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EDITORIAL

A new age for (mucosal) NeuroImmunology

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Neurosciences have a long history, tracing back to Antiquity, in the quest for understanding the senses, the mind, and the brain. Immunology, in contrast, was born at the end of the 19th century from the necessity to understand how we survive microbes, just shown to be the source of infectious diseases. The 19th century also gave rise to neuroimmunology, largely to unravel the mechanisms driving pathologies of the nervous system, an aim still shared by most clinical neuroscience departments.

Immunology and neurosciences have since grown into rich and complex disciplines. Nevertheless, only on rare occasions have the fields crossed paths to reveal how the two systems crosstalk to maintain health, regulate physiology and alter behavior. Sickness behavior is probably the best-studied effect of the immune system on the brain[1]. Conversely, Pavlovian immunity, explored in the 1920s by Sergei Metalnikov, is among the first attempts to explore how the brain modulates immune responses[2]. Fast forward 100 years, we have come to realize that the immune system is modulated by diverse and unique sensory and motor inputs from the nervous system[3,4], and conversely, that the brain is not as isolated from the immune system (immune-privileged)[5] and the rest of the body as initially postulated[6], but requires it for normal function[7,8]. Both fields have benefitted from the development of extraordinarily powerful research methods to study single molecules, cells, or whole organs, as well as to manipulate single genes and cells with increasingly specific tools[9,10]. These newly acquired capabilities provide us with exciting opportunities to reconnect Immunology and Neurosciences. (Fig. 1).

Recent data show how the nervous system senses information that is relevant to immunity[11], how such information is sent and stored in the brain[12], how the brain and peripheral neurons modulate immunity, and how this crosstalk can contribute to pathology[13]. The immune and nervous systems share a molecular language that includes neuropeptides[14], neurotransmitters[15], cytokines[16], chemokines[17], complement proteins[18], MHC molecules[19], as well as a key phenomenon for both systems: memory. Maybe the two systems even share a common memory. The current surge of interest in Neuroimmunology tells us that, indeed, it has entered a new age. It is an evolution that *Mucosal Immunology* wishes to actively support and welcome within its pages.

To imagine how the future may look like in (mucosal) Neuroimmunology, we have invited prominent immunologists, neuroscientists, neuroimmunologists and immunoneurologists to share their visions. Below is my attempt to synthesize their ideas, which I have grouped into five themes. I wish to warmly thank you for your willingness to participate: Aleksandra Deczkowska (Institut Pasteur), Asya Rolls (Technion), Caroline Sokol (Harvard), Daniel Mucida (Rockefeller), Elaine Hsiao (UCLA), Francisco Quintana (Harvard), Gabriel Lepousez (Institut Pasteur), Henrique Veiga-Fernandes (Champallimaud), Isaac Chiu (Harvard), Jun Huh (Harvard), Maria Rescigno (Humanitas, Milan), Marco Prinz (Freiburg University), Michal Schwartz (Weizmann Institute), Michel Neunlist (Université Nantes), Pierre-Marie Lledo (Institut Pasteur), Robert Dantzer (MD Anderson Cancer Center), Sarkis Mazmanian (Caltech), Vassilis Pachnis (Crick Institute) and Yuuki Obata (UT Southwestern Medical Center).

1. Neuronal sensing of the mucosal environment (CS, DM, EH, IC, MN, YO).

The intestine is sometimes referred to as the 2nd brain, because of the presence of 10^8 neurons in the human gut (yet still far less neurons than the 10^{11} neurons in the 1st brain). Visualization of neuronal fibers in intestinal villi reveals a stunningly dense network[20], which makes interactions between the enteric nervous system, the microbiota and the local immune system seem inevitable[21,22]. The intestine also harbors two layers of neurons, the submucosal and the myenteric plexi, which coordinate intestinal movements and communicate with the central nervous system (CNS) through the parasympathetic vagal and pelvic nerves, the sympathetic celiac and mesenteric ganglia, and fibers to the spinal cord. A key question is: *What do these neurons sense in the intestine (and lung, skin, …) and how do they impact immunity?* Food and microbiota are sensed by epithelial cells and immune cells via innate and adaptive receptors. Do neurons sense food and microbes via similar or distinct receptors, how do they connect to immune, epithelial and stromal cells in such sensing processes and how is this information shared with the immune system during homeostasis, defense and pathology? A simplistic view would posit that each system and its cells collect information functionally relevant to itself: the immune system senses pathogens, epithelial cells sense nutrients, the nervous system senses noxious/painful stimuli, temperature, odors, movement. However, we tend to shift away from such system-centric view to a more niche-centric view, where different cell types and receptors sense elements present in a specific niche and process information via the systems they are linked to. For example, intestinal epithelial cells can sense nutrients, microbes and movement, and transfer information to the immune and nervous system via cell-bound and soluble factors[23–25]. At the molecular level, neurons express receptors for bacterial components, such as TLR5 and NOD2[26,27]. Olfactory receptors, traditionally associated with olfactory epithelium, are also expressed by perivascular macrophages[28].

2. Microbiota and mucosa to brain communication (AD, JH, DM, MR).

The proposition that microbes manipulate the brain is thought-provoking, and thus arises much interest in the scientific community and in the general public. This is probably because we tend to think that the brain is, as the mind should be, insulated from the lowly microbial world by multi-layered mucosal, immune and vascular barriers[29,30]. This was also the view of immunologists, in the past, to comprehend how the individual can deal with the presence of large symbiotic microbial communities: by walling them off, and thus, ignoring them. Obviously, this view is as wrong for the brain as it is for the gut. The intestinal immune system manufactures large amounts of antibodies "just" to maintain an

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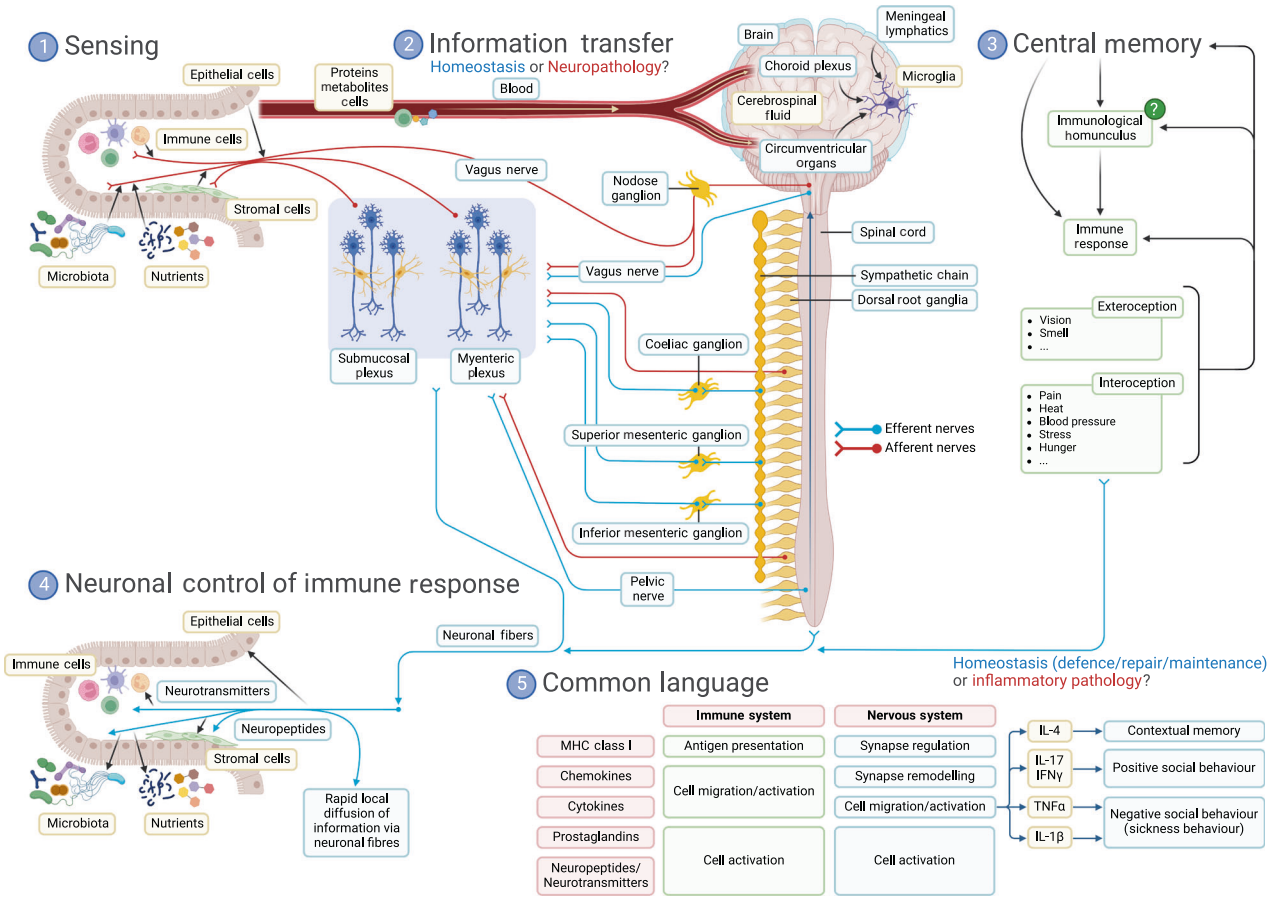

Fig. 1 Synergy between the mucosal immune system, the nervous system and the brain. 1) Neuronal sensing of the mucosal environment: what do neurons sense in mucosae and skin, and how do they impact immunity? Neurons can sense nutrients and microbiota directly, or receive information from immune, epithelial or stromal cells. **2)** Microbiota and mucosa to brain communication: how is information conveyed from mucosae to the central nervous system? Several neuronal routes link the enteric nervous system to the brain. Information also reaches the brain through the blood and is sensed by the choroid plexus, transferred to the cerebrospinal fluid and sensed by circumventricular organs, or transferred to the brain parenchyma and sensed by microglia, and eventually collected by meningeal lymphatics. Such information transfer is involved in homeostasis, but may also be involved in the genesis of neuropathologies. **3)** Brain encoding of immunological information: does the brain memorize information from microbiota and immunity, and therewith modify subsequent immune responses? The brain may encode an "immunological homunculus", instructed by the immune system, as well as by internal and external information collected by the nervous system. An immunological homunculus would regulate subsequent immune responses. **4)** Neuronal control of immune responses: to what (quantitative and qualitative) extent are local neurons and neuronal fibers involved in immune responses? Neuronal fibers at mucosae can autonomously release neurotransmitters and neuropeptides to regulate immune responses locally and rapidly spread information to the broader microregion. The local nervous system also receives information from the spinal cord and the brain, via autonomous feedback loops, or instructed by central memory. **5)** A common language: do molecules involved in communication in both the nervous and the immune systems reflect common functions? Different communication modalities familiar to immunologists are also key in the development and function of the nervous system. This common language may be key to the crosstalk between the two systems, during homeostasis, as well as during pathogenesis. (This figure has been created by Matthew Macowan, Monash University, Melbourne, Australia).

equilibrium with its resident microbiota[31], and normal brain functions require bacterial products[32]. Nevertheless, the question remains open and fascinating: *How do the microbiota and mucosae communicate with the brain?* Which are the significant routes of information transfer, the molecules/receptors involved, the cells activated?[33] The answers will point to a broad and diverse set of modalities, as microbial factors may be sensed at mucosae and information transferred via nerves to the CNS or immune cells that migrate to the CNS, sensed in the brain by structures that are in direct contact with the blood, such as circumventricular organs or the choroid plexus[34], or by cells of the brain parenchyma[35]. But, going back to the original model of the insulated brain: how is the brain shielded from pathogenic over-exposure to microbial triggers (as the gut is by mucus)[36]? In this aspect, can we compare mucosal and brain borders[37,38]?

3. Brain encoding of immunological information, and back (AR, DM, FQ, GL, MS, PML, SM, YO).

We immunologists have been educated with the powerful concept of memory encoded by the selection of antigen-specific cells among a nearly endless pool of B and T cell clones. Memory is nevertheless a broad phenomenon, found in any system that carries traces of the past, such as fingerprints in a crime scene, modifications in cell activation status, rewiring of neuronal networks or editing of the epigenetic code. Since the brain receives information from the microbiota and the immune system, it is tempting to ask *whether the brain can encode and memorize information from microbiota and immunity, and therewith modify subsequent immune responses*. The brain also receives exteroceptive and interoceptive information of very diverse nature, such as social interaction, vision, stress or hunger, which may contribute to

the shaping of immune responses[3]. On the basis of such information, the brain may block immune responses in the context of acute external stressors, e.g., a predator, or potentiate immune responses when facing a risk of infection, e.g., being in the vicinity of a visibly infected individual[33]. Can the brain go further and specify the type of immune response to be engaged or the body site to be protected or modified? Does the brain encode an immunological homunculus, as it does encode a sensory and a motor homunculus[12,39]?

4. Neuronal control of immune responses (CS, FQ, GL, HVF, IC, MN, MS, RD).

Peripheral neurons and CNS neurons projecting to the periphery are an integral part of local functional niches. Sensory neurons in mucosae sense cues from the microenvironment and send information to the CNS[40], but they can also react promptly on site and deliver effectors locally, such as neuropeptides[41–43]. The high speed of information transfer in neurons allows for rapid dissemination of that information from one microregion to another, and thus, for coordination of local (immune) responses[44]. *To what (qualitative and quantitative) extent are local neurons and neuronal fibers involved in immune responses?* In other words, which are the contexts in which, or during which, the local neurons become key players in the immune response. Is a local neuro-immune crosstalk key to maintain local homeostasis, to recruit and activate immune cells (providing signal 2 for the activation of lymphocytes), or to coordinate defense and repair? Is memory encoded in local fibers and neurons that shapes subsequent immune challenges? And ultimately, is the brain involved is such local regulation of immunity, based for example on an immune homunculus? A corollary of such considerations is the role of local neuro-immune interactions in immunopathology, such as inflammatory bowel disease (IBD), with a possible involvement of the brain[12]. And since information flows both ways, can local neuro-immune crosstalk contribute to the progression of neuropathology and neurodegeneration of the CNS?

5. A common language (AD, EH, MP, VP).

And finally, the language. I could have mentioned them first: the very molecules involved in the crosstalk between the nervous system and the immune system. It usually comes as a surprise that molecules we thought were fully dedicated to the immune system also work in the (normal) brain. For example, the role of complement factors and MHC class I in the regulation of synapses[18,19], chemokines and prostaglandins in the activation of neurons, and chemokines and cytokines in the development of the brain[16,17]. One may argue that these molecules may have had other names had they been discovered first by neuroscientists. In any case, *do molecules common to communication in the nervous system, the immune system, and the microbiota, reflect common functions?* Or do they rather reflect shared developmental, maturation and migration paradigms? Understanding how cytokines and chemokines produced during an immune response are sensed by the nervous system, to what (cognitive) aim or (pathological) consequences, possibly opens new avenues for unraveling neuropathologies such as autism, mood disorders and neurodegeneration. The pro-inflammatory cytokine IL-17a promotes aggregation behaviors and social interactions[45,46], whereas TNFα and IL-1β induce sickness behavior upon infection[1], forcing withdrawal from social interactions. But what is the impact of chronic activation of the immune and nervous system by a dysbiotic microbiota at mucosae, over weeks, months, or years? Does the common language between the immune and nervous systems provide a basis for crosstalk and cross-regulation, and at the same time, a basis for cross-perturbation and cross-pathology[47]?

CONCLUSION

I would like to conclude by inviting you to open a new chapter in *Mucosal Immunology*, and hope that this short discussion will convey the growing excitement in neuroimmunology. I believe that we enter a new age in biological research, where different disciplines are able, more than ever, to crossbreed and generate new physiological concepts. Physiological, because our physical and mental states are, after all, the sum of the interactions of all bodily systems. Towards a genuine understanding (or modeling) of the holobiont[48], the basis for personalized medicine.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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