (HPA) axis⁴. In addition to regulating virtually every other cell type in the body, these biochemical manifestations of CNS-perceived external conditions regulate the cells of the immune system (BOX 1).

The hypothalamic-pituitary-adrenal axis. The earliest identified CNS-mediated immunoregulatory function involved the brain's ability to suppress the transcription of both pro-inflammatory and antiviral gene programmes by stimulating

glucocorticoid release from the HPA axis^{11–13}. Activation of the glucocorticoid receptor inhibits the transcription of many immune response genes. This effect is mediated by three mechanisms, namely: suppressive binding of the glucocorticoid receptor to gene promoter sequences; glucocorticoid receptor-mediated transcriptional induction of anti-inflammatory genes (such as *NFKBIA*, which encodes I κ B α); and non-genomic antagonism of pro-inflammatory transcription factors (such as NF- κ B and AP1) via protein–protein interactions¹⁴.

The brain detects peripheral pro-inflammatory and antiviral cytokines via multiple pathways (BOX 2) and stimulates glucocorticoid release from the HPA axis to systemically inhibit immune response gene transcription when inflammation levels become damagingly high or energetic resources need to be shifted elsewhere^{3,15}. Glucocorticoid-mediated feedback inhibition of immune response gene transcription is now recognized as the most fundamental physiological mechanism for protection against hyper-inflammatory disease and as a prototype of our most effective anti-inflammatory drugs^{14,15}.

The sympathetic nervous system. In addition to the global anti-inflammatory effect of glucocorticoids, a second neural pathway mediated by the SNS allows the CNS to ‘steer’ innate immune responses between pro-inflammatory and antiviral programmes^{16,17}. The neural fibres of the SNS distribute the neurotransmitter noradrenaline into tissue microenvironments in which immune response gene transcription occurs, including all primary and secondary lymphoid organs, the vasculature and perivascular tissues, and most visceral organs and musculoskeletal structures¹⁸. Noradrenaline modulates leukocyte gene expression via stimulation of β -adrenergic receptors, which are associated with the signalling cascade that involves G α_s , adenylyl cyclase, cyclic AMP and protein kinase A¹⁸. β -adrenergic signalling was initially found to modulate adaptive immune responses by stimulating the transcription of T helper 2 (T_H2)-type cytokine genes (such as *IL4* and *IL5*) and suppressing the expression of T_H1-type genes (such as *IFNG* and *IL12B*)^{19–21}. Recent studies have discovered a similar SNS-mediated steering of innate immune response programmes, which involves suppression of type I IFN-mediated antiviral responses¹⁷ and upregulated transcription of pro-inflammatory cytokine genes (such as *IL1B*, *IL6* and *TNF*)^{16,22}.

Box 1 | Neural regulation of the innate immune response

Several molecular pathways allow the central nervous system (CNS) to regulate the transcription of immune response genes in peripheral tissues³. These mechanisms include:

- Hypothalamic–pituitary–adrenal axis production of glucocorticoids, which circulate throughout the body to alter a variety of metabolic and developmental processes, in addition to suppressing both pro-inflammatory and antiviral immune response gene programmes;
- Sympathetic nervous system (SNS) innervation of primary and secondary lymphoid organs. This delivers the neurotransmitter noradrenaline directly into parenchymal tissues involved in haematopoiesis and interactions between antigen-presenting cells and lymphocytes¹⁸;
- SNS innervation of the vasculature and peripheral organs and tissues. This releases noradrenaline into the local microenvironment of many acute and chronic inflammatory responses;
- SNS innervation of the adrenal gland. This releases the hormone adrenaline into systemic circulation, which suppresses type I interferon-mediated antiviral responses¹⁷ and upregulates transcription of pro-inflammatory cytokines²³;
- Efferent neural distribution into peripheral tissues of pain-related neuropeptides, enteric system-regulating neuropeptides and a diverse array of other physiologically specialized neuromodulators that can stimulate receptors present on cells of the innate and adaptive immune systems;
- CNS-mediated release of circulating mediators, such as growth hormone, insulin-like growth factor, endogenous opioids and a diverse range of other hormones that can affect cells of the innate and adaptive immune systems.

Activation of the SNS has also been found to alter the production and trafficking of innate immune cells, for example through the upregulation of myelopoiesis and the mobilization of haematopoietic stem cells, natural killer cells and splenic neutrophils and monocytes¹⁸. Collectively, these studies of neuro–immune regulation have provided new insights into the mechanistic relationships between the cellular and microbial microenvironment in which immune responses have traditionally been analysed and the broader macroenvironment of the host body and its surrounding social and physical ecology, as perceived by the CNS^{6,23,24} (BOX 1).

Neural influences on disease. Epidemiological studies have long identified a link between adverse social and environmental conditions — such as the death of a spouse, low socio-economic status or social isolation — and an increased risk of infectious disease (presumably owing to insufficient expression of immune response genes). The risk of inflammation-associated cardiovascular, autoimmune, neurodegenerative and neoplastic diseases is also increased (presumably owing to excessive expression of immune response genes)^{7,16,25,26}. Efforts to account for this pattern of infectious versus inflammation-associated disease risk based on glucocorticoid-mediated suppression of an immune response were obviously unsuccessful, but the discovery that the SNS could simultaneously inhibit antiviral genes and activate pro-inflammatory genes has provided a more plausible mechanistic explanation.

Laboratory animal and human studies have confirmed that experimental induction of acute psychological stress can increase circulating levels of IL-6 and IL-1 β ²⁷, activate NF- κ B in peripheral blood mononuclear cells^{27,28} and prime leukocytes for increased *ex vivo* production of pro-inflammatory cytokines in response to stimulation by the PAMP lipopolysaccharide (LPS) and other Toll-like receptor ligands^{5,29,30}. Some of these effects may be mediated by mobilization of specific leukocyte subsets³¹, but their net effect is to acutely increase the pro-inflammatory potential of the circulating innate immune system.

Additional insights into the immunological effects of long-term social stress have come from transcriptional profiling of circulating leukocytes in human populations^{6,23,26,32} and experimental analyses of repeated social threat in animal models (such as encountering an aggressive intruder)^{5,33,34}. People confronting long-term social adversities — such as the mortal illness of a spouse, low socio-economic status, post-traumatic stress disorder or long-term social isolation — have repeatedly been found to show increased expression of pro-inflammatory immune response genes, despite the presence of stable or elevated glucocorticoid levels^{6,23,26,32,35}.

Promoter-based bioinformatic analysis of the transcription factors involved in these responses suggests a genome-wide reduction in glucocorticoid-mediated transcription (not just among immune response genes) as a mechanistic explanation for this apparent paradox. Reduced levels of

Box 2 | Inflammatory regulation of brain function

Several molecular pathways allow peripherally generated pro-inflammatory signals to alter neural activity in the central nervous system (CNS). These mechanisms include:

- Interaction of circulating cytokines with brain cytokine receptors in circumventricular organs that lack a functional blood–brain barrier;
- Stimulation of brain vascular endothelial cells to release second messengers that stimulate subsequent cytokine production within the brain;
- Active transport of cytokines across the blood–brain barrier via carrier molecules;
- Peripheral inflammatory stimulation of afferent nerves that subsequently stimulate CNS tissues to produce cytokines.

Brain structures that show functional alterations in response to cytokine signalling include:

- The hypothalamus, which has a key role in the regulation of systemic physiological function and organism-level biobehavioural dynamics (such as metabolism, sleep and feeding);
- The amygdala, which mediates fear- or threat-related responses and processes social information;
- The hippocampus, which has a key role in learning and short-term memory, general information processing, spatial information processing, and navigation and mobility;
- The pre-frontal cortex, which is involved in complex information processing and planning;
- The anterior cingulate cortex, which is involved in a diverse array of cognitive–emotional interactions;
- The ventral striatum, which is involved in positive motivation and reward.

In many cases, cytokines directly interact with receptors in one brain structure (for example, the brainstem), which subsequently influences the functional activity of other brain structures (for example, the hypothalamus) via distant neural projections⁸⁰.

glucocorticoid-mediated gene transcription despite elevated circulating glucocorticoid levels have also been observed in animal models of chronic social threat^{5,33,34} and appear to reflect a functional desensitization of the glucocorticoid receptor¹⁵. As a result of reduced glucocorticoid-mediated feedback inhibition, gene transcription shifts towards increased NF- κ B- and AP1-mediated pro-inflammatory gene expression both under basal conditions and in response to stimulation by PAMPs. Recent analyses suggest that chronic threat-induced glucocorticoid receptor desensitization may stem from increased myelopoietic generation of immature LY6C^{hi} monocytes (CD16⁻ monocytes in humans) that express constitutively high levels of mitogen-activated protein kinases^{33,34}, which constitutively inhibit glucocorticoid receptor function¹⁵. A similar desensitization of glucocorticoid receptor genomic signalling has been observed in monocytes from humans confronting extended social adversity²⁶.

Transcriptome analyses of leukocytes from humans undergoing chronic social adversity have also begun to identify some of the specific neurobehavioural pathways through which stressful life circumstances affect innate immune responses. Wake–sleep cycles have emerged as prominent regulators of inflammatory biology, with experimental sleep restriction studies showing upregulated leukocyte expression of pro-inflammatory cytokine genes and

increased NF- κ B activity^{36,37}. Observational studies have also identified elevated levels of C-reactive protein and other inflammation-related biomarkers in night-shift workers, insomniacs and people suffering poor sleep duration or quality³⁸. Experimentally induced sleep loss (whole night) or restriction (partial reduction over several days) has also been found to increase circulating pro-inflammatory biomarkers³⁹. These effects are especially pronounced in females^{37,40}, possibly owing to sex difference in SNS upregulation of IL-6 production⁴¹, and this might contribute to sex differences in the incidence of inflammation-related behavioural and autoimmune diseases.

In sum, the CNS orchestrates the perception of the external physical and social environment and the evaluation of environmental conditions as threatening versus salutary. In cases of threat, the CNS activates stress signalling pathways (such as the HPA axis and the SNS) to regulate multiple internal physiological processes, including broad patterns of transcriptional activity in innate immune cells. Activation of the HPA axis inhibits both antiviral and pro-inflammatory gene modules, whereas SNS activation suppresses antiviral responses while stimulating pro-inflammatory genes. In turn, circulating pro-inflammatory cytokines evoke a glucocorticoid-mediated negative feedback response from the CNS, raising the possibility that other brain-mediated processes might also be altered.

Inflammatory regulation of behaviour

Several molecular signalling pathways have been identified to convey peripheral pro-inflammatory and antiviral signals into the brain^{3,42} (BOX 2). Within the brain, pro-inflammatory cytokines decrease the activity of key behaviour-modulating neurotransmitters, including noradrenaline, dopamine and serotonin⁴³. Moreover, these cytokines activate physiological and behavioural responses, such as fever and social withdrawal, which function together with leukocyte activation dynamics to limit the spread of infectious disease both within and between individuals^{3,44,81}.

Sickness. Prostaglandin E2 released from brain endothelial cells is well known to trigger CNS-mediated febrile and metabolic responses to infection³. Recent studies also show that pro-inflammatory cytokines can activate the CNS to produce a broader array of 'sickness behaviours', which include emotional alterations (anhedonia, fatigue and dysphoria), reductions in exploratory and reward-seeking motivation, altered cognitive and motor function, sleep alterations and reduced social and reproductive motivation^{3,44}. These behaviours are triggered in part via IL-1 receptors in the hypothalamus and hippocampus^{3,44}. Experimental administration of type I IFNs or pro-inflammatory cytokines in mice has been found to activate sickness behaviour syndromes^{3,44}, although the exact behavioural dynamics vary somewhat with the specific triggering cytokine.

Functional neuroimaging studies in humans have begun to map the specific neural circuits associated with cytokine-induced sickness behaviours. The findings have shown altered connectivity between the subgenual anterior cingulate cortex, amygdala and medial prefrontal cortex^{45,46}, and a reduced ventral striatum response to reward cues⁴⁷. The functions of these areas of the brain are described in BOX 2. Given the strong evolutionary conservation of cytokine-induced sickness behaviour^{3,44}, these dynamics appear to play a key role in coordinating the overall mammalian response to acute infection by regulating systemic physiological processes and altering behaviour. Such physiological or behavioural modifications include redirecting energy resources to the immune response, reducing circulating iron levels, raising the body temperature above the optimal levels for some pathogens, immobilization to conserve energy and avoid predation, and reducing social and/or reproductive contact to limit the spread of infection^{3,44,81}.

Depression. Sickness behaviours are highly reminiscent of some common adverse behavioural syndromes with poorly understood aetiology, suggesting that dysregulated activation of cytokine-mediated sickness behaviours might underlie some cases of medically unexplained fatigue, sleep impairment or major depressive disorder (MDD)⁴³. Consistent with this hypothesis, epidemiological studies have linked IL-6 and TNF levels with the risk of developing MDD⁴⁸, and documented increased rates of MDD in clinical conditions involving high levels of inflammation (for example, in patients with cancer)^{43,49}.

Pharmacological administration of IFN α to patients with cancer induces an array of MDD symptoms, including anhedonia and sadness, disturbed sleep, fatigue and loss of appetite^{43,50,51}. Conversely, pharmacological antagonism of TNF has been shown to reduce depressive symptoms⁵². Gene polymorphisms that result in the increased expression of *IL1B* and *TNF* are associated with increased MDD risk and reduced clinical response to antidepressant medication^{43,53}. Elevated circulating pro-inflammatory biomarkers such as IL-6 and TNF also predict poor clinical response to antidepressant medications^{43,54}.

These results suggest that blockade of pro-inflammatory cytokines might diminish the risk and improve the treatment response of depression. In addition, they raise the possibility that circulating pro-inflammatory biomarkers and inflammation-related genetic polymorphisms could be used to help guide targeted therapies for specific MDD subtypes that are thought to have an inflammatory component (such as depression in older adults or in those with inflammation-associated disease). Links

between inflammation and depressive symptoms have also led to the hypothesis that contemporary increases in the prevalence of MDD may stem from dysregulated pro-inflammatory signalling that is due to the decreased exposure to tolerogenic microorganisms in modern industrialized societies (a psychiatric version of the 'hygiene hypothesis')⁵⁵.

Sleep. Pro-inflammatory cytokines and type I IFNs also have a role in the homeostatic regulation of sleep⁵⁶. Animal genetic studies and LPS administration studies in humans^{56,57} have linked changes in non-rapid eye movement sleep (NREM sleep) to elevated levels of circulating type I IFNs and pro-inflammatory cytokines. Moreover, pharmacological administration of IL-6 and IFN α in humans results in decreases in NREM slow-wave sleep and complementary increases in REM sleep^{56,58}, although animal studies show that other cytokines (such as TNF) increase NREM sleep and decrease REM sleep⁵⁶. Elevated daytime levels of TNF have also been linked with sleepiness, fatigue and altered sleep architecture, and pharmacological antagonism of TNF can reduce these effects^{59,60}. TNF antagonism can also normalize REM sleep levels (for example, in abstinent alcohol-dependent individuals, who have elevated amounts of REM sleep)⁶¹.

Given the substantial fraction of time we spend asleep and the general immunological activation that occurs during sleep³⁸, as well as the epidemiological links between abnormally high levels of REM sleep and mortality⁶², regulation of sleep architecture by the innate immune system may play a substantial role in structuring overall inflammatory homeostasis^{38,56}.

Fatigue. Pro-inflammatory gene expression can induce profound fatigue during waking hours⁶³ — one of the most debilitating burdens of chronic inflammatory disease. Clinical studies have documented links between inflammation-related biomarkers and the development of fatigue both in healthy older adults⁶⁴ and in individuals with inflammatory diseases such as multiple sclerosis⁶⁵, Sjogren's syndrome⁶⁶, rheumatoid arthritis⁶⁷ and cancer⁶⁸. Patients with cancer often experience substantial increases in NF- κ B inflammatory signalling owing to tumour-derived cytokines, the effects of cancer treatment (for example, radiation and chemotherapy) on tissue⁶⁹ and therapeutic administration of type I IFNs⁴⁹.

Even when chemotherapy and/or radiation treatments are completed, approximately one-third of breast cancer survivors suffer from persistent, medically unexplained fatigue. This fatigue is associated with increased circulating biomarkers of IL-1 β and IL-6 activity⁷⁰, increased NF- κ B-mediated gene transcription⁷¹ and enhanced IL-6 and TNF production in response to *ex vivo* LPS-mediated stimulation of circulating leukocytes⁷⁰. Fatigue in breast cancer survivors is also particularly elevated among patients with *IL1B*, *IL6* or *TNF* polymorphisms that cause high-level expression of the respective cytokines⁷². Pharmacological antagonism of TNF can reduce chemotherapy-related fatigue⁶⁰, confirming a key functional role for pro-inflammatory cytokines in the aetiology of cancer-associated fatigue.

In sum, peripheral innate immune responses can influence CNS functions (including neurotransmitter metabolism, regional brain activity and sleep-wake cycles) and behavioural processes (including depression, sleep and fatigue), and this has implications for neuropsychiatric disease.

Glossary

Conspecific

Belonging to the same species.

Glucocorticoids

A class of steroid hormones that are involved in carbohydrate, protein and fat metabolism. These hormones are anti-inflammatory and immunosuppressive.

Hypothalamic–pituitary–adrenal

(HPA). This term refers to a complex set of direct influences and feedback interactions between the hypothalamus, the pituitary gland (a pea-shaped structure located below the hypothalamus) and the adrenal glands (small, conical organs on top of the kidneys).

Non-rapid eye movement sleep

(NREM sleep). The sleep stages 1–3 (previously known as stages 1–4) are collectively referred to as NREM sleep. Rapid eye movement (REM) sleep is not included. There

are distinct electroencephalographic and other characteristics seen in each stage, and there is usually little or no eye movement during NREM sleep. Dreaming is rare during NREM sleep, and muscles are not paralyzed as in REM sleep.

Social ecology

A broad range of complex physical and symbolic features of the environment that are created by the presence of conspecifics (including social structures such as cultural systems or socio-economic status), as well as physical processes, such as transmission of communicable diseases, provision of medical care or physical aggression.

Sympathetic nervous system

(SNS). One of three parts of the autonomic nervous system (along with the enteric and parasympathetic systems). The SNS serves to mobilize the body's resources during flight-or-flight stress responses.

The neuro-immune circuit

Understanding and controlling innate immune responses is complicated by the fact that immune response genes are regulated by both external influences (through neural activity) and internal factors (such as pathogens and cell damage)¹⁶ (FIG. 2). Furthermore, the reciprocal regulation of neural activity by immune response genes would seem to hopelessly complicate matters. However, such reciprocal regulation provides exactly the feedback required by dynamic systems theory to stabilize the circuit as a whole, particularly given the fact that CNS function is itself regulated by both the internal (inflammatory) and external (ecological) environments simultaneously.

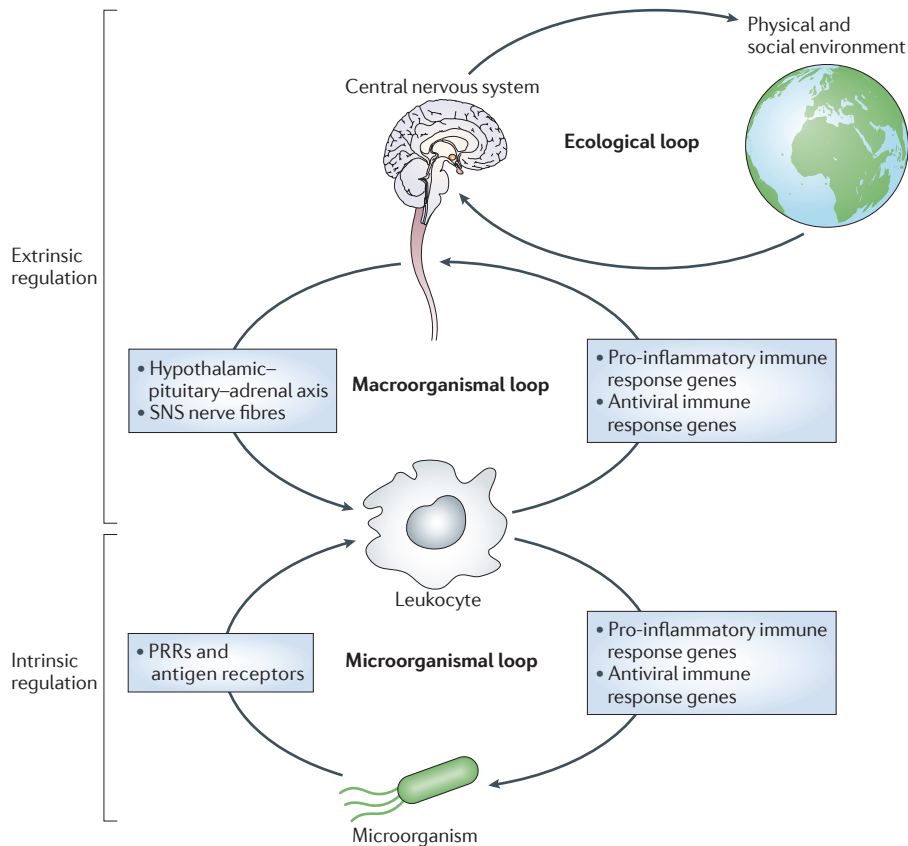


Figure 2 | Multi-circuit control of the innate immune transcriptome. Leukocyte transcription of immune response gene programmes is regulated by both intrinsic immunological signals representing local tissue and microbial conditions and extrinsic neural and endocrine signals representing global physiological and environmental conditions. Intrinsic circuits detect microorganisms via pattern recognition receptors (PRRs) and stimulate pro-inflammatory and antiviral immune response gene programmes via transcription factors such as nuclear factor- κ B (NF- κ B) and interferon regulatory factors (IRFs). The resulting production of innate immune effector molecules reduces microbial burden, and thereby feeds back to reduce PRR and antigen receptor signalling and immune response gene transcription. Extrinsic regulation of immune response gene transcription is mediated by central nervous system (CNS) integration of information regarding general physiological and ecological conditions. This can either globally suppress immune response gene transcription via the hypothalamic–pituitary–adrenal axis or steer immune response gene transcriptional profiles away from antiviral programmes and towards more robust pro-inflammatory gene expression. CNS-mediated transduction of information from the social and physical ecology allows extra-organismal environmental conditions to indirectly regulate the immune response gene transcriptional profiles of immune cells. SNS, sympathetic nervous system.

What the organism as a whole gains by superimposing the ‘extrinsic’ CNS–leukocyte–CNS regulatory circuit on the more immunologically fundamental ‘intrinsic’ microorganism–leukocyte–microorganism circuit is the opportunity to coordinate the microbiological battle between pathogen and immune response within the context of the broader macrobiological conditions that affect overall survival and natural selection. For example, this crosstalk allows the organism to suppress the immobilizing effects of inflammation and sickness behaviour to facilitate fight-or-flight responses to predation or conspecific aggression. There are lots of other ways to die or fail to reproduce besides

infection, and an optimal immune response needs to be adapted to the total array of conditions that confront the organism rather than blindly pursuing its microbial antagonists. The fitness advantage of innate immune regulation by the extrinsic circuit is demonstrated by the reduced survival of organisms that are challenged with pathogens following blockade of CNS signalling to leukocytes, as well as by the reduced individual and population-level resistance to infectious disease in the absence of leukocyte signalling to the CNS^{44,81}. These whole-organism fitness implications provide a teleological rationale for the evolution of CNS–immune interactions, as well as new opportunities for therapeutic intervention.

Biobehavioural control of inflammation

Several behavioural interventions have been applied to modulate pro-inflammatory signalling in the innate immune system. Randomized controlled trials have documented reductions in pro-inflammatory cytokine activity following several types of behavioural intervention (BOX 3), including cognitive behavioural therapy⁷³, aerobic exercise⁷⁴, meditation⁷⁵ and Tai Chi^{76,77}. The regulation of leukocytes by the CNS may also contribute to the neurobiological impact of behavioural interventions if, for example, CNS-mediated reductions in peripheral inflammation feed back to reciprocally reduce sickness behaviour. SNS-mediated regulation of pro-inflammatory and antiviral genes also suggests potential neuropharmacological strategies for mitigating the long-observed effects of environmental adversity on disease risk⁴. For example, β -adrenergic receptor blockade has been shown in animal models to reverse several stress-induced alterations in immune response gene transcription^{22,34,78}. Therefore, it may provide a strategy for redirecting the leukocyte transcriptome via the induction of multiple *trans*-acting transcription factors by β -adrenergic receptors.

Teleological considerations

Perhaps the most striking implication of neuro–immune circuitry is the possibility that the innate immune response may be controlled in part by an anticipation of future environmental conditions by the CNS, in addition to its regulation by the present microbial and host cell environment. Allostatic theories of physiology⁴ propose that natural selection favours ‘prepared’ physiological systems that actively anticipate homeostatic challenges and proactively alter their function to mitigate these challenges. Given that the HPA axis and the SNS both regulate leukocyte gene transcription, and both show CNS-mediated anticipatory activation⁴, CNS-mediated perceptions of potential threat may be sufficient to alter the basal leukocyte transcriptome in ways that subsequently affect responses to pathogens (for example, by altering inflammatory responses in myeloid lineage cells)^{5,6,16,26,78}. This ‘forward-looking’ view of the immune system represents a significant departure from traditional pathogen- or damage-reactive models of immune regulation. But it does provide a parsimonious account of epidemiological data that link social–ecological conditions to immune response gene expression and disease resistance, as well as a plausible evolutionary rationale for the specific pattern of transcriptional alterations observed.

Box 3 | Behavioural interventions that modulate inflammation

Several types of behavioural intervention have been found to reduce cellular and plasma biomarkers of inflammation.

Cognitive behavioural therapy (CBT)

CBT uses a programme of specific verbal and/or written protocols that guide participants through exercises designed to change specific targeted thoughts, feelings and behavioural patterns. As an example, CBT for depression involves a restructuring of dysfunctional thoughts and ruminations that contribute to negative perceptions of self and the environment. Benefits on the cellular expression of pro-inflammatory cytokines were found after 16 weeks in individuals whose depression was improved⁷³.

Aerobic exercise

This involves moderate-intensity physical activities, such as walking for 20–30 minutes per day, which provides aerobic training without activating anaerobic respiration. Benefits on inflammatory markers were found after 12 months⁷⁴.

Meditation

Meditation involves thought-focusing and relaxation exercises that calm cognitive and emotional processes and reduce sympathetic nervous system activity and related peripheral physiological processes. The practices found to alter inflammatory responses to stress used concentrative and mindfulness exercises to establish focus and awareness, followed by analytical exercises designed to challenge unexamined assumptions regarding feelings and actions towards others, with a focus on generating spontaneous empathy and compassion for themselves and others. Benefits on inflammatory markers were found after 6 weeks⁷⁵.

Tai Chi Chih

Tai Chi Chih is a westernized form of the Chinese martial art Tai Chi, which involves slow movement and meditation. It combines the practice of 20 aerobic exercises with relaxed breathing, attentional focus and body awareness. Benefits on inflammatory markers were found after 25 weeks⁷⁶.

Biomarkers affected by such interventions include indicators of pro-inflammatory cytokine activity (for example, C-reactive protein) and *ex vivo* cellular production of tumour necrosis factor and interleukin-1 β in response to lipopolysaccharide stimulation.

undermining our innate antiviral defences. Nevertheless, it may still be possible to harness reciprocal neural-immune regulation through pharmacological or behavioural interventions to redirect the basic transcriptional stance of the innate immune system and more effectively accommodate the health ecology that we now inhabit.

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Social ecology of immune responses. Specific patterns of neural and endocrine activity are associated with distinctive social or ecological conditions, and these conditions affect the nature of the injuries and pathogens we confront. Thus, a natural selective pressure arises for immune response genes to develop a sensitivity to these neural and endocrine signals⁶. Such sensitivity could explain why, for example, the SNS has evolved the capacity to steer the innate immune transcriptome away from antiviral responses and towards pro-inflammatory responses. As threat-induced SNS signalling has historically been associated with a near-term increase in the likelihood of wound-mediated bacterial infection (for example, via predation of isolated organisms or conspecific hostility), SNS priming of the pro-inflammatory gene programme would seem to be highly adaptive.

By contrast, viral infections disseminate predominately through close social contact. Therefore, there would be little need for antiviral priming under hostile or isolated social conditions, but a much greater value in priming an antiviral transcriptional bias under long-term salutary social conditions (when SNS activity levels are generally low). Similarly, in response to more profound threats — such as trauma, starvation or exhaustion — that markedly activate the HPA

axis, it makes good evolutionary sense for the body to redirect resources away from both types of long-term antimicrobial defence (antiviral and pro-inflammatory) in favour of more immediate physiological survival needs.

Conclusion

The whole-organism fitness advantages of a forward-looking, neurally regulated and neurally regulating innate immune response have clarified a variety of previously puzzling phenomena. These include: environmentally dependent variations in the basal transcriptome of unstimulated immune cells^{6,16,23,26,32,35,36,79}; the striking co-morbidity of neuropsychiatric symptoms and inflammatory disease; the biological rationale for specific HPA- and SNS-related patterns of immune response gene transcription; and the distinctive impact of effector systems of the CNS (the HPA axis and the SNS) on peripheral myeloid lineage cells. As the relationship between environmental conditions and infectious disease has changed over the past century¹⁰, the historically beneficial crosstalk between the CNS and the immune system has become misaligned with our current ecology. Now, this crosstalk may allow abstract non-physical threats to induce inflammation-related cardiovascular, neurodegenerative and neoplastic diseases, while

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Competing interests statement

The authors declare no competing financial interests.

FURTHER INFORMATION

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