NEUROIMMUNOLOGY IN 2017

The central nervous system: privileged by immune connections

Jonathan Kipnis and Anthony J. Filiano

Over the past few years, interest in the field of neuroimmunology has expanded dramatically, thanks largely to new technologies that have advanced our understanding of the intimate connections between the nervous and immune systems[1]. Here, we highlight key advances in 2017 that have defined new roles for microglia in brain maintenance, for cytokines as neuromodulators and for the immune system in peripheral nerve activity.

Neuroimmunology is an interdisciplinary field that began in the 1930s and can now be divided into several core areas of research (FIG. 1). There have been many insightful and important findings in neuroimmunology in 2017, but here, due to limited space, we focus on some of the most exciting and paradigm-shifting works.

One important recent technological advance that impacts many fields including neuroimmunology is single cell sequencing. In 2017, this approach was used by several groups to study microglia (the brain-resident macrophages), but the results of one such study stand out to us[2]. The authors of this study characterized microglia from healthy individuals and patients with Alzheimer disease, and identified distinct populations of microglia in disease states. They termed these cells disease-associated microglia (DAM). The transition from healthy microglia to DAM requires *TREM2*, a gene that is strongly associated with increased risk for Alzheimer disease. During the transition from healthy microglia to DAM, the cells progress through a TREM2 (triggering receptor expressed on myeloid cells 2)-independent intermediate stage; the function of this intermediate phenotype is unclear. Although *TREM2* mutations are not associated with brain ageing or with amyotrophic lateral sclerosis (ALS), the DAM-associated gene expression signature was also found in 'normal' ageing brains and in patients with ALS, suggesting that the presence of DAM is not specific to a particular disease but to an overall state of the brain. Future studies will determine the role of each of the microglia states and their contribution during disease progression.

The activation of microglia by cytokines is one of the many mechanisms proposed to explain how cytokines affect brain function, with the most studied examples being the effects of IL-1, IL-6 and tumour necrosis factor in the context of sickness behaviour[3]. However, in recent years, the role of cytokines as neuromodulators — that is, acting directly on neurons — has been increasingly appreciated, and in 2017, IL-17 has been in the spotlight. IL-17 has a crucial role in mediating immune responses against enteric infections and in several inflammatory and autoimmune diseases, including multiple sclerosis. More recently, IL-17 was shown to be a major mediator linking maternal immune activation in pregnancy to abnormal brain development and behavioural abnormalities in offspring, characteristic of autism and schizophrenia[4]. In elegant work recently published[5], the authors demonstrate that maternal immune activation results in cortical malformations with heightened pyramidal neuron activity in offspring, which was associated with autistic behaviour. The neurons are activated by IL-17-induced signalling, and silencing of the cortical neurons, using optogenetic stimulation, ameliorated the abnormalities in offspring behaviour. Remarkably, activation of the same neurons in control mice induced abnormal behaviour. This work identifies an area in the brain that responds directly to cytokines by changing its level of activity, in turn affecting behaviour.

Another paper describing similar mechanisms but in a different model system showed that IL-17 could directly activate sensory neurons in *Caenorhabditis elegans* nematode worms and change their behaviour[6]. Further studies are needed to understand how cytokines reach their target neurons (especially in the adult brain), how specific the neuroimmune signalling is and whether these interactions change or drive pathological responses.

Most work in the field of neuroimmunology is concerned with the effects of immune cells and molecules on the central nervous system (CNS), but neuroimmune communications also take place outside the CNS, for example, in barrier tissues. Barrier tissues rely on type 2 immunity (for protection against extracellular parasites and tissue repair) and are often highly innervated. A recent study shows how the type 2 cytokine IL-4 promotes chronic itch by directly binding to and sensitizing sensory neurons[7]. In addition, three independent studies have described how neurons activate group 2 innate lymphoid cells (ILC2s) in the lungs and intestines to promote type 2 immunity[8–10].

Despite the established role for type 2 cytokines in atopic dermatitis, their influence on the concomitant itching was unknown. Oetjen *et al.*[7] noted that sensory neurons in the dorsal root ganglia (DRG) express IL-4 receptor-α. A subset of these DRG sensory neurons were directly activated by exogenously applied IL-4, and activation was dependent on TRPV1 channels (which are non-selective cation channels activated by numerous ligands, including capsaicin). Surprisingly, despite being able to directly activate sensory neurons, IL-4 did not induce itching when injected into the cheek of a mouse. Instead, IL-4 — acting like a neuromodulator — sensitized neurons

Key advances

- Microglia acquire a unique disease-associated phenotype that is associated with neurodegeneration and ageing[2]
- IL-17 impacts neuronal function directly through IL-17 receptor expressed on neurons[5,6]
- IL-4 modulates pain through a direct effect on sensory neurons[9]
- Neurotransmitters regulate immunity in barrier tissues[8–10]

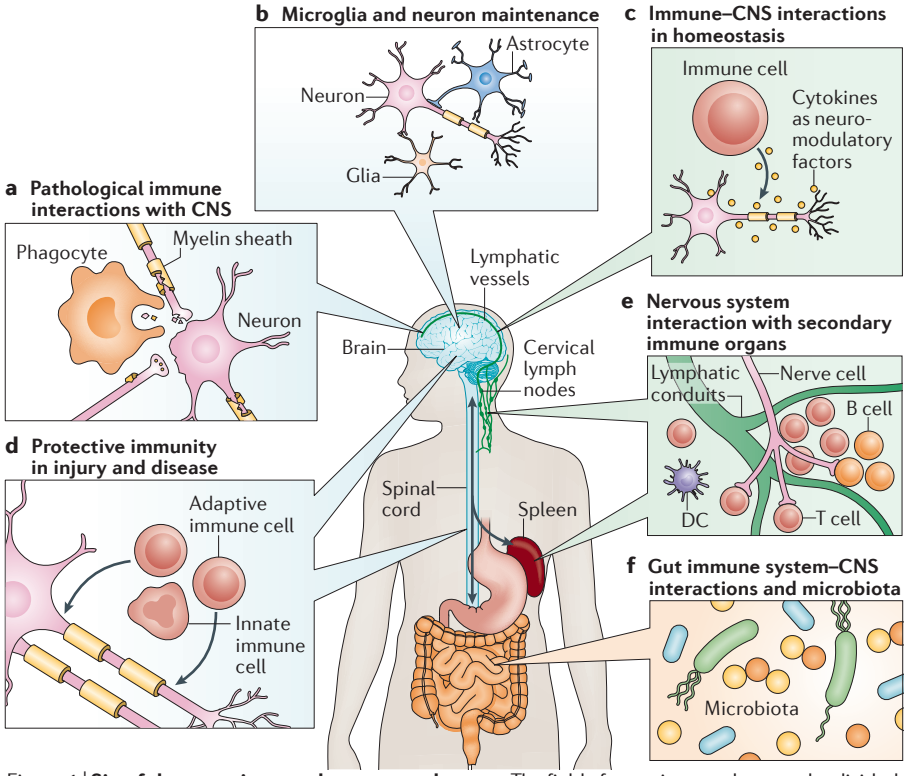

Figure 1 | **Six of the neuroimmunology research areas.** The field of neuroimmunology can be divided into several core areas of research, six of which are depicted here. **a** | Understanding the mechanisms of immune cell entry to the central nervous system (CNS) and the pathological interactions between immune cells and the nervous system. **b** | The study of microglia as brain sentinels and their newly ascribed roles in fine-tuning developing neuronal circuits and in the maintenance of neuronal synapses. **c** | Defining the interactions between the immune and nervous systems under physiological conditions and their effects on brain function, including a new view of cytokines as neuromodulators. **d** | The study of 'protective immunity', addressing beneficial immune infiltrates into the CNS following injury and in neurodegenerative diseases. **e** | Investigating the innervation of secondary lymphoid organs and the regulation of immune activity by the CNS and, conversely, the signals that immune cells and their products relay back to peripheral nerves. **f** | Exploring the mechanisms underlying the gut–immune–brain axis.

to histamine and other substances that cause itching. In a mouse model of atopic dermatitis, deletion of *Il4ra* in sensory neurons reduced scratching behaviour and skin inflammation. Interestingly, deleting the downstream signalling molecule Janus kinase 1 in sensory neurons reduced scratching behaviour without affecting skin inflammation, thus disassociating the itch from inflammation. It will be interesting to determine whether these mechanisms extend to tissues other than the skin, for example, the brain and meninges. Can these pathways explain other conditions, such as headaches or other forms of neuropathic pain? Which cell types produce IL-4 in these conditions and what other types of neurons can respond to IL-4?

ILC2s are activated by host-derived signals and have roles in tissue homeostasis and repair. By comparing expression data sets from ILC2s with those from other ILCs (groups 1 and 3) and T helper cells, neuromedin U (NMU) receptor was found to be preferentially expressed by ILC2s[8–10]. Further experiments demonstrated that ILC2s are in close proximity to neurons in the lungs and intestines and that these cholinergic neurons express NMU, suggesting a potential neuron–ILC2 connection. Importantly, NMU receptor signalling in ILC2s was crucial for defence against infections that require ILC2s for clearance. Treating mice infected with the parasite *Nippostrongylus brasiliensis* with recombinant NMU stimulated a robust ILC2 response, decreased tissue pathology and reduced parasite burden. Although these studies focused on the lungs and intestines, ILC2s reside in numerous tissues, including the meninges, where they are activated and are protective in spinal cord injury. The roles of NMU and ILC2s in CNS injury and other neurological conditions are relatively unexplored.

The studies discussed here describe different neuro-immune circuits and highlight a paradigm shift that has emerged (and is ongoing) in neuroimmunology. Classical neuroimmunology studies concentrated on diseases, primarily multiple sclerosis and its animal model experimental autoimmune encephalomyelitis, and provided great insight into not only neuroimmunology and neuroinflammatory diseases, but also our understanding of basic immunology. The field has now expanded to also investigate intricate neuroimmune communication during development, homeostasis and neurodegenerative diseases that have no obvious inflammatory component, such as Alzheimer disease, autism and schizophrenia.

The brain is not as 'immune privileged' as once thought, and with this understanding new areas of neuroimmunology are emerging. Although neurons remain the most important functional unit of the nervous system, they should no longer be considered the sole target for therapies in neurological conditions. Immune cells, acting directly and indirectly on brain function, are more accessible and easily manipulated targets than neurons. Understanding of the complex neuro-immune interactions will pave the way for the development of new therapies that target the immune system (and/or glia) for the benefit of the brain.

Jonathan Kipnis is at the Center for Brain Immunology and Glia, Department of Neuroscience, University of Virginia, Charlottesville, Virginia 22908, USA.

Anthony J. Filiano is at the Robertson Clinical and Translational Cell Therapy Program and the Department of Neurosurgery, Duke University, Durham, North Carolina 27710, USA.

Correspondence to J.K.
kipnis@virginia.edu

doi:10.1038/nri.2017.152
Published online 27 Dec 2017

1. Kipnis, J. Multifaceted interactions between adaptive immunity and the central nervous system. *Science* **353**, 766–771 (2016).
2. Keren-Shaul, H. *et al.* A unique microglia type associated with restricting development of Alzheimer's disease. *Cell* **169**, 1276–1290 (2017).
3. Dantzer, R. *et al.* From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* **9**, 46–56 (2008).
4. Choi, G. B. *et al.* The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. *Science* **351**, 933–939 (2016).
5. Shin Yim, Y. *et al.* Reversing behavioural abnormalities in mice exposed to maternal inflammation. *Nature* **549**, 482–487 (2017).
6. Chen, C. *et al.* IL-17 is a neuromodulator of *Caenorhabditis elegans* sensory responses. *Nature* **542**, 43–48 (2017).
7. Oetjen, L. K. *et al.* Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell* **171**, 217–228 (2017).
8. Wallrapp, A. *et al.* The neuropeptide NMU amplifies ILC2-driven allergic lung inflammation. *Nature* **549**, 351–356 (2017).
9. Klose, C. S. N. *et al.* The neuropeptide neuromedin U stimulates innate lymphoid cells and type 2 inflammation. *Nature* **549**, 282–286 (2017).
10. Cardoso, V. *et al.* Neuronal regulation of type 2 innate lymphoid cells via neuromedin U. *Nature* **549**, 277–281 (2017).

Acknowledgements
The authors thank A. Impagliazzo for help with the figure.

Competing interests statement
The authors declare no competing interests.