Neuroimmunology – the past, present and future

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Abstract

Neuroimmunology as a separate discipline has its roots in the fields of neurology, neuroscience and immunology. Early studies of the brain by Golgi and Cajal, the detailed clinical and neuropathology studies of Charcot and Thompson's seminal paper on graft acceptance in the central nervous system, kindled a now rapidly expanding research area, with the aim of understanding pathological mechanisms of inflammatory components of neurological disorders. While neuroimmunologists originally focused on classical neuroinflammatory disorders, such as multiple sclerosis and infections, there is strong evidence to suggest that the immune response contributes to genetic white matter disorders, epilepsy, neurodegenerative diseases, neuropsychiatric disorders, peripheral nervous system and neuro-oncological conditions, as well as ageing. Technological advances have greatly aided our knowledge of how the immune system influences the nervous system during development and ageing, and how such responses contribute to disease as well as regeneration and repair. Here, we highlight historical aspects and milestones in the field of neuroimmunology and discuss the paradigm shifts that have helped provide novel insights into disease mechanisms. We propose future perspectives including molecular biological studies and experimental models that may have the potential to push many areas of neuroimmunology. Such an understanding of neuroimmunology will open up new avenues for therapeutic approaches to manipulate neuroinflammation. Neuroimmunology encompasses fundamental and applied biology, immunology, chemistry, neurology, pathology, psychiatry and virology of the central nervous system (CNS). Scientists in the field study the interactions of the immune and nervous system during development, homeostasis and response to injuries with the major aim of developing approaches to treat or prevent neuroimmunological diseases.The immune system has been generally regarded as autonomous and the brain protected by the blood–brain barrier, (BBB) and in the words of Rudyard Kipling (Barrack-room ballads, 1892), 'never the twain shall meet'. In the past decades these dogmas have been strongly challenged and dispelled with the wealth of evidence showing that not only does the nervous system receive messages from the immune system, but that signals from the brain regulate immune functions that subsequently control inflammation in other tissues 1. Communication between the immune system and the CNS is exemplified by the finding that many molecules associated with the immune system are widely expressed and functional in the nervous system and vice versa. Cross-talk between microglia and neurones is known to be essential for maintaining homeostasis, yet such cross-talk also occurs between oligodendrocytes and microglia 2. Disturbance in this communication due to peripheral infections in mice are known to trigger microglia activation and augment neurodegeneration 3. Similarly, recent experimental studies show that maternal infections lead to long-term changes in microglia and abnormal brain development in the offspring.Despite this evidence, it is surprising that the term 'neuroimmunology' was only first used on PubMed in 1982, coinciding with the first Neuroimmunology Congress in Stresa, Italy (Fig. and following the launch of the Journal of Neuroimmunology in 1981. Although neuroimmunology research has focused on multiple sclerosis (MS; using the search term 'neuroimmunology', 43% of papers on PubMed in 2018 were on MS), immune responses are also observed in Guillain–Barré syndrome (GBS), white matter diseases, psychiatric disorders, infections, trauma and neurodegenerative diseases traditionally considered to be 'cell autonomous' (Table (Table11). One of the greatest misconceptions that impeded progress in neuroimmunology was the idea that the blood–brain barrier (BBB) and the perceived immunological privilege of the brain prevent cross-talk between the CNS and immune systems. This long-standing dogma has been challenged by recent studies and the discovery of glymphatics and meningeal lymphatic vessels 43. Although this paradigm shift is a recent advancement in thinking of nervous-immune system cross-talk, such changes in the field, beginning over 150 years earlier, have been generally linked to technological advances, some of which have yielded Nobel Prizes in neuroimmunology (Table (Table2),2), including the development of mutant and transgenic mice to examine disease mechanisms, stem cell technologies and the novel CRISPR/cas9 system, that allows gene editing enabling personalized treatments. Here, we review the developments in neuroimmunology since its roots in the first descriptions of immunological processes and neurological diseases, as well as the development of technologies and clinical trials for such diseases. Important events are given in major timelines or eras,

along with the Nobel Prizes considered relevant by their impact on the field of neuroimmunology. The review also includes a perspective on the future of neuroimmunology that should herald prospective approaches to understanding these diseases, and we address several outstanding questions in the field. The long-term goal of this rapidly developing field of neuroimmunology is to further the understanding of how immune responses shape the nervous system during development and ageing, how such responses lead to neurological diseases, and ultimately to develop new pharmacological treatments. These aspects are thus the major topics of the International Society of Neuroimmunology meetings (ISNI.