Current Clinical Neurology
Series Editor: Daniel Tarsy

Syed A. Rizvi
Jonathan F. Cahill
Patricia K. Coyle *Editors*

Clinical Neuroimmunology

Multiple Sclerosis and Related Disorders

Second Edition

Humana Press

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Series Editor

Daniel Tarsy
Beth Israel Deaconness Medical Center
Department of Neurology
Boston, MA
USA

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Syed A. Rizvi • Jonathan F. Cahill
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Editors
Syed A. Rizvi, MD, EMHL
Rhode Island Hospital and Alpert
Medical School of Brown University
Brown Neurology
Providence, RI
USA

Jonathan F. Cahill, MD
Rhode Island Hospital and Alpert
Medical School of Brown University
Brown Neurology
Providence, RI
USA

Patricia K. Coyle, MD
Department of Neurology
MS Comprehensive Care Center
Stony Brook University Medical Center
Stony Brook, NY
USA

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Preface

Immune activation of the central or peripheral nervous system (CNS or PNS) has been shown to play a key role in the pathogenesis of many neurological disorders. Basic concepts in clinical neuroimmunology have changed significantly during the last 10 years and are constantly evolving. New data has driven treatment concepts for a large number of autoimmune diseases, none more so than multiple sclerosis. As this area of research has become increasingly active and productive, the need for a comprehensive up-to-date second edition of this handbook has become apparent.

Clinical Neuroimmunology: Multiple Sclerosis and Related Disorders (Second Edition) has been written with the clinician in mind and targets residents, fellows, internists, nurse practitioners, as well as general neurologists. The aim of this book is to make recent developments in neuroimmunology accessible to the clinicians who feel daunted by such advances and requires a clear explanation of the scientific and clinical issues. The chapters have been written by experts in their field and been extensively revised and updated. Two new chapters have been added. *Part I* provides a logical and straightforward overview of neuroimmunology. *Part II* consists of eight chapters focused on multiple sclerosis and includes a chapter on clinical decision-making and a chapter on vitamin D in MS. *Part III* has four chapters and focuses on other CNS inflammatory disorders including neuromyelitis optica, ADEM, vasculitis, autoimmune encephalopathies, and immunological aspects of cancer. *Part IV* includes two chapters that describe autoimmune disorders of the PNS. *Part V*, the final part, includes a single chapter that focuses on neurologic manifestation of systemic rheumatologic diseases such as systemic lupus erythematosus (SLE), neuro-sarcoidosis, and Behcet's. We hope health professionals who are interested in neuroimmunological disorders will find this book useful.

Finally, we would like to thank our contributing authors for their hard work and guidance.

Providence, RI, USA — Syed A. Rizvi, MD
Providence, RI, USA — Jonathan F. Cahill, MD
Stony Brook, NY, USA — Patricia K. Coyle, MD

Series Editor's Introduction

The role of the immune system in the pathophysiology of central and peripheral nervous system disorders continues to be a topic of great interest among clinicians and researchers in the field. As stated by Drs. Rizvi, Cahill, and Coyle, the editors of *Clinical Immunology, Second Edition,* basic concepts in this field have changed significantly due to a constant evolution of knowledge since the publication of the first edition of this book in 2011. This comprehensive and up-to-date second edition of this useful handbook is therefore a welcome addition to the field.

Clinical Immunology, Second Edition, continues to be written primarily for clinicians in the field and targets general neurologists, internists, fellows, residents, and nurse practitioners. Although clinically oriented, the chapters all include updated authoritative information on new understandings of the basic mechanisms of the disorders being discussed. Section 1 begins with two useful chapters which provide an excellent introduction and overview of clinical neuroimmunology and the principles of immunotherapy. Section 2 covers multiple sclerosis and includes new chapters on clinical decision-making in the management of multiple sclerosis and the role of vitamin D in this disease. Section 3 covers other central nervous system inflammatory disorders, such as neuromyelitis optica, acute disseminated encephalomyelitis, and CNS vasculitis, and a new chapter on paraneoplastic disorders. Section 4 covers immunologic disorders of muscle and peripheral nerve, and Section 5 provides a new chapter concerning the neurologic manifestations of systemic rheumatologic disorders. The readers of this volume will discover that the quantity of new knowledge accumulated in the past 10 years is worthy of this new and highly comprehensive summary of the field.

Daniel Tarsy, MD
Professor in Neurology, Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, MA, USA

Contents

Contributors

Shamik Bhattacharyya, MD, MS Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA

Michael J. Bradshaw, MD Department of Neurology, Chicago Medical School, Rosalind Franklin University of Medicine and Science, Billings Clinic, Billings, MT, USA

Guy J. Buckle, MD, MPH Shepherd Center, Multiple Sclerosis Institute, Atlanta, GA, USA

Jonathan F. Cahill, MD Rhode Island Hospital and Alpert Medical School of Brown University, Brown Neurology, Providence, RI, USA

Leigh Elkins Charvet, PhD Department of Neurology, Multiple Sclerosis Comprehensive Care Center, NYU Langone Health, New York, NY, USA

Saima T. Chaudhry, MD MS Fellow, Brown Neurology, Providence, RI, USA

Patricia K. Coyle, MD Department of Neurology, MS Comprehensive Care Center, Stony Brook University Medical Center, Stony Brook, NY, USA

Philip L. De Jager, MD, PhD Department of Neurology, New York – Presbyterian Hospital, New York, NY, USA

John E. Donahue, MD Department of Neuropathology, Rhode Island Hospital, Providence, RI, USA

James M. Gilchrist, MD Department of Neurology, Southern Illinois University School of Medicine, Springfield, IL, USA

Jennifer O. Grimes, MA, MD Candidate Alpert Warren Medical School of Brown University, Providence, RI, USA

Nichola Haddad, BA Alpert Warren Medical School of Brown University, Providence, RI, USA

Michael F. Holick, PhD, MD Department of Medicine, Boston University Medical Center, Boston, MA, USA

Dejan Jakimovski, MD Department of Neurology, Buffalo General Hospital, University of Buffalo, Buffalo, NY, USA

Jennifer Joscelyn, MS, OT Thought Leader Liaison, Hooksett, NH, USA

Lloyd Kasper, MD Department of Microbiology/Immunology, Dartmouth College, Hanover, NH, USA

Symbiotix Biotherapies, Boston, MA, USA

Lauren B. Krupp, MD Department of Neurology, Multiple Sclerosis Comprehensive Care Center, NYU Langone Health, New York, NY, USA

Alexander Mohler, MD Alpert Medical School of Brown University, Providence, RI, USA

Department of Neurology, Rhode Island Hospital, Providence, RI, USA

Mayra Montalvo, MD Department of Neurology, Rhode Island Hospital, Providence, RI, USA

Javier Ochoa-Repáraz, PhD Eastern Washington University, Cheney, WA, USA

Deepa P. Ramasamy, MD Department of Neurology, Buffalo General Hospital, University of Buffalo, Buffalo, NY, USA

Jacques Reynolds, MS/DO Department of Neurology, Midcoast Hospital, Brunswick, ME, USA

Syed A. Rizvi, MD, EMHL Rhode Island Hospital and Alpert Medical School of Brown University, Brown Neurology, Providence, RI, USA

Tina Roostaei, MD, MPH Department of Neurology, Center for Translational and Computational Neuroimmunology, Columbia University Medical Center, New York, NY, USA

Jacqueline F. Rosenthal, MD Shepherd Center, Multiple Sclerosis Institute, Atlanta, GA, USA

Julie Roth, MD Alpert Medical School of Brown University, Providence, RI, USA

Department of Neurology, Rhode Island Hospital, Providence, RI, USA

George Sachs, MD, PhD Department of Neurology, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI, USA

James M. Stankiewicz, MD Partners Multiple Sclerosis Center, Harvard Medical School, Boston, MA, USA

Joshua A. Stone, MD MS Fellow, Brown Neurology, Providence, RI, USA

Charles D. Tyshkov, MD Department of Pediatrics/Child Neurology, New York Presbyterian Weill Cornell Medical Center/Brooklyn Methodist Hospital, New York, NY, USA

Nagagopal Venna, MD, MRCP(I), MRCP (UK) Neuro-Infectious Diseases, Harvard Medical School, Boston, MA, USA

Division of Neuroimmunology, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

Brian Wong, MD Department of Neurology, Hartford Healthcare, University of Connecticut School of Medicine, Southington, CT, USA

David S. Younger, MD, MPH, MS Department of Neurology, White Plains Hospital, New York, NY, USA

Robert Zivadinov, MD, PhD Department of Neurology, Buffalo General Hospital, University of Buffalo, Buffalo, NY, USA

Part 1

Introduction

Introduction to Neuroimmunology

1

Patricia K. Coyle

Introduction

The nervous system can be considered the single most important body organ. It encompasses both the central nervous system (CNS) (brain, spinal cord, and optic nerve) and the peripheral nervous system (PNS) (peripheral nerves, neuromuscular junction, skeletal muscle). The autonomic nervous system can be considered a functional subdivision, with both CNS and PNS components.

Historically, the CNS has been described as a sequestered compartment protected from the systemic immune system. However, more recent studies not only support clear communication links between the CNS and specific extraneural systems, but the existence of a brain innate immune system (Table 1.1) [1, 2]. The CNS is more accurately characterized as an immunologically privileged site [3].

Neuroimmunology is the neuroscience specialty that focuses on interactions between the nervous system and immune system. It includes both basic science fields and clinical disciplines which deal with a special set of CNS and PNS disorders (Table 1.2) [4–6]. These disorders result from immune-mediated damage and require diagnostic and therapeutic approaches that recognize and address this fact. Some are truly autoimmune, with a recognized pathogenic neural autoantigen target, while others are not. Most will be covered in subsequent chapters.

Sometimes unusual diseases are characterized as neuroimmune based on their pathology and/or therapeutic response. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a recently described rare disorder that predominantly targets brainstem, cerebellum, and spinal cord. The MRI pattern is suggestive, with punctate (<3 mm) homogeneously enhancing pontine and cerebellar nodules [7]. Neuropathology shows dense perivascular and parenchymal lymphocyte infiltration (particularly CD4+ T cells, with some B cells and plasma cells) without loss of myelin. CSF changes are nonspecific, but proteomic studies support roles for complement activation, IgG deposition, and altered extracellular matrix [8]. Patients show a marked corticosteroid response.

Table 1.1 CNS and immune system connections

CNS innate immune system
Glial cells and neurons (in certain circumstances) secrete immune factors (chemokines, cytokines)
CNS meningeal lymphatic system
Found in mice, primates, humans
CNS undergoes constant immune surveillance within the meningeal spaces
Paravascular glymphatic system
CNS-gut-microbiome axis
Microbiota impacts CNS, immune system

P. K. Coyle (✉)
Department of Neurology, MS Comprehensive Care Center, Stony Brook University Medical Center, Stony Brook, NY, USA
e-mail: patricia.coyle@stonybrookmedicine.edu

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Table 1.2 Neuroimmune disorders

CNS
Acute disseminated encephalomyelitis (ADEM)/ postinfectious encephalomyelitis
Autoimmune encephalitis/cerebellitis
Multiple sclerosis
Neuromyelitis optica spectrum disorder
Acute transverse myelitis
Optic neuritis
MOG-associated syndromes
Tropical spastic paraparesis—HTLV1-associated myelopathy
Rasmussen encephalitis
Stiff person syndrome
Poststreptococcal movement disorders
Pediatric autoimmune neuropsychiatric disorders (PANDAS)
Hashimoto's and other misc. autoimmune encephalopathy/encephalitis
Paraneoplastic syndromes (can involve PNS)
CNS vasculitis
CLIPPERS
Susac syndrome
PNS
Peripheral nerve
Guillain-Barre syndrome
Chronic relapsing/inflammatory demyelinating polyneuropathy
Multifocal motor neuropathy
Other immune polyneuropathies (anti-MAG, anti-sulfatide, GALOP, POEMS, etc.)
Neuromuscular junction
Myasthenia gravis
Lambert-Eaton myasthenic syndrome
Arthrogryposis multiplex congenital
Muscle
Polymyositis
Dermatomyositis
Inclusion body myositis (degenerative plus inflammation components)

Rasmussen's encephalitis is another rare disorder characterized by unilateral hemispheral inflammation, with refractory seizures and progressive neurologic deterioration [9]. Average age at onset is 6 years. Rasmussen's encephalitis appears to involve a cytotoxic CD8+ T cell response that may be enhanced by autoantibodies. There is marked microglial and astrocyte activation, and adjacent brain injury may be mediated by T cell-microglia interactions. The only cure for the refractory seizures involves removal of the hemisphere.

Susac syndrome is a presumed immune-mediated disorder that involves a retino-cochleacerebral microangiopathy. There are occlusions of precapillary arterioles in the brain, retina, and cochlea [10]. Patients develop subacute encephalopathy with headache with or without focal deficits, branch retinal artery occlusions with or without visual issues, and sensorineural hearing loss. Only 13% of patients show the complete clinical triad at onset however [11]. Brain MRI shows multifocal round hyperintense T2 and FLAIR lesions with invariable central corpus callosum involvement and characteristic retinal fluorescein angiography abnormalities (occlusions and segmental vessel wall staining) [11]. Treatments have included a variety of immunosuppressive approaches (corticosteroids, cyclophosphamide, anti-CD20 monoclonal antibody, intravenous immune globulin, azathioprine, mycophenolate) [10].

Recently autoimmune encephalitis/cerebellitis (also referred to as antibody-mediated encephalitis) has emerged as an ever-increasing group of disorders with prominent neuropsychiatric symptoms and antibodies against neuronal cell surface proteins, ion channels, or receptors [12].

Finally, there are several disorders of unclear etiology where a neuroimmune basis has been suggested but not proven. They include postural orthostatic tachycardia syndrome [13, 14], fibromyalgia with central sensitization syndrome and associated small fiber neuropathy, and chronic fatigue syndrome/systemic exertion intolerance disease [15]. Further studies are needed before they can be considered to be neuroimmune. The rest of this chapter will describe various CNS aspects, components, and cell populations as a foundation to better understand neuroimmunology.

Unique Anatomy

CNS anatomy is unique. Because the CNS is encased by bone, with a relatively inelastic dura lining, small volume changes can result in injury. The brain and spinal cord are encased in the bony protective skull and vertebral column, as well as a three parts membranous covering (pia, arachnoid, dura). The pia and arachnoid membranes form the subarachnoid space, which is filled with cerebrospinal fluid (CSF). In essence, the brain

and spinal cord float in a water bath, since CSF is 99% water [16, 17]. It acts as a buoyancy fluid. CSF is an active product of the secretory epithelium of the choroid plexus, but up to 40% is formed by extracellular fluid from the CNS parenchyma. This extracellular fluid is added to CSF at virtually all points along the neuraxis. CSF circulates from within the ventricles (where the choroid plexi are situated) into the subarachnoid space, flowing down the spinal axis and back up, to be resorbed into the venous blood system via the arachnoid villi. These arachnoid villi are outpouchings of the arachnoid membrane that extend into the venous sinuses of the cerebral hemispheres. CSF is made continually, at approximately 20 cc/h. The total volume (125–150 cc in a typical adult) is completely turned over 4–1/2 times every 24 h.

Since the ependymal cells which line the ventricles lack tight junctions, there is essentially free communication between CNS white matter extracellular fluid and ventricular CSF. CNS gray matter fluid at the brain surface also communicates with CSF via the Virchow-Robin spaces, specialized perivascular spaces associated with penetrating arteries that are continuous with the subarachnoid space.

CSF leukocyte count in normal controls ranges up to 5 WBCs/mm^3. WBCs are largely (80%) CD4+ memory T cells [18]. About 5% are monocytes, while <1% are B cells. CSF T cells express CD27 and CD45 RO, markers of central memory T cells. Very late antigen-4 (VLA-4) expression is also increased compared to peripheral T cells. CSF T cells show higher expression of CXC chemokine receptor 3, compared to other chemokines. CSF memory T cells can encounter potential antigen-presenting cells (APCs) at several sites, including the ependyma, Virchow-Robin spaces, and choroid plexus.

Blood-Brain Barriers

The blood-brain barrier (BBB) can be demonstrated by inhibition of entry of intravenous dyes into the CNS [19, 20]. It is formed by specialized features unique to CNS blood vessels. CNS capillaries not only lack fenestrae, but they have interendothelial cell tight junctions which prevent cell migration. They have a continuous basal lamina. They also do not pinocytose effectively and only have a few pinocytic vesicles. The BBB is not absolute. It is relative or even selective, limiting entry of large hydrophilic proteins, but allowing entry of smaller lipophilic compounds and small gaseous molecules [21]. The endothelial basement membrane and perivascular glia limitans do not seem to play a role in the BBB.

Although the choroid plexus capillaries are fenestrated, with 80 nm openings [3], the choroid plexus epithelium has tight junctions. This is the anatomic basis for the blood-CSF barrier. There are specific CNS regions which do not have a barrier. The circumventricular organs (area postrema, organum vasculosum of the lamina terminalis, median eminence, subfornical organ) lack tight junctions between capillary endothelial cells. At these sites molecules can diffuse very easily into the CNS. The nasal barrier is another leaky site, where there is continuing turnover of olfactory receptor neuron axons which pass through the subarachnoid CSF to terminate on olfactory bulb mitral cells [22].

The BBB and blood-CSF barrier, along with the CSF circulation, provide bidirectional control of flow. Damaging CNS factors can be removed via efflux transporters into the blood, while influx transporters can promote nutrients into the CNS. The PNS has a similar blood-nerve barrier in peripheral nerve, but this is absent in spinal roots and at the dorsal root ganglia.

CNS Lymphatics

A meningeal lymphatic system has been discovered in mice, nonhuman primates, and humans [23, 24]. This system carries macromolecules (fluids and immune cells) from the CNS CSF and interstitial fluids and connects to deep cervical lymph nodes [25]. The lymphatics are found along large blood vessels and cranial nerves in the dura mater [24]. Meningeal lymphatic disruption in young mice leads to impaired brain CSF perfusion and learning and memory deficits [25].

There are several other CSF draining pathways. The subarachnoid space surrounding the

olfactory bulb crosses the cribriform plate at the base of the ethmoid bone, into nasal submucosal lymphatics [26]. In animals, CSF drains from the subarachnoid space along cranial and spinal nerve roots, and to a lesser extent the dura mater, to cervical and lumbar lymph nodes [26]. This route is also present in humans [27]. CSF moves directly into venous circulation through the arachnoid villi granulations in the walls of the venous sinuses. CNS soluble antigens within the CSF can access lymphoid tissue via both cervical lymphatics and venous drainage [3].

CNS Immunity

The CNS is composed of neurons, glia, blood vessels, and meninges. Neurons contain dendritic, somatic, axonal, and synaptic regions. Glia consists of neuroectodermal cells (astrocytes, oligodendrocytes, ependymal cells) as well as bone marrow-derived cells (microglia).

The CNS has a resident immune system. Both microglia and astrocytes play key roles in CNS innate immune responses. They are complemented by infiltrating monocytes and dendritic cells from the blood that accumulate at nonparenchymal CNS sites [28]. Innate immune responses can be neuroprotective or neurotoxic.

In contrast, acquired immune responses are more difficult to initiate within the CNS. Activated T cells (regardless of antigen specificity) penetrate into the CNS as a normal phenomenon, but then rapidly exit. CD4+ and CD8+ T cells penetrate by different mechanisms [29]. Usually T cells accumulate in the perivascular Virchow-Robin spaces and subarachnoid spaces. These T cells cause problems only if they recognize specific antigens in the context of major histocompatibility complex (MHC). CD4+ T cells recognize antigen in the context of MHC Class II, while CD8+ T cells recognize antigen in the context of MHC Class I. Normally the CNS has low level of MHC expression. Since microglia and astrocytes are nonprofessional APCs, they express low levels of MHC and costimulatory molecules. They are more likely to induce T cell anergy rather than activate naïve T cells [28].

Dendritic cells are recognized as the most potent professional APCs. There are no resident dendritic cells within the CNS, although recent reports describe a resident population in mouse brain [30, 31]. Dendritic cells can infiltrate into CSF, choroid plexus, meninges, perivascular spaces, and CNS parenchyma as part of a neuroinflammatory response [32]. Along with macrophages, they probably reactivate T cells which enter the CNS [29]. Diverse chronic inflammatory processes can result in peripheral dendritic cells entering the brain [33]. Dendritic cells can be derived from monocytes or lymphoid precursors. Both myeloid and lymphoid dendritic cells are capable of entering the CNS under inflammatory conditions.

The CNS immune/inflammatory response differs from that in other organ systems. CNS neurons are largely postmitotic and nonregenerating. Neuronal necrosis induced by neurotoxin injection does not elicit a typical inflammatory response. Virus inoculated into the parenchyma is cleared slowly and inefficiently [34]. Yet neuroinflammation is how the CNS responds to altered homeostasis [35]. It involves resident glia, infiltrating immune cells, cytokines and cytokine signaling, and the BBB.

There are three distinct routes of entry for white blood cells (WBCs) into the CNS [3, 36]. The first pathway involves cells moving from blood vessels into the stroma of the choroid plexus and then crossing the blood-CSF barrier into CSF. This appears to be the most likely site for physiologic entry of leukocytes into CSF. A second route of cell entry is also across the blood-CSF barrier, into the subarachnoid space, involving postcapillary venules at the pia into the subarachnoid space and the Virchow-Robin perivascular spaces. The endothelial cells express adhesion molecules, which promote T cell adherence, allowing direct exchange between circulating leukocytes and perivascular cells [37, 38]. The third route involves activated T cells moving from blood to the parenchymal perivascular space, across the BBB [29].

Leukocyte transmigration into tissue, including the CNS, involves a coordinated stepwise process [39]. There is initial contact, then tether-

ing/rolling (involving selectins and glycoprotein ligands), activation (involving chemokines and G protein-coupled receptors), adhesion (involving integrins and adhesion molecules), and diapedesis with migration to vascular junctions, penetration into the subendothelial compartment, and breach of the vascular basement membrane into tissue [39]. T cell migration into the CNS under inflammatory conditions involves α (alpha) 4ß (beta) 1 integrin expressed on T cells, interacting with vascular cell adhesion molecule 1 on activated endothelial cells. Expression of chemokines and chemokine receptors also plays a role in T cell trafficking. The rate-limiting step in transmigration is crossing the basement membrane laminins. T cells migrate across laminin 411 but not laminin 511. Laminin α (alpha) 4 (a component of laminin 411) preferentially involves CD4+ T cell migration, but not CD8+ T cell macrophages or dendritic cells.

It has been suggested that WBC extravasation into the spinal cord may differ somewhat from that into the brain, but very little work has been done in this area [40].

CNS immune surveillance may occur primarily within the subarachnoid space [29]. This is thought to be the initial site of T cell infiltration, where cells can be reactivated by MHC Class II APCs, with T cell proliferation and formation of large cellular aggregates. There can be a rapid T cell response within the subarachnoid space to antigen challenge. This reactivation of T cells promotes further inflammation and cell entry into the perivascular space and then the brain parenchyma.

Major Histocompatibility Molecule Expression

In the CNS resting state, there is absent or minimal expression of MHC Class I and II molecules [41, 42]. MHC expression is generally limited to low-level expression on microglia and endothelial cells, but can be induced in a variety of CNS components [43]. Interferon gamma (IFNγ) induces MHC expression on neurons [28]. Astrocytes can also express MHC.

CNS Cell Components

Microglia

Microglia make up the primary CNS resident immune cell [44]. They are the main APCs in the CNS, responsible for innate immune surveillance [45, 46]. Microglia are derived from erythro-myeloid progenitors in the yolk sac before embryonic day 1 [47]. They continuously proliferate throughout the lifetime of the individual. Microglia make up about 10–15% of all glial cells [48]. They are usually in a resting state. Microglial activation and proliferation is increased when there is any sort of CNS injury including neurodegeneration. These glia are present throughout the CNS but enriched in certain areas, with more microglia in gray matter than white matter [49]. Mature cells express macrophage-specific markers including toll-like receptors (TLRs), CD11b integrin, and the F4/80 glycoprotein, but show lower expression of CD45. Based on morphology, microglia are classified as resting ramified, activated, or ameboid phagocytic cells [44]. Ameboid phagocytic microglia predominate in the perinatal brain, but become ramified resting microglia during postnatal development. They can be activated by injury, infection, or neurodegenerative processes [46]. Microglia are constantly active, surveying the brain and interacting with synapses. They help to prune redundant synapses and actively participate in synaptic remodeling along with astrocytes [35].

In macrophage biology, responses are classified as M1 (upregulation of proinflammatory mediators and production of reactive oxygen species) and M2a (anti-inflammatory activity) and M2c (deactivation/wound healing activity) [50]. It remains controversial whether microglia can truly be classified as M1/M2.

Microglial function is driven by CNS microenvironment changes. Microglia monitor their microenvironment and conduct routine surveillance of the CNS via pinocytosis and neuronal interaction [48, 51]. They respond to a complex mix of excitatory and inhibitory input, including cell-cell contact and soluble factor exposures.

Activation by inflammatory or injury factors provokes a preprogrammed response designed to both kill and promote recovery and repair. Classical activation, alternative activation, and acquired deactivation are all going on, but may differ within regional areas. As examples, substance P neurotransmitter causes activation, while neuronal activity inhibits MHC class II expression to IFNγ. A neuronal surface molecule (CD200) appears to be an important regulator of microglial function. Soluble factors such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage-CSF (MO-CSF) affect microglia function and development.

Resting ramified microglia are activated by detecting lipopolysaccharides, amyloid beta, thrombin, IFNγ, and other proinflammatory cytokines [52]. Microglia express TLR. They can initiate innate immune responses by producing cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor α (TNFα); chemokines such as monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1, and RANTES; and nitric oxide (NO) (Table 1.3). The net result is local cell production of more proinflammatory cytokines and chemokines, and upregulation of immunomodulatory surface markers, with injury to the BBB and subsequent entry of soluble factors and systemic immune cells. Microglial activation precedes this systemic cell entry. CNS injury results in phagocytic and cytotoxic activities of microglia. Complement and Fc gamma receptors are upregulated, leading to enhanced phagocytic ability. Cytotoxic superoxide radicals and NO are released into the microenvironment.

Resting microglia are very poor APCs. However, activation causes marked expression of MHC and costimulatory molecules [53, 54]. The activation state involves morphological changes as well as gene expression changes, migratory and proliferative responses, and phagocytic behavior. Activated microglia will express CD40, CD80, CD86, and MHC class II molecules. Subsequent interaction with T cells leads to microglial release of nitric synthase. IFNγ promotes MHC class II as well as adhesion and costimulatory molecule expression.

Table 1.3 Activated microglia products

Chemokines
Complement proteins
Cytokines
Neurotrophic factors
Prostaglandins
Proteinases
Reactive oxygen species/reactive nitrogen species (nitric oxide, peroxynitrite, superoxide)

Microglia have an important role in the development and plasticity of synapses [55]. In essence they shape normal CNS circuitry and modify circuits during inflammation. Microglia also play an important role in regulation. Microglia express Fas ligand, which can bind to Fas receptor on T cells, leading to activation-induced T cell apoptosis. Cytotoxic microglial products, such as NO, can lead to death of immune cells (Table 1.3). Thus, activation of microglia can be self-limited, as it leads ultimately to removal of effector immune cells.

Microglia dynamically modulate neurons and astrocytes, share receptors, and produce factors that activate these surrounding cells. Microglia modulate glutamate levels and can protect or injure neurons [56]. They are a central immune system player in the CNS and interact with and regulate astrocytes. Disease-associated microglia have been identified in areas of neurodegeneration; they appear to be generated through the detection of neurodegeneration-associated molecular pattern, using Trem2 signaling pathways [57].

Astrocytes

Astrocytes are the most common glial cell in the CNS and make up 20–40% of the total number of CNS cells. They play multiple roles, including neural circuit formation with trophic as well as structural support to neurons, promoting formation of synapse as well as their pruning (Table 1.4) Astrocytes maintain microenvironment homeostasis and contribute to recovery after CNS injury [58, 59]. They produce antioxidants (glutathione), recycle neurotransmitters (glutamate,

Table 1.4 Role of astrocytes

Neuronal support
Microenvironmental ion, pH homeostasis
Glycogen storage
Clearance of toxic waste products
Neural circuit formation and support
Synapse formation Synapse pruning
Synaptic transmission modulation
Glutamate uptake
Release of neuromodulatory factors
Astrocyte neuron gap junction
Neuron and glial survival
Production of neurotrophins: brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), at baseline; BDNF, nerve growth factor (NGF) on injury
Astrocyte-mediated growth factor production
Maintenance of blood-brain barrier
Astrocyte end feet surround CNS capillaries and perivascular macrophages
Astrocyte products can increase or tighten permeability
Immune function
Contribute to both innate and acquired immunity

GABA), and maintain the BBB. The astrocyte foot process helps to form the BBB and glymphatic system [60].

There is regional variation in astrocyte to neuron ratio, with higher ratios in areas that are dense with dendrite and axons [59]. Overall astrocyte to neuron ratio is controversial, ranging from four to five times more astrocytes, down to a one to one ratio [61].

Astrocyte morphology can differ. Protoplasmic astrocytes are found in gray matter, where their processes envelope synapses [61]. They show numerous ramified branches contacting neurons and blood vessels [21]. Fibrous astrocytes are found in white matter, where their processes contact nodes of Ranvier [59]. They show longer, thinner processes.

All astrocytes express intermediate filament glial fibrillary acidic protein (GFAP). Activation results in upregulation of GFAP as part of gliosis. Astrocytes are dynamic and plastic. A host of CNS insults (trauma, stroke, infection, neurodegenerative disease) can trigger astrocytes moving from the resting to reactive state. Two distinct types of reactive astrocytes are described, A1 and A2 [58]. A1 astrocytes are induced by classically activated neuroinflammatory microglia, via release of IL1α, TNF, and C1q. A1 astrocytes upregulate destructive complement cascade genes and induce rapid death of neurons and oligodendrocytes. In contrast A2 astrocytes upregulate neurotrophic factors and can be considered neuroprotective. It has been postulated that A1 astrocytes contribute to the death of neurons and oligodendrocytes in neurodegenerative diseases.

It is also known that astrocytes can process glucose to lactate. They may provide lactate as an energy source to neurons during periods of increased demand [62].

Astrocytes play an important role in regulating CNS inflammation and cell trafficking. In vitro, they can produce proinflammatory cytokines and chemokines, and reactive oxygen species (ROS) to enhance inflammation, as well as regulatory cytokines and ROS scavengers to limit inflammation [63]. Astrocytes have important interactions with blood vessels. Reactive astrocytes can act as perivascular barriers to restrict leukocyte entry during pathologic states.

With regard to the role of the astrocyte as an immune cell, they appear to function in both innate and acquired immunity, both in the normal and inflamed CNS. Astrocytes have dual actions, both beneficial and injurious. Astrocytes can express a variety of pattern recognition receptors, including TLRs, dsRNA-dependent protein kinase, complement receptors, mannose receptors, and scavenger receptors. Astrocytes also show APC-like function in vitro. They can be induced to express MHC class I and II molecules, to upregulate costimulatory molecules CD80 and CD86, to activate CD4+ and CD8+ T cells, and to present antigen to CD4+ T cells [4, 21]. During inflammation astrocytes release a variety of cytokines (IL-1, IL-6, and IL-10; TNFα; transforming growth factor β (TGFβ)) that influence T cell responses. Astrocytes can contribute to lymphocyte penetration into the CNS in three ways: by a BBB effect, by expression of adhesion molecules such as ICAM-1 and VCAM-1, and by release of chemokines such as CCL5, CCL2, CXCL8, and CXCL10. Therefore astrocytes can participate in amplifying CNS inflammatory responses, but

also appear to suppress T cell activation by upregulating cytotoxic T lymphocyte antigen (CTLA)-4 on activated T cells [21]. Astrocytes can also induce regulatory T cells exhibiting suppressor activity. Activated astrocytes release IL-17 to suppress Th17 cells.

Astrocytes both impede and promote CNS repair mechanisms. By forming a glial scar there is an additional physical barrier producing multiple biochemical changes, including expression of molecules on the astrocyte surface that can block axon regeneration as well as oligodendrocyte precursor cells. By production of certain chemokines, cytokines, and matrix metalloproteinases, as well as their tissue inhibitors, repair is promoted.

Oligodendrocytes

Oligodendrocytes are the myelin-making glial cells of the CNS. Oligodendrocytes form a myelin sheath around multiple axons to electrically insulate them. This results in sodium channel clustering at the nodes of Ranvier, to allow saltatory conduction. Normal axonal transport and neuronal viability seems to require proper myelination, which also boosts axon diameter. Oligodendrocytes provide trophic support to neurons via neurotrophic factors such as glial derived (GDNF), brain derived (BDNF), and insulin-like 1 (IGF-1) growth factors [64].

At peak myelination, an oligodendrocyte supports a membrane weight 100 times its cell body [65]. Oligodendrocytes do not just myelinate, but facilitate transfer of metabolites to neurons and support axonal health.

Oligodendrocyte precursor cells (OPCs) with high mitochondrial demands are highly susceptible to metabolic stress injury. They are glucose dependent. Oligodendrocytes also show extremely high metabolic rates and consume large quantities of oxygen and adenosine triphosphate (ATP), leading to high levels of intracellular hydrogen peroxide and ROS [66, 67]. The numerous myelin synthesis enzymes, which require iron as a cofactor, results in OPCs containing the highest intracellular iron stores in the brain [64]. This can result in free radical formation and lipid peroxidation. Oligodendrocytes also have only low concentrations of the anti-oxidative enzyme glutathione. The capacity of the oligodendrocyte's endoplasmic reticulum to produce and fold proteins is susceptible to minimum changes causing marked disturbances. All of this makes oligodendrocytes particularly vulnerable to oxidative damage and mitochondrial injury and more vulnerable to bystander damage than neurons or astrocytes.

Oligodendrocytes are vulnerable to excitotoxic cell damage; they express glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors and the ATP receptor P2x7. Proinflammatory cytokines such as TNFα induce oligodendrocyte apoptosis by binding to the p55 TNF receptor [67]. Although IFNγ has no negative effect on mature oligodendrocytes, it is highly toxic for proliferating OPCs and mildly toxic for immature oligodendrocytes. A variety of proinflammatory cytokines can induce mitochondrial injury, indirectly damaging the more vulnerable oligodendrocyte population. Autoantibodies which bind to surface myelin or oligodendrocyte epitopes can lead to damage via complement activation or Fc receptor recognition on activated neurophages.

Oligodendrocytes do not express MHC antigens, but in vitro exposure to IFNγ results in MHC class I induction.

Neurons

Although neurons have been said not to express MHC, recent work indicates they most likely do express MHC class I that can be up- or down-regulated by various factors [68]. In vitro exposure to IFNγ induces MHC class I expression on human axons [69]. This would make them vulnerable to attack by CD8+ T cells. Natural killer (NK) cells can also lead to neuronal destruction. MHC class II was also noted on discrete subsets of human neural stem cells during development, independent of inflammatory stimuli [70].

Neurons can regulate T cell activities either directly or indirectly, using a variety of contact-dependent and contact-independent mechanisms. They release soluble factors (neurotransmitters, neuropeptide, neurotrophins, cytokines, soluble Fas ligand, soluble ICAM-5) that can reduce microglial and T cell activation. This downregulation occurs predominantly within the perivascular and subarachnoid spaces [28]. Neurons can also interact directly with microglia and T cells via contact-dependent mechanisms involving neuronal glycoproteins such as CD22, CD47, CD200, neural cell adhesion molecule, and semaphorins [28].

Endothelial Cells

CNS endothelial cells express MHC class I but not class II antigen. Brain capillary endothelium contain enzymes not otherwise found in the CNS (alkaline phosphatase and γ-glutamyl transpeptidase). They have much fewer cytoplasmic vesicles than non-CNS endothelium, which will contribute to lower penetration into the CNS. Pericytes (of mesodermal origin) are found along the length of the cerebral capillaries and partially surround the endothelium and contribute to the basal lamina [19, 71]. They play a critical role in BBB maturation and maintenance [72]. (C, E). Astrocytes have integrins on their end feet that bind to laminin in the basal membrane to provide an additional seal to the BBB. There is actually a dual basement membrane surrounding the endothelium, a three-dimensional mesh as thick as 200 nm, consisting of proteins including integrins, dystroglycans, collagens, and laminins. Disruption of extracellular matrix increases BBB permeability [73].

Other Immunologic Factors

Cytokines

Immune system cells produce cytokines that can have important effects on the nervous system. Cytokines such as IL-1, IL-6, and TNF cross the BBB around the hypothalamus, due to fenestration as well as active transport mechanisms. They have direct impact on the hypothalamic neurons which regulate temperature, appetite, and sleep [5].

Matrix Metalloproteinases (MMPs)

MMPs are a family of calcium-dependent zinc-containing endopeptidases that degrade extracellular matrix to increase capillary permeability and permit cell penetration. They also proteolytically process many signaling molecules [74]. They are involved in post-injury remodeling, axonal growth, neurogenesis, angiogenesis, myelinogenesis, CNS barrier disruption, demyelination, and a variety of immune factor actions [75]. They can be divided into four groups of enzymes: collagenases, stromelysins, gelatinases, and membrane-type metalloproteinases [56]. They are activated by cleavage, plasmin, or reactive oxygen radicals. MMP-2 (gelatinase A) is normally present in brain tissue and CSF. MMP-9 (gelatinase B), MMP-3, and MMP-12 are induced during an inflammatory response involving immediate early genes (c-FOS, c-JUNE) and cytokines such as TNFα (alpha) and IL-1B. Astrocytes stain for MMP-2. MMP-9 appears in endothelial cells and neutrophils during CNS injury. MMP-3 has been detected in microglia and neurons during ischemia, while MMP-12 is expressed by activated microglia and macrophages.

Toll-Like Receptors (TLRs)

TLRs are part of the innate immune system. They are pathogen recognition receptors, type I transmembrane glycoprotein receptors with a highly variable extracellular region, and a highly conserved intracellular tail, localized to the cell surface or within endosomes [76]. They protect the host against pathogens. Many different TLRs are expressed by microglia [77]. They trigger a standardized cytokine and chemokine response, regardless of the inciting antigen, that can be

beneficial or harmful. Activation of astrocytes, oligodendrocytes, and neurons can also result in TLR expression. These TLRs play various roles which are cell specific and include cell migration and differentiation, limiting inflammation, and mounting repair processes.

Nervous Immune and Endocrine System Network

There is a strong reciprocal relationship between the nervous, immune, and endocrine systems. These three systems participate in an extensive tri-directional network that involves both cell to cell contact and soluble factors (cytokines/chemokines, growth factors, hormones, neurotransmitters/neuropeptides). Sharing regulatory molecules allows coordinated responses to homeostasis disturbance produced by inflammation, infection, or stress [78]. These three body organ systems are anatomically and functionally connected. Neuroimmune activation and neuroinflammation play an important role even in diseases not considered to be classically neuroimmune, such as stroke, Alzheimer disease, and Parkinson disease.

Neurotransmitters help regulate the host response to injury and infection. Immune cells express neurotransmitter receptors. Catecholamines can affect antigen presentation by dendritic cells, enhance antibody responses, and suppress cellular immune responses, clonal lymphocyte expansion, and cell migration and trafficking [79]. Net effects reflect whether α (alpha) or ß (beta) adrenergic receptors are activated.

The brain helps control immune activation. The cholinergic vagus nerve excites sympathetic neurons that innervate the spleen and synapse directly on immune cells [80]. Immune cells express receptors for pituitary hormones (prolactin, human growth hormone, thyroid-stimulating hormone, insulin-like growth factor 1) as well as neurotransmitters (acetylcholine, glutamate, norepinephrine, endorphins). In turn, MHC Class I molecules modulate neural synapse formation during brain development and can regulate these synapses as well in the mature brain [81]. Cytokines such as TNF regulate the AMPA class of glutamatergic receptors.

The brain and immune system communicate via the hypothalamic-pituitary-adrenal gland (HPA) axis and the sympathetic nervous system. The HPA axis maintains homeostasis by regulating the neuroendocrine, sympathetic nervous system, and immune system. Abnormalities in HPA axis have been implicated in autoimmune-/immune-mediated disorders [82]. It is an important feedback loop and a major component of how the nervous and endocrine systems communicate. The paraventricular nucleus of the hypothalamus secretes two peptides, vasopressin and corticotropin-releasing hormone (CRH). They in turn act on the anterior lobe of the pituitary gland to secrete adrenocorticotropic hormone (ACTH). In turn, ACTH acts on the adrenal gland cortex to produce glucocorticoid hormones (chiefly cortisol), which in a negative feedback loop suppress CRH and ACTH release. CRH synthesis is influenced by stress cortisol blood levels and the diurnal sleep-wake cycle. Cortisol normally rises 30–45 min after awakening in the morning, and in the late afternoon, and is lowest in the middle of the night.

Psychoneuroimmunology is a reflection of the organ system links outlined above. It studies the interactions between psychological processes, such as stress and anxiety, and the nervous and immune systems. Traumatic life events, personality traits, coping mechanisms, and strong emotions can impact on nervous and immune function. For example, cell-mediated immunity can be impaired in individuals who lose a loved one. Stress can make individuals more vulnerable to infections. Psychoneuroimmunology evaluates models such as sickness behavior, neuropsychiatric disorders, and the effects of stress on the nervous system.

Summary

The immune system plays a pivotal role in neuroimmune disorders. In addition, it is increasingly recognized to be a factor in most major

neurologic diseases. It also determines how the body responds behaviorally to external factors. Practicing neurologists who are familiar with basic neuroimmunology concepts will have a better understanding of current and future advances in understanding and treating nervous system disorders.

References

1. Gruol D. Advances in neuroimmunology. Brain Sci. 2017;7(10) https://doi.org/10.3390/brainsci7100124.
2. Martin CR, Osadchiy V, Kalani A, et al. The brain-gut-microbiome axis. Cell Mol Gastroenterol Hepatol. 2018;6:133–48.
3. Ransohoff RM, Kivisakk P, Kidd G. Three or more routes for leukocyte migration into the central nervous system. Nat Rev Immunol. 2003;3:569–81.
4. Pender MP. An introduction to neuroimmunology. In: Pender MP, McCombe PA, editors. Autoimmune neurological disease. Cambridge: Cambridge University Press; 1995. p. 14–25.
5. Bhat R, Steinman L. Innate and adaptive autoimmunity directed to the central nervous system. Neuron. 2009;64:123–32.
6. Diamond B, Huerta PT, Mina-Osorio P, et al. Losing your nerves? Maybe it's the antibodies. Nat Rev Immunol. 2009;9:449–56.
7. Tobin WO, Guo Y, Krecke KN, et al. Diagnostic criteria for chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). Brain. 2017;140:2415–25.
8. Blaabjerg M, Hemdrup AL, Drici L, et al. Omics-based approach reveals complement-mediated inflammation in chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). Front Immunol. 2018;9:741.
9. Varadkar S, Bien CG, Kruse CA, et al. Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances. Lancet Neurol. 2014;13:195–2015.
10. van der Kooij SM, van Buchem MA, Overbeek OM, et al. Susac syndrome: a report of four cases and a review of the literature. Neth J Med. 2015;73(1):10–6.
11. Kleffner I, Dörr J, Ringelstein M, et al. Diagnostic criteria for Susac syndrome. J Neurol Neurosurg Psychiatry. 2016;87:1287–95.
12. Dalmau J, Graus F. Antibody-mediated encephalitis. N Engl J Med. 2018;378(9):840–51.
13. Vernino S, Stiles LE. Autoimmunity in postural orthostatic tachycardia syndrome: current understanding. Auton Neurosci. 2018; https://doi.org/10.1016/j.autneu.2018.04.005.
14. Doherty TA, White AA. Postural orthostatic tachycardia syndrome and the potential role of mast cell activation. Auton Neurosci. 2018; https://doi.org/10.1016/j.autneu.2018.05.001.
15. Blomberg J, Gottfries CG, Elfaitouri A, et al. Infection elicited autoimmunity and myalgic encephalomyelitis/chronic fatigue syndrome: an explanatory model. Front Immunol. 2018;9:229.
16. Regeniter A, Kuhle J, Mehling M, et al. A modern approach to CSF analysis: pathophysiology, clinical application, proof of concept and laboratory reporting. Clin Neurol Neurosurg. 2009;111:313–8.
17. Maurer MH. Proteomics of brain extracellular fluid (ECF) and cerebrospinal fluid (CSF). Mass Spec Rev. 2010;29:17–28.
18. Svenningsson A, et al. Adhesion molecule expression on cerebrospinal fluid T lymphocytes: evidence for common recruitment mechanisms in multiple sclerosis, aseptic meningitis, and normal controls. Ann Neurol. 1993;34:155–61.
19. Engehardt B, Sorokin L. The blood-brain and the blood-cerebrospinal fluid barriers: function and dysfunction. Semin Immunopathol. 2009;31:497–511.
20. Palmer AM. The role of the blood-CNS barrier in CNS disorders and their treatment. Neurobiol Dis. 2010;37:3–12.
21. Nair A, Frederick TJ, Miller SD. Astrocytes in multiple sclerosis: a product of their environment. Cell Mol Life Sci. 2008;65:2702–20.
22. Dhuria SV, Hanson LR, Frey WH II. Intranasal delivery to the central nervous system: mechanisms and experimental considerations. J Pharm Sci. 2010;99:1654–73.
23. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatics. Nature. 2015;523(7560):337–41.
24. Goodman JR, Adham ZA, Woltjer RL, et al. Characterization of dural sinus-associated lymphatic vasculature in human Alzheimer's dementia subjects. Brain Behav Immun. 2018; https://doi.org/10.1016/j.bbi.2018.07.020.
25. Da Mesquita S, Louveau A, Vaccari A, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. Nature. 2018;560(7717):185–91.
26. Weller RO, Kida S, Zhang ET. Pathways of fluid drainage from the brain: morphological aspects and immunological significance in rat and man. Brain Pathol. 1992;2:277–84.
27. Johnston M, Zakharov A, Papaiconomou G, et al. Evidence of connections between cerebrospinal fluid and nasal lymphatic vessels in humans, non-human primates and other mammalian species. Cerebrospinal Fluid Res. 2004;1:2–15.
28. Tian L, Rauvala H, Gahmberg CG. Neuronal regulation of immune responses in the central nervous system. Trends Immunol. 2009;30:91–9.
29. Goverman J. Autoimmune T cell responses in the central nervous system. Nat Rev Immunol. 2009;9:393–407.
30. Bulloch K, Miller MM, Gal-Toth J, et al. CD11c/EYFP transgene illuminated a discrete network of dendritic cells within the embryonic, neonatal, adult, and injured mouse brain. J Comp Neurol. 2008;508:687–710.

31. Felger JC, Abe T, Kaunzner UW, et al. Brain dendritic cells in ischemic stroke: Time course, activation state, and origin. Brain Behav Immun. 2010;24(5):724–37.
32. Hatterer E, Touret M, Belin MF, et al. Cerebrospinal fluid dendritic cells infiltrate the brain parenchyma and target the cervical lymph nodes under neuroinflammatory conditions. PLoS One. 2008;3:1–15.
33. Gottfried-Blackmore A, Kaunzner UW, Idoyaga J, et al. Acute in vivo exposure to interferon-γ enables resident brain dendritic cells to become effective antigen presenting cells. Proc Natl Acad Sci U S A. https://doi.org/10.1073/PNAS.0911509106.
34. Stevenson PG, Austyn JM, Hawke S. Uncoupling of virus-induced inflammation and anti-viral immunity in the brain parenchyma. J Gen Virol. 2002;83:1735–43.
35. Ransohoff RM, Schafer D, Vincent A, et al. Neuroinflammation: ways in which the immune system affects the brain. Neurotherapeutics. 2015;12(4):896–909.
36. Kivisakk P, Mahad DJ, Callahan MK, et al. Human cerebrospinal fluid central memory CD4+ T cells: evidence by trafficking through choroid plexus and meninges via P-selectin. Proc Natl Acad Sci U S A. 2003;100:8389–94.
37. Lassman H, Schmied M, Vass K, et al. Bone marrow derived elements and resident microglia in brain inflammation. Glia. 1993;7:19–24.
38. Hickey WF. Leukocyte traffic in the central nervous system: the participants and their roles. Semin Immunol. 1999;11:125–37.
39. Lee BPL, Imhof BA. Lymphocyte transmigration in the brain: a new way of thinking. Nat Immunol. 2008;9:117–8.
40. Vajkoczy P, Laschinger M, Engelhardt B. α4-integrin-VCAM-1 binding mediates G protein-independent capture of encephalitogenic T cell blasts to CNS white matter microvessels. J Clin Invest. 2001;108:557–65.
41. Yang I, Kremen TJ, Giovannone AJ, et al. Modulation of major histocompatibility complex class I molecules and major histocompatibility complex-bound immunogenic peptides induced by interferon-alpha and interferon-gamma treatment of human glioblastoma multiforme. J Neurosurg. 2004;100:310–9.
42. Stoll M, Capper D, Dietz K, et al. Differential microglial regulation in the human spinal cord under normal and pathological conditions. Neuropathol Appl Neurobiol. 2006;32:650–61.
43. Cebrián C, Loike JD, Sulzer D. Neuronal MHC-I expression and its implications in synaptic function, axonal regeneration and Parkinson's and other brain diseases. Front Neuroanat. 2014;8:114.
44. Ling EA, Wong WC. The origin and nature of ramified and amoeboid microglia: a historical review and current concepts. Glia. 1993;7:9–18.
45. van Rossum D, Hanisch UK. Microglia. Metab Brain Dis. 2004;19:393–411.
46. Block ML, Hong JS. Microglia and inflammation-mediated neurodegeneration: multiple triggers with a common mechanism. Prog Neurobiol. 2005;76:77–98.
47. Schetters STT, Gomez-Nicola D, Garcia-Vallejo JJ, et al. Neuroinflammation: microglia and T cells ready to tango. Front Immunol. 2018;8:1905.
48. Barres BA. The mystery and magic of glia: a perspective on their roles in health and disease. Neuron. 2008;60:430–40.
49. Rivest S. Regulation of innate immune responses in the brain. Nat Rev Immunol. 2009;9:429–39.
50. Biber K, Owens T, Boddeke E. What is microglia neurotoxicity (not)? Glia. 2014;62:841–54.
51. Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science. 2005;308:1314–8.
52. Bsibsi M, Ravid R, Gveric D, et al. Broad expression of Toll-like receptors in the human central nervous system. J Neuropathol Exp Neurol. 2002;61:1013–21.
53. De Simone R, Giampaolo A, Giometto B, et al. The costimulatory molecule B7 is expressed on human microglia in culture and in multiple sclerosis acute lesions. J Neuropathol Exp Neurol. 1995;54:175–87.
54. Kreutzberg GW. Microglia: a sensor for pathological events in the CNS. Trends Neurosci. 1996;19:312–8.
55. Wu Y, Dissing-Olesen L, MacVicar BA, et al. Microglia: dynamic mediators and synapse development and plasticity. Trends Immunol. 2015;36(10):605–13.
56. Wang J, Tsirka SE. Contribution of extracellular proteolysis and microglia to intracerebral hemorrhage. Neurocrit Care. 2005;3:77–85.
57. Deczkowska A, Keren-Shaul H, Weiner A, et al. Disease-associated microglia: a universal immune sensor of neurodegeneration. Cell. 2018;173(5):1073–81.
58. Liddelow SA, Guttenplan KA, Clarke LE, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature. 2017;541(7638):481–7.
59. Khakh BS, Sofroniew MV. Diversity of astrocyte functions and phenotypes in neural circuits. Nat Neurosci. 2015;18(7):942–52.
60. Snyder JM. Nervous system. In: Comparative anatomy and histology: a mouse, rat, and human atlas. 2nd ed. Seattle: Elsevier; 2018.
61. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. Acta Neuropathol. 2010;119:7–35.
62. Jha MK, Morrison BM. Glia-neuron energy metabolism in health and diseases: new insights into the role of nervous system metabolic transporters. Exp Neurol. 2018;309:23–31.
63. Voskuhl RR, Peterson RS, Song B, et al. Reactive astrocytes form scar-like perivasculasr barriers to leukocytes during adaptive immune inflammation of the CNS. J Neurosci. 2009;37:11511–22.
64. Bradl M, Lassmann H. Oligodendrocytes: biology and pathology. Acta Neuropathol. 2010;119:37–53.
65. Rosko L, Smith VN, Yamazaki R, et al. Oligodendrocyte bioenergetics in health and disease. Neuroscientist. 2018; https://doi.org/10.1177/1073858418793077.
66. McTigue DM, Tripathi RB. The life, death, and replacement of oligodendrocytes in the adult CNS. J Neurochem. 2008;107:1–19.

67. Jurewicz A, Matysiak M, Tybor K, et al. Tumour necrosis factor-induced death of adult human oligodendrocytes is mediated by apoptosis inducing factor. Brain. 2005;128:2675–88.
68. Shatz CJ. MHC class I: an unexpected role in neuronal plasticity. Neuron. 2009;64:40–5.
69. Clarkson BDS, Patel MS, LaFrance-Corey RG, et al. Retrograde toll like re-gamma signaling induces major histocompatibility class I expression in human-induced pluripotent stem cell-derived neurons. Ann Clin Transl Neurol. 2018;5(2):172–85.
70. Vagaska B, New SEP, Alvarez-Gonzalez C, et al. MHC-class-II are expressed in a subpopulation of human neural stem cells in vitro in an IFNγ-independent fashion and during development. Sci Rep. 2016;6:24251.
71. Krueger M, Bechmann I. CNS pericytes: concepts, misconceptions, and a way out. Glia. 2010;58:1–10.
72. Yamazaki T, Mukouyama YS. Tissue specific origin, development, and pathological perspectives of pericytes. Front Cardiovasc Med. 2018;5:78.
73. Abbott NJ, Patagbendige AAK, Dolman DEM, et al. Structure and function of the blood-brain-barrier. Neurobiol Dis. 2010;37:13–25.
74. Andries L, Van Hove I, Moons L, et al. Matrix metalloproteinases during axonal regeneration, a multifactorial role from start to finish. Mol Neurobiol. 2017;54:2114–25.
75. Brkic M, Balusu S, Libert C, et al. Friends of foes: matrix metalloproteinases and their multifaceted roles in neurodegenerative diseases. Mediat Inflamm. 2015;2015:620581.
76. Fukata M, Vamadevan AS, Abreu MT. Toll-like receptors (TLRs) and Nod-like receptors (NLRs) in inflammatory disorders. Semin Immunol. 2009;21:242–53.
77. Van Noort JM, Bsibsi M. Toll-like receptors in the CNS: implications for neurodegeneration and repair. Prog Brain Res. 2009;175:139–48.
78. Chesnokova V, Melmed S. Minireview: neuro-immuno-endocrine modulation of the hypothalamic-pituitary-adrenal (HPA) axis by gp130 signaling molecules. Endocrinology. 2002;14:1571–4.
79. Tracey KJ. Reflex control of immunity. Nat Rev Immunol. 2009;9:418–28.
80. Pavlov VA, et al. Brain acetylcholinesterase activity controls systemic cytokine levels through the cholinergic anti-inflammatory pathway. Brain Behav Immun. 2009;23:41–5.
81. Goddard CA, Butts DA, Shatz CJ. Regulation of CNS synapses by neuronal MHC class I. Proc Natl Acad Sci U S A. 2007;104:6828–33.
82. Morale C, Brouwer J, Testa N, et al. Stress, glucocorticoids and the susceptibility to develop autoimmune disorders of the central nervous system. Neurol Sci. 2001;2:159–62.

Principles of Immunotherapy

2

Jennifer Joscelyn, Javier Ochoa-Repáraz, and Lloyd Kasper

Introduction

Immunotherapeutic intervention varies from immunomodulation, which adjusts the immune system back toward a state of homeostasis, to immunosuppression, which ablates specific compartments or pathways involved in the pathologic process. These approaches carry both benefit and risk. This chapter will discuss current and future principles of immunotherapeutic approaches.

Autoimmunity

Autoimmune disease results from failure of tolerance, the ability to discriminate between self and nonself. The immune system may then attack the individual's own cells and tissues. An inflammatory state may arise due to excessive activation of effector cells (resulting in a pro-inflammatory state) or insufficient regulatory cells leading to a loss of immune tolerance [1]. Several mechanisms work together to prevent autoimmunity. These mechanisms include central and peripheral tolerance, including T cell depletion, clonal anergy, and immune suppression provided by an important subpopulation of T regulatory (Treg) cells. These cells may carry either a CD4+ or CD8+ phenotype and include CD25+FoxP3+Tregs. Immunologic tolerance is controlled by this population of T cells [2]. Restoration of tolerance may be critical to the effective resolution of autoimmune disease processes (Fig. 2.1).

In addition to the loss of immune homeostatic balance in those with autoimmune conditions, genetic predisposition provides a further complex association. Multiple gene loci, most importantly the MHC/HLA haplotypes, are fundamental for the presentation of peptide antigens to T cells. Environmental variables such as geography, exposure, commensal microbiota, and infection also play a key role. Infections may activate self-reactive lymphocytes and lead to the development of autoimmune diseases in predisposed individuals.

Many autoimmune diseases follow a relapsing-remitting course, with periods of exacerbation followed by stability. This may relate to infection-triggered immune changes. The initiating response amplifies rapidly via activation of the

J. Joscelyn
Thought Leader Liaison, Hooksett, NH, USA
e-mail: j.joscelyn@comcast.net

J. Ochoa-Repáraz (✉)
Eastern Washington University, Cheney, WA, USA
e-mail: jochoareparaz@ewu.edu

L. Kasper
Department of Microbiology/Immunology, Dartmouth College, Hanover, NH, USA

Symbiotix Biotherapies, Boston, MA, USA

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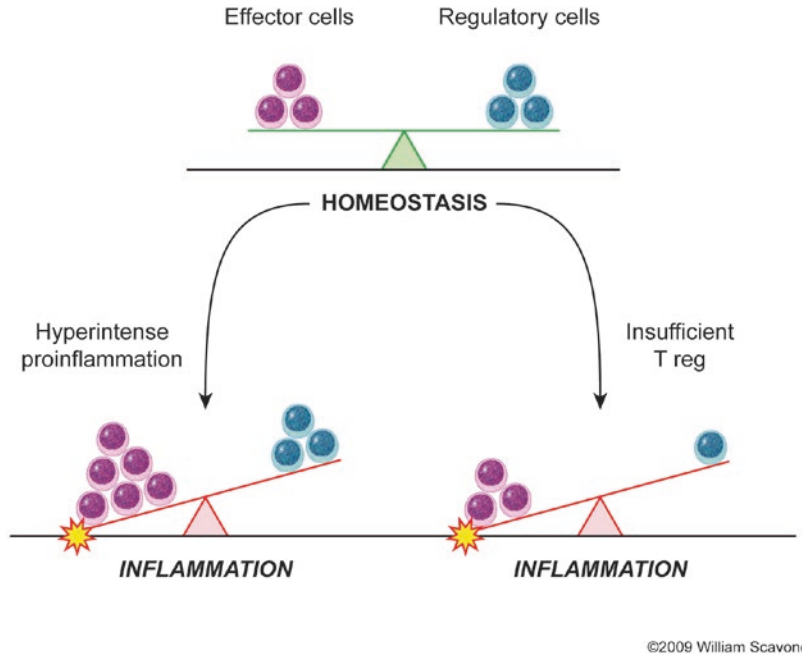

Fig. 2.1 Homeostatic balance of immune system. (Reprinted with permission from William Scavone)

innate immune system but is soon followed by a more target-specific response via the adaptive immune system. This includes antigen-specific T cells and antibody-producing B cells. Cytotoxic T cells and antibodies lead to efficient destruction of the invading microbe by eliciting specific inflammatory molecules, such as the interleukins that further activate the immune system and destroy the target in a variety of ways (including direct cell to target contact and oxidative molecules such as nitric oxide). Once the invading organism is eliminated the reduction in the immune response is rapid, limiting the damage to host tissue. Memory cells persist and provide the basis for secondary antigen-specific response. In autoimmune disorders, the tissue damage and immunological response does not completely subside, although clinical remissions are commonplace [3].

Clinical autoimmunity arises as a result of an altered balance between autoreactive effector cells and regulatory [1, 4]. The goal of treating autoimmune disease is to re-establish immune homeostasis and restore the balance between effector and regulatory T lymphocytes. Current immunotherapies are primarily used to intervene early and reduce epitope spread, induce and support the "quiescent" stage, and prevent future exacerbations.

The immune system may often seem overwhelming and too complex for the non-immunologist to fully understand, but there are recognized patterns to make organizing the information and concepts easier. The immune system is always trying to maintain balance, so for each action, there is an equal and opposite reaction. Cell lineage and generative lymphoid organs form a second pattern (Fig. 2.2).

T Cells

In T cell-mediated autoimmunity one of the most important players is the CD4+ T cell. Emerging from the thymus, naïve CD4+ cells differentiate into subtypes based on the cytokines they encounter in the periphery and/or within the CNS. Each CD4+ T cell subtype exhibits unique functions largely based on the cytokines they produce [5]. CD4+ T cells are both effector and regulatory. Effector CD4+ T cells can be categorized as either Th1 or Th2 T cells by their cytokine production. The signature cytokine for Th1 cells is interferon (IFN)-γ and for Th2 cells is IL-4 (Fig. 2.3). Upon encounter with antigen/MHC complexes, naive T cells become activated

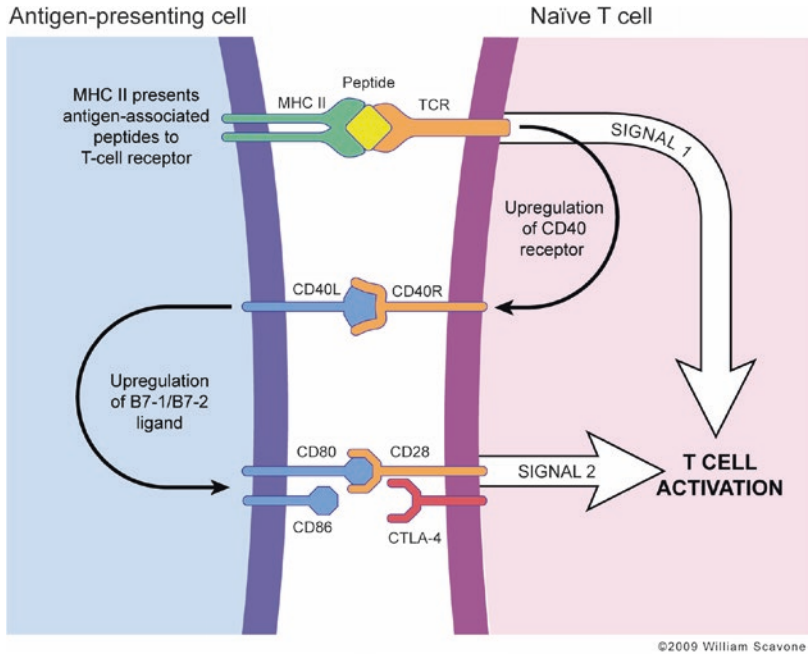

Fig. 2.2 Adaptive immune activation. Co-stimulation and T cell activation: full activation of T cells in the periphery is dependent on the recognition of co-stimulation factors on antigen-presenting cells (APCs) and completion of the two-signal activation. The first signal is comprised of antigen recognition: the APC presents MHC-associated antigenic peptides to the T cell receptor (TCR) on the naive T cell. Chemokines are released from the APC that react with the G-protein-coupled receptor (GPCR) on the T cell, increasing the affinity and avidity of the T cell/APC adhesion. Once the first signal is complete another set of molecules participate in increasing co-stimulatory signaling and secreting polarizing cytokines; for example, CD40 receptor is upregulated on the APC and engages with the constitutively expressed CD40 ligand on the T cell. The second signal is comprised of an upregulation of B7-1/B7-2 (CD80/CD86) ligand on the APC, following antigen recognition, that binds to the CD28 receptor on the T cell. Once the second signal is complete, the T cell is activated leading to clonal expansion and differentiation into effector functions. It is important to note that without the completion of the second signal the T cells become functionally inactive, anergic. (Reprinted with permission from William Scavone)

and can polarize into either a Th1 or Th2 cell. The process is influenced by a variety of factors, the most important of which is the cytokine milieu. The principal cytokines produced by antigen-presenting cells (APCs) for influencing Th1 cell polarization is IL-12, and for the TH2 it is IL-4 (Fig. 2.3). Once polarized, on the single-cell level the CD4+ Th1 and Th2 cells are committed and cannot revert back to a naive phenotype or convert to the other lineage. Using the early definition of T cell functions, IFN-γ facilitates macrophage activation and IL-4 facilitates the production of certain immunoglobulin subtypes. However, the lines between Th1 and Th2 functions have become blurred. IFN-γ is also required for the production of certain immunoglobulin (Ig) subtypes, and IL-4 can also be involved in macrophage activation [5]. The Igs induced by IL-4 serve specific functions, separating the activity of the two T cells. IL-4 is required for the production of IgG1 and IgE. IgE sensitizes mast cells, a consequence of which can be allergic reactions; IgG1 is involved in opsonization of pathogens. The IFN-γ-induced or classically activated macrophages produce nitric oxide (NO), which is pro-inflammatory and drives chronic inflammation and tissue injury. Other cytokines produced by Th2 cells that influence the immune response include IL-5, IL-6, and IL-13 (Fig. 2.3). Th1 T cells also produce IL-2, IL-15, granulocyte macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF)-α, and other cytokines (Fig. 2.3). Like CD8+ T cells, Th1 cells also have the capac-

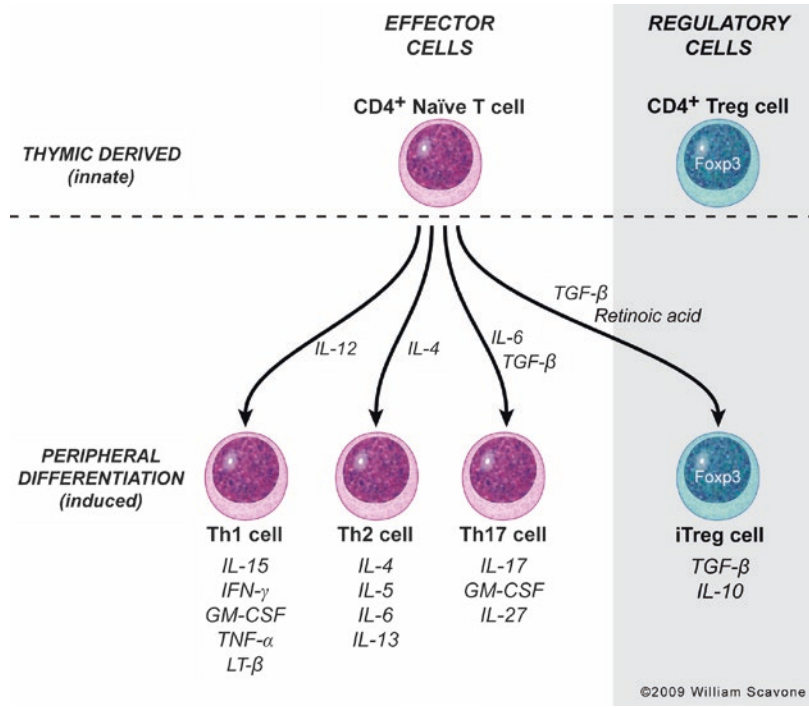

Fig. 2.3 Naive CD4+ lineage. Naive CD4+ cells emerge from the thymus and further differentiate into subtypes based on the cytokine microenvironment. Each subtype of CD4 T cells exhibits unique functions largely based on the cytokines that they produce. Treg cells are both thymic derived and induced in the periphery (iTreg). (Reprinted with permission from William Scavone)

ity to induce cytotoxicity of target cells by several different mechanisms. The immune response can be shaped by controlling the phenotype of the responding CD4 T cell [5].

Treg cells are essential in the everyday control of immune responses and maintaining peripheral tolerance [6, 7]. Two populations of T_{regs} control inflammation: natural (constitutive) Treg cells and induced Treg cells (iT_{reg}) (Fig. 2.3). Natural T_{reg} cells are a population of CD4+ lymphocytes residing in the thymus that express the interleukin (IL)-2 receptor CD25 and the transcription repression factor FoxP3. These cells constitute 5–12% of the entire CD4+ cell population and represent a very small proportion of the circulating WBC population. Specific populations of natural T_{reg} cells are generated principally by interaction with immature APCs in the periphery. They recognize major histocompatibility complex (MHC) molecules in association with autoantigens with high specificity. These natural T_{reg} cells are normally anergic but can be activated by exposure to antigens or to high concentrations of IL-2 released from activated TH1 cells. Induced T_{reg} cells are derived from either naïve CD8+ or CD4+ precursor cells in the thymus in response to the local antigen or cytokine environment. Three subpopulations of iT_{reg} cells can be distinguished on the basis of surface markers: CD8+ T_{reg} cells, TH3 cells, and TR1 cells. The latter two are derived from CD4+ precursors. In autoimmune disease, autoantigens can stimulate the differentiation of these iT_{reg} cells. iT_{reg} cells release cytokines such as IL-10 and TGF-β (Fig. 2.3) that suppress the activity of effector T cells as well as of APCs. Effector cells and APCs may be inhibited by direct contact with natural and induced T_{reg} cells and involve interactions of cell surface proteins. This helps prevent the development of hypersensitivity reactions of allergies, autoimmune disease, and promotes long-term graft tolerance. On the other hand, there may also be detrimental effects of inhibition of immune function by T_{reg} cells; it attenuates immunity to pathogens and reduces both immunological surveillance and prevention of tumorigenesis.

The best-studied T_{reg} cell to date is the Foxp3+ CD4+ T cell, a key regulatory molecule in the development and function of T_{reg} cells. FoxP3 is a