The authors also speculate that SdrG may bind its ligand through a catch bond—that is, a bond strengthened by tensile force, as observed with the *Escherichia coli* adhesin FimH (10). Supporting this idea, a recent single-molecule study demonstrated that the mechanical strength of ClfB increases dramatically as mechanical force is applied (11). The results suggested that ClfB-mediated adhesion is enhanced through force-induced conformational changes in the adhesin, which changes from a weakly binding folded state to a strongly binding extended state. This force-dependent ligand-binding mechanism may help *S. aureus* to attach firmly to biomaterials under high shear stress, and to detach under low shear stress to colonize new sites.

The study by Milles et al. has important implications for many fields. In molecular microbiology, the combined use of AFM experiments and SMD simulations should greatly contribute to the identification of new binding mechanisms in bacterial adhesins, thus helping to show how they regulate biofilm formation. In diagnosis and therapy, this combined approach could represent a powerful platform for the treatment of microbial infections. For instance, correlative single-molecule experiments and simulations could be used to screen antiadhesion compounds for their potential to prevent or treat biofilm-associated infections (12). The binding mechanism reported here may also serve as a basis for the development of bioinspired glues that stick under water and outperform traditional adhesives.

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**NEUROIMMUNOLOGY**

### Neuronal-immune system cross-talk in homeostasis

**Interactions between immune and neuronal cells are pillars in tissue homeostasis**

*By Henrique Veiga-Fernandes* and *David Artis*

Maintenance of mammalian tissue homeostasis and function requires coordinated actions of multiple cellular and molecular networks. This complexity is reflected in the immune system, which is composed of a plethora of cells that constitute the innate and adaptive immune system and which can sense multiple endogenous and exogenous factors. Similarly, the nervous system includes a myriad of distinct neurons that perceive, integrate, and respond to ever-changing environmental conditions. Functional interactions between the neuronal and immune systems have been reported in health and disease, such as in multiple sclerosis, autism, cancer, and chronic inflammatory disorders (1). More recently, a number of studies have revealed that discrete neuronal and immune cells share anatomical localization and interact functionally, forming neuroimmunecell units (NICUs) that orchestrate tissue homeostasis and integrity (2). These findings are provoking a fundamental paradigm shift in our understanding of neuronal–immune cell interactions. A recent noteworthy example is the finding that the nervous system can have a major regulatory effect on multiple innate immune cells with functional impact in several physiological processes (3–8).

Earlier studies established that signals from the parasympathetic vagus nerve, which connects the brainstem with peripheral organs, can have an anti-inflammatory effect via tuning the activity of macrophages, innate immune cells that engulf pathogens and cell debris, leading to the production of macrophage-derived immunomodulatory molecules (9). Bidirectional neuronal–macrophage interactions were also shown to regulate important aspects of intestinal physiology. Notably, intestinal macrophages control myenteric neuron activity and small intestine peristalsis (muscular contractions that move food down the intestine) in response to microbial signals in the intestines (3), whereas intestinal pathogenic bacterial infections activate neurons to produce noradrenaline that induces a tissue-protective program in enteric macrophages (4). Notably, neuron-associated macrophages are also present in adipose tissue and were shown to buffer sympathetic neuronal activity and fat tissue physiology, thus controlling obesity and organisinal metabolism (10). Dendritic cells and mast cells (both components of the innate immune system) also interact with peripheral neurons (1). For example, upon chemical irritation or infection with fungi, sensory neurons in the skin instruct dermal dendritic cells to produce the cytokine interleukin-23 (IL-23), which activates adaptive T lymphocytes to produce pro-inflammatory cytokines (11). Reciprocally, lymphocyte-derived type 2 cytokines—such as IL-4, IL-5, and IL-13—were also shown to induce chronic itch via sensory neuron activation (12). Together, these findings demonstrate that neurons can trigger functional molecular cascades that lead to the activation of innate and adaptive immune cells, influencing immunity to infection, chronic inflammation, and restoration of tissue homeostasis. Nevertheless, defining additional pathways that operate in the opposing direction, whereby immune cells can modulate neuronal activity, requires further study.

But how widespread and biologically important is this neuronal-immune interaction? Over the past decade, we have witnessed the formal discovery of innate lymphoid cells (ILCs) and their roles in development, infection, inflammation, metabolic disease, and cancer (13). ILCs are a relatively rare cell type, but they are particularly abundant at barrier surfaces that are exposed to the external environment, which are also densely populated with neuronal cells. Group 2 ILCs (ILC2s) are associated with allergy and parasitic worm infections and were reported to respond to vasoactive intestinal peptide signals that were presumably derived from neuronal cells (14), suggesting that neuronal-
ILC interactions could also occur at mucosal barriers. Consistent with this concept, group 3 ILCs (ILC3s) were shown to control intestinal health as part of a glial cell–ILC3 unit orchestrated by neurotrophic factors (5). Glial cells, considered to provide support and protection to neurons, are adjacent to ILC3s and integrate microbial-derived and host alarmin (danger molecules that are released upon tissue damage)–derived signals to control neurotrophic factor production (5). In turn, these neuroregulatory molecules activate RET-expressing ILC3s that produce the tissue-protective cytokine IL-22 (5). Thus, glial cells translate microbial and host cues into neurotrophic factor production, which target coordinated neuronal and ILC3 functions to promote intestinal tissue repair after exposure to infectious and inflammatory stimuli (see the figure).

Adding to the growing understanding of NICUs, other recent studies revealed that mucosal neurons regulate the production of ILC-derived type 2 cytokines via the production of the neuropeptide neuromedin U (NMU) (6–8). NMU-producing cholinergic neurons are adjacent to intestinal and pulmonary ILC2s, whereas NMU receptor 1 (NMUR1) is selectively expressed by ILC2s (6–8). Notably, activation of ILC2s with this neuropeptide leads to a rapid and potent production of type 2 inflammatory and tissue-protective cytokines (6, 7). Consistent with this, activation of this signaling axis in ILC2s in vivo leads to rapid type 2 cytokine responses after exposure to parasite infections or allergens (6–8). The capacity of neuronal-derived signals to rapidly trigger ILC2 responses may also explain in part why, despite their relatively low numbers, ILC2s can be rapidly activated and have profound effects across large barrier surfaces.

In addition to the activating functions of cholinergic nerve–derived NMU, catecholaminergic neurons—a component of the sympathetic nervous system that is a potent source of molecules such as norepinephrine that binds the β2-adrenergic receptor (β2AR)—were shown to act as a potent “off switch” that dampens ILC2 responses (15). β2AR deficiency resulted in exaggerated ILC2 responses and type 2 inflammation in intestinal and lung tissues, whereas β2AR agonist treatment, a frontline therapy for asthma patients, was associated with impaired ILC2 responses and reduced inflammation in vivo (15). Together, these new findings demonstrate that neuronal-ILC units are poised to trigger immediate barrier tissue protection programs through a neuronal-immune “fast track” response that can both switch on and switch off ILC2 responses, whereas activation by cytokines and alarmins appears to follow a “regular track,” inducing and sustaining ILC2 function with comparatively delayed kinetics.

How do neuronal cells sense environmental perturbations to instruct immune responses? Enteric neurons and glial cells can sense microbial products, parasites, and host alarmins through myeloid differentiation primary response 88 (MYD88) signaling in the neuronal cells to produce ILC-activating neuroregulators (5, 6). Although this local neuronal–innate immune cell interaction is critical during pathogen insults (5, 6), the nature of the efferent nervous signals (impulses emerging from the central nervous system) that may also regulate peripheral immune cells remain elusive. Nevertheless, perhaps local neuronal networks function as relay stations of environmental stimuli, amplifying these local insults through the increased expression of neuroregulators that maximize rapid tissue-protective responses of immune cells.

Understanding the broader roles of NICUs in the regulation of tissue homeostasis in the context of health and disease is certainly a major challenge ahead. Notably, clarifying cellular and molecular players of NICUs could identify new putative therapeutic targets in the context of chronic inflammation, cancer, metabolic health, and beyond. Because pathogens and other environmental triggers have been major drivers of mammalian evolution, connecting immune and neuronal responses may therefore be considered a paradigm of coordinated multi-tissue physiology, suggesting that throughout evolution, neuroimmune networks may have also been selected at an organismal level. The neuroimmune system is out there to be explored.

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ACKNOWLEDGMENTS
H.V.-F. is supported by the European Research Council, EU, Crohn’s and Colitis Foundation of America, USA; and Fundação para a Ciência e Tecnologia, Portugal. D.A. is supported by the U.S. National Institutes of Health (grants AI061570, AI087990, AI074878, AI083480, AI095466, AI095608, AI092942, and AI097333), the Burroughs Welcome Fund, and the Crohn’s & Colitis Foundation of America.

Published by AAAS

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Science 359 (6383), 1465-1466.
DOI: 10.1126/science.aap9598