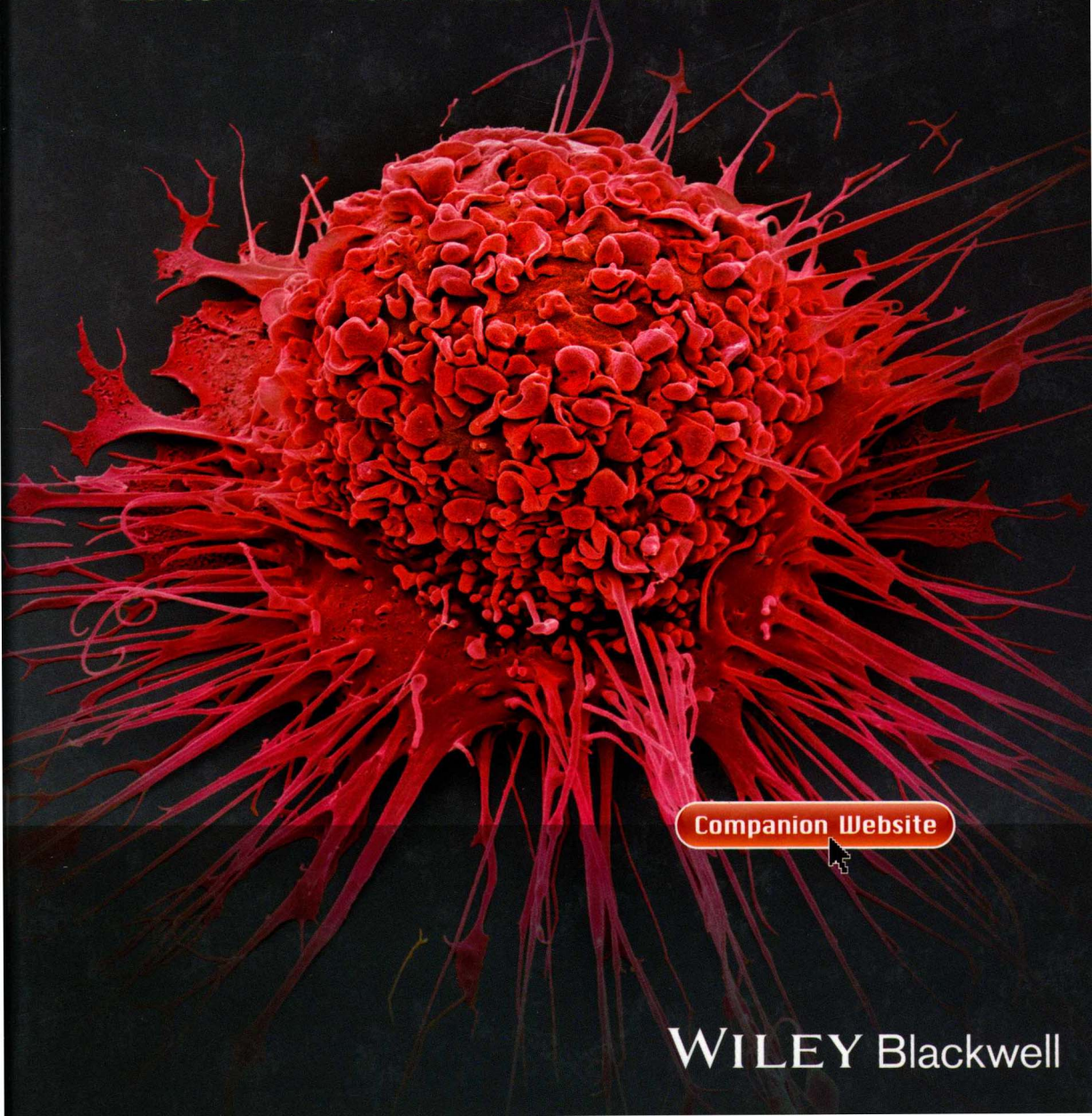
Neuroinflammation and CNS Disorders

Editors Nicola Woodroofe Sandra Amor



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Preface

It is widely assumed that the central nervous system is an immune-privileged site, suggesting that antigens gaining entry to the brain and spinal cord do not invoke an immune response.

While this idea was first discussed over 70 years ago, it is clear that immune privilege is not absolute since immune responses do take place in the central nervous system and are crucial for shaping the brain during development and for controlling infections in the brain. As well as these examples, in the last decade there has been an explosion of information on the role of immune responses in neurodegenerative disorders. In many of these diseases, it is still unclear whether the innate and adaptive responses are pathogenic or play a role in repair, and thus understanding their precise roles is key to controlling these diseases by designing immune-therapeutic approaches.

It is for this reason that we undertook the task of compiling the latest information on the interactions between the immune system and central nervous system.

In the first section of this book, the chapters are dedicated to the communication between the immune system and the central nervous system that is best exemplified by cross-talk between glia and neurons shown to be essential for maintaining homeostasis. This section is specifically designed as an introduction to the topic and forms the basis for the second section devoted to specific neurological diseases.

We are indebted to our many colleagues who have taken time from their busy schedules to help us compile this book. In particular, we would like to especially thank Stan Appel and his team, who underwent the hardship of tragically losing a colleague, Jenny Henkel, during the production of the chapter. Likewise, we also sincerely thank Andrew Harkin, who took over from Tom O'Connor who lost his life during the writing of their chapter. We hope that their memory will live on through their work and help inspire new generations in their fields.

We are not unaware that this will not be the last work on how the immune system interacts with the central nervous system, but we are confident that this book forms the basis of what is to come in the field.

Introduction: Interactions between the Immune and Central Nervous Systems

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In this introductory chapter, we briefly trace the history of the field and highlight the important influence that research in neuroimmunology has had on modern immunologic and neurological ideas. The link between many neurological diseases is the realisation that the immune and nervous systems are inextricably linked, and that perturbations in this delicate balance are involved in many disorders. This has opened up new avenues for therapeutic approaches to the treatment of central nervous system (CNS) inflammatory and neurodegenerative and neoplastic disorders. In this introduction to the book, we provide links to other chapters in the book that expand upon these key features. For those new to the field we have included a section (Chapters 1–5) highlighting the key basic concepts in the field, while the second section (Chapters 6–15) covers the role of the immune response in specific disorders of the CNS.

Origins

The field of neuroimmunology developed from sub-specialities in immunology and neurology into a rapidly expanding discipline of its own. While the first international congress of neuroimmunology was held in Stresa, Italy in 1982, the International Society of Neuroimmunology (ISNI) was only founded after the second congress in 1987 in Philadelphia, United States. The *Journal of Neuroimmunology* had been launched in March 1981, and the *Journal*

of Clinical and Experimental Neuroimmunology in 1988. The origins of neuroimmunology predate the establishment of the society by nearly a century, and the discipline has its roots in several interdisciplinary topics. It is a discipline that now encompasses a wide range of disorders including peripheral neuropathies and those affecting the CNS (Table I.1) (Amor *et al.*, 2010, Amor and Woodroofe, 2013; Peferoen *et al.*, 2013). The milestones in the history of neuroimmunology are outlined in Table I.2.

By invitation only

It is widely assumed that the CNS is an immune-privileged tissue, suggesting that antigens gaining entry to the brain and spinal cord do not invoke an immune response (Chapter 1). While this idea was first discussed over 70 years ago, it is clear that immune privilege is not absolute since immune responses do take place in the CNS and are crucial for shaping the brain during development and controlling infections in the brain. However, immune cells do not freely patrol the brain as with other organs, and those that enter are by invitation only. The gatekeeper of the CNS is the blood–brain barrier, which when compromised is unable to control such selection, thereby contributing to the tissue damage. In many neurological disorders there is evidence that the blood–brain barrier, and indeed the barriers that maintain immune privilege in the spinal cord and optic nerve, are less effective. However, whether such damage precedes or is the result of inflammation is still a 'chicken and egg' topic of discussion. As well as the physical barriers, the CNS attempts to maintain control by expression of immunomodulatory molecules on neurons and oligodendrocytes (Peferoen *et al.*, 2013). Thus, as well as damaging the CNS, both the innate and adaptive immune responses regulate and suppress inflammation (Chapters 2 and 3) and aid repair (Chapter 5). While such approaches are very effective in controlling immune responses in the CNS, this strategy is also exploited by tumours to interfere with or evade the immune system, thereby establishing a permissive environment in which to expand (Chapter 15). As well as these examples, in the last decade there has been an explosion of information on the role of immune responses in neurodegenerative disorders. In many of these diseases it is still unclear whether the innate and adaptive responses are pathogenic or play a role in repair, and thus understanding their precise roles is key to controlling these diseases by designing immune-therapeutic approaches.

Cross-talk between the immune system and CNS

As discussed in this introduction, neurons have a profound influence on the immune system, which is called neuroimmunomodulation. This influence is shaped by neurotransmitters, such as serotonin, histamine and gamma-aminobutyric acid; neuropeptides, such as adrenocorticotropin, vasoactive

Table I.1 Neuroimmunological aspects of disorders of the central nervous system (CNS)

Disorder	Clinical characteristics and immune involvement	Chapter
Alzheimer's disease (AD)	Pathology of human tissues, *in vitro* studies and animal models of AD provide evidence for involvement of immune activation pathways. Long-term use of anti-inflammatory drugs is linked with reduced risk of developing the disease.	6
Parkinson's disease	Movement disorder due to deterioration of the nigrostriatal system. Chronic activation of microglia is observed to be associated with neurodegeneration.	6
Huntington's disease and other polyglutamine expansion diseases	Microglia expressing a mutant huntingtin protein are blunted in their ability to migrate, leading to immune dysfunction.	6
Infections	Encephalitis, encephalomyelitis, meningitis, polyradiculitis or polyneuritis. Characteristics depend on infectious agents [e.g. human T-lymphotropic virus type 1 (HTLV1)-associated myelopathy (HAM)]. Immune responses depend on infectious agents.	7
Amyotrophic lateral sclerosis (Lou Gehrig's disease)	Immune abnormalities in the CNS and peripheral immune responses. Microglia activation is associated with the production of neurotoxic as well as neurotrophic factors.	8
Multiple sclerosis (MS)	Demyelination and neurodegeneration in brain, spinal cord and optic nerve. Innate and adaptive immune activation. Oligoclonal immunoglobulin in cerebrospinal fluid.	9
Acute demyelinating encephalomyelitis (ADEM)	Usually associated with or following a viral infection or following vaccination. Most cases are in children and adolescents (average ages 5–8). Demyelinating lesions are associated with immune activation (like MS).	9
Neuromyelitis optica (NMO)	Inflammatory disorder of the CNS predominantly affecting the optic nerves and spinal cord. Most patients have antibodies to aquaporin-4 (AQP4) which are thought to directly attack astrocytes.	9
Systemic lupus erythematosus (SLE), diabetes and gluten ataxia	Neurodegeneration and inflammation affect a large number of patients with SLE. Persons with gluten ataxia display a loss of Purkinje cells associated with immune activation in the CNS.	10
Depression	Link between levels of pro-inflammatory cytokines and depression in susceptible individuals. Changes in serotonergic and/or glutamatergic transmission in the CNS and reduced neurotrophic factor expression.	11

(*continued*)

Table I.1 (*Continued*)

Disorder	Clinical characteristics and immune involvement	Chapter
Epilepsy	A predisposition to develop seizures is frequently associated with cognitive and psychological sequelae. Both the innate and adaptive immune responses have been linked with disease. Anti-inflammatory agents are used to control some forms of epilepsy.	12
Stroke and intracerebral haemorrhage	Dramatic increase in the systemic inflammation and innate immune activation triggered to resolve debris as well as neutrophil traffic into infarcted brain tissue.	13
Spinal cord injury	Direct damage to axons, neuronal cell bodies and glia causes functional loss. The injury triggers an inflammatory response that contributes to secondary tissue damage.	14
Primary brain tumours	Cellular and molecular mechanisms that mediate tumour escape from natural immune surveillance (e.g. tumours down-regulate major histocompatibility complex expression).	15

Table I.2 Milestones in the history of neuroimmunology

Year	Milestone
1825–1893	Jean-Martin Charcot was a French neurologist and professor of anatomical pathology. He recognized the neurological diseases multiple sclerosis (MS), Charcot–Marie–Tooth disease and amyotrophic lateral sclerosis.
1949	Induction of experimental autoimmune encephalomyelitis in mice
1960	Nobel Prize: Peter B. Medawar (1915–1987) and Frank Macfarlane Burnet (1899–1985). The immune system can distinguish between self and non-self, and the brain is immune-privileged.
1980	Nobel Prize: Baruj Benacerraf (1920–2011), Jean Dausset (1916–2009) and George Davis Snell (1903–1996), "for discovery of the Major histocompatibility complex genes which encode cell surface molecules important for the immune system's distinction between self and non-self".
1981	Launch of *Journal of Neuroimmunology*
1982	First international neuroimmunology meeting
1996	Nobel Prize: Peter C. Doherty and Rolf M. Zinkernagel. Importance of major histocompatibility complex molecules in the detection, removal and killing of virus-infected cells
1999	Alemtuzimab (antibody to CD52; Campath 1H) effective in suppression of active inflammation in MS
2005	Recognition that antibodies to aquaporin-4 (AQP4) are present in people with optic-spinal MS (now classified as neuromyelitis optica) and bind to the AQP4 water channel
2011	Effective use of Rituximab (to deplete B cells) in MS to reduce relapses
2011	Nobel Prize in Physiology or Medicine: Bruce Beutler, Jules Hoffman and Ralph M. Steinman. Identification of dendritic cells and importance in T cell activation and specifically the role of the innate immune response

intestinal peptide, neuropeptide Y, endorphins and substance P; and neurotrophic growth factors, such as nerve growth factor and ciliary neurotrophic growth factor. In return, the immune system influences neuronal functions by producing immune and inflammatory mediators, such as cytokines and chemokines, leading to conditions such as sickness behaviour and depression (Chapter 11). That many autoimmune disorders are influenced by hormones is reflected by the high association of autoimmune disorders in females compared to males, including MS. These studies have now led to therapeutic approaches (so-called neuroendocrine immunomodulation) that may also be applicable to other CNS disorders in which the immune system is involved.

Of mice and men

The field of neuroimmunology has contributed to advancements in modern neuroimmune disorders largely through discoveries made in experimental models. Nevertheless, these concepts that have emerged from *in vivo* animal studies must also be valid in humans. These studies, including tracking immune responses in the brain, have yielded important insights into the mechanisms of damage as well as immunoregulation in neuroimmune disease. With the advent of powerful tools such as multifunctional flow cytometry, gene expression profiling, proteomics and mass spectrometry imaging, these studies now offer increased insight into how the immune system and CNS interact and indeed how such cross-talk can be manipulated. The new developments in human cellular immunology have also advanced the application of immune therapies to target specific arms or pathways involved in these immune-mediated disorders. This field will allow the development of novel approaches to treatment of neurodegenerative disorders, although it must be borne in mind that effective therapies can only arise from the correct use, application and interpretation of data arising from animal models and, most critically, the translation of these data to humans.

Immune responses and neurodegenerative disorders

The role of the innate and adaptive immune responses in neurodegenerative diseases has become a major focus of neuroimmunologists. This is partly due to the increasing ageing community, since the average life expectancy now extends late into the eighth decade in the Western world. Many neurodegenerative disorders occur more frequently in people of advanced age. In 2000, the number of persons with dementia was estimated at 25 million worldwide, but this figure does not include neurodegenerative diseases that are not classically associated with cognitive decline, such as traumatic brain injury and systemic lupus erythematosus (Chapter 10).

The major challenge in this area is to understand why and how the immune system is activated and the precise roles of immune responses in neuronal damage and dysfunction and in cognitive decline. Clearly, ageing plays a key role in neurodegenerative disorders, and this may partly rely on the decreased effectiveness of the ageing immune system (Chapter 4). It is probable that while subtle differences between diseases are observed, common pathways may imply that broad therapeutic approaches may be applied to these diseases. Such an understanding will be a key to developing therapeutics targeting the relevant component of the immune system.

In summary, this introductory section has chronicled the emergence of neuroimmunology in the latter part of the 20th century as well its contributions to modern immunology. More details are provided in the separate chapters in this book by experts in their fields.

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References

Amor S, Puentes F, Baker D, van der Valk P. Inflammation in neurodegenerative diseases. Immunology 2010;129:154–69.

Amor S, Woodroofe MN. Review series on immune responses in neurodegenerative diseases: Innate and adaptive immune responses in neurodegeneration and repair. Immunology 2013 Jun 12. doi:10.1111/imm.12134. [Epub ahead of print]

Peferoen L, Kipp M, van der Valk P, van Noort JM, Amor S. Review series on immune responses in neurodegenerative diseases: Oligodendrocyte-microglia cross-talk in the CNS. Immunology 2013 Aug 24. doi:10.1111/imm.12163. [Epub ahead of print]

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/woodroofe/neuroinflammation

The website includes:

- Powerpoints of all figures from the book for downloading
- PDFs of all tables from the book for downloading

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