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Neuro-Immune nteractions in the Adult Central Nervous System

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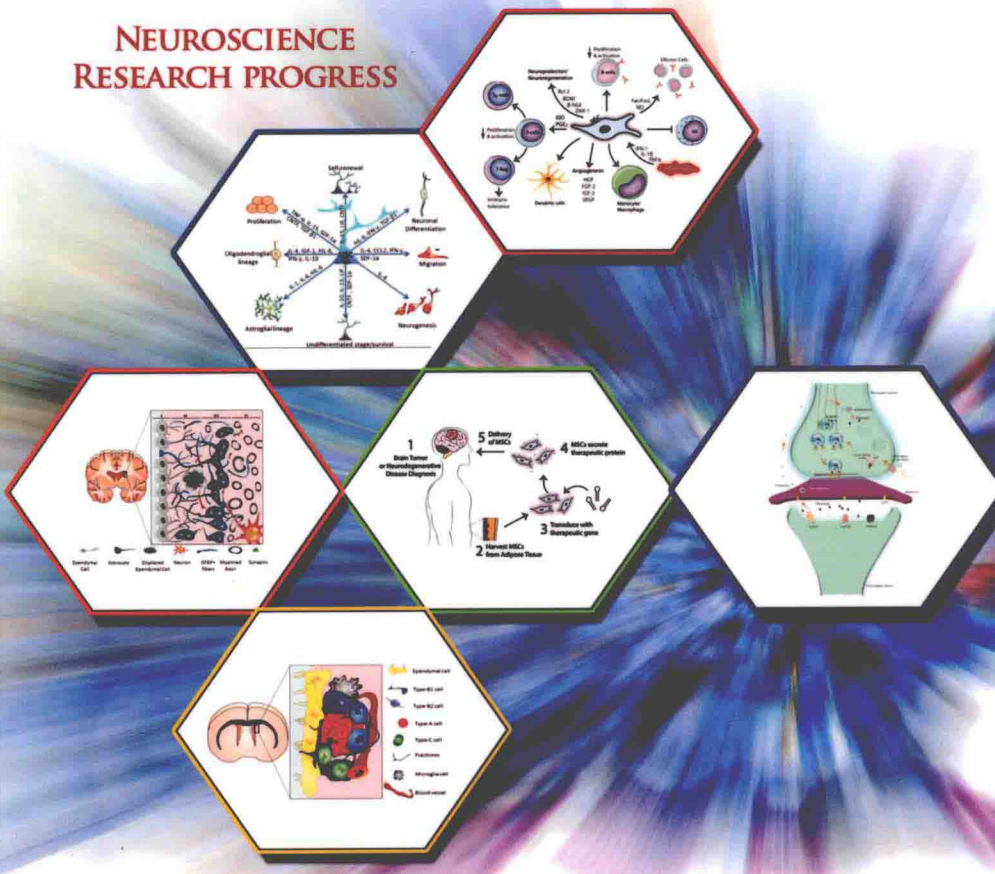

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NEURO-IMMUNE INTERACTIONS IN THE ADULT CENTRAL NERVOUS SYSTEM

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Dedicated to

My three adored and inspiring distractions: Elizabeth, Oscar Jr. and Daniel who were not help in the writing of this book

In memory of my beloved father

In honor of my loving mother

PREFACE

Increasing evidence indicates that inflammatory cells and immunological cytokines can enter into the brain and modulate a number of biological and cognitive functions. Under physiological conditions, only a few immune cells, such as: macrophages, lymphocytes and dendritic cells can cross the blood-brain barrier and gain access to neural tissue. For many years, these findings supported the notion that the brain was an immunologically privileged organ. To date, increasing evidence strongly challenges this conjecture. In fact, neuroinflammation triggers a significant infiltration of immune cells into the cerebral parenchyma. The infiltration of inflammatory cells is accompanied by the release of a number of cytokines that target neurons, astrocytes and microglia. This interaction between the immune system and the central nervous system modulates many cerebral functions, such as: neural remodeling, synaptic plasticity, neurotransmitter releasing, stress-associated response, cognitive and mental disease progression, and others.

The book *Neuro-Immune interactions in the adult central nervous system* summarizes the latest discoveries, from basic to clinical science, regarding the interactions between the immunological mediators and the neural tissue under physiological and pathological conditions. In this book, it is discussed the influence of immune cells and cytokines in neural-regulated systems. Herein, the readers can find comprehensive descriptions in diverse fields, such as: lipids and obesity, neuronal activity, neurotransmission, stress pathogenesis, rheumatologic diseases, spinal cord injuries, regulation of neural stem cells, neural control of reproduction, and others. To ensure that most of readers obtain clear and complete information, all chapters have been written by prominent experts in their respective fields. The authors have made their best effort to present all these information in an easy-to-understand language,

which will benefit to a wide variety of readers, from undergraduate students to postdoctoral fellows or scientific colleagues from many disciplines.

On behalf of the authors and my-self, I hope that readers find in this book a very useful compendium for their academic and research activities. I want to expresses his gratitude to the staff of *Nova Science Publishers* involved in this book production. I am particularly grateful to my dear mentors: Arturo Alvarez-Buylla at the *University of California at San Francisco*, Jose M Garcia-Verdugo at the *University of Valencia* and Dr. César Ramos-Remus at the *Instituto Mexicano del Seguro Social*, as outstanding sources of insights, personal support and academic guidance. Finally, I would like to express a great appreciation and gratitude to all my colleagues over the years. They are too many to list here, but I want them to know my gratitude. Recent collaborators include Rocio E. Gonzalez-Castañeda, Sonia Luquin, Alfredo Quiñones-Hinojosa, Alma Y. Galvez, Norma Moy, Jorge Guzman and Jorge Collas. Present students include Fernando Gutierrez-Fernandez, Veronica Lopez-Virgen, Tania Campos-Ordoñez, Jimena Rocha, Fabian Adirsch, David Zarate, Salvador Magallon, Maria F. Pinto and many others. I thank you for your hard work, personal support, scientific contributions, and invaluable friendship.

CONTENTS

In: Neuro-Immune Interactions ...
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Chapter 1

INFLUENTIAL EFFECTS OF NEURONAL REGULATION OF IMMUNE CELLS ON BRAIN DISEASES

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ABSTRACT

A homeostatic maintenance of neuroimmune interaction during development and adulthood is critical to prevent the onset or progression of psychiatric diseases. Within the CNS, while studies on glial cells, especially microglia, have highlighted the importance of this cell type in innate immune responses of the CNS, the immune regulatory functions of other cell types, especially neurons are largely unknown. How the neuroimmune crosstalk is homeostatically maintained in neurodevelopment and adult plasticity is even more elusive. Inspiringly, accumulating evidences suggest that neurons may also actively participate in immune responses by controlling glial cells and infiltrated immune cells.

The aim of this review is to address the immune function of both glial cells and neurons, and the roles they play in regulating inflammatory processes and maintaining homeostasis of the CNS. The potential clinical application of this knowledge warrants a deeper understanding of the mutual interactions between neurons and other types of cells during

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neurological and immunological processes within the CNS, which will help for the progress on diagnosis, prevention and intervention of various neurological diseases. I will especially emphasize and provide relevant evidences on how neurons mechanistically control the activation of microglia and infiltrated immune cells.

Keywords: Microglia, neuron, immune genes, neuroinflammation, neurological diseases

ABBREVIATIONS

A-β	amyloid β
AD	Alzheimer's disease
APC	antigen presenting cell
ATP	adenosine tri-phosphate
BDNF	brain-derived neurotrophic factor
CD	cluster of differentiation;
CR	complement receptor
CNS	central nervous system
EAE	experimental autoimmune encephalomyelitis
FasL	Fas ligand
GABA	γ-amino butyric acid
ICAM	intercellular adhesion molecule
IFN	interferon
IL	interleukin
LFA-1	leukocyte function-associated antigen-1
IgSF	immunoglobulin superfamily
LPS	lipopolysaccharide
MHC	major histocompatibility complex
MS	multiple sclerosis
NGF	nerve growth factor
NO	nitric oxide
PRR	pattern recognition receptors
SIRP	α signal regulatory protein-α
TGF-β	transforming growth factor-β;
Th	T helper
TNF	tumor necrosis factor
Treg	regulatory T cells

TREM	triggering receptor expressed on myeloid cells
VIP	vasoactive intestinal peptide

INTRODUCTION

Our understanding on the reciprocal relationship between the nervous and immune systems has developed rapidly within the past decade. Inflammatory response has been associated with pathological processes in a wide range of brain disorders, including not only the conventional inflammatory conditions in autoimmune diseases, traumatic brain injuries, stroke and neurodegenerative diseases [1, 2], but more importantly also neurodevelopmental defects in schizophrenia, epilepsy and autism [3-5]. However, immune responses are specialized within the brain and differ considerably from those in the periphery. Such differences endow the central nervous system (CNS) with an immune-privileged status, and provide challenges for therapeutic interventions to various CNS diseases [6-8]. Hence, a thorough insight into the immunological processes within the CNS and their involvement in neurodevelopment and neuropathology is pivotal for current researchers. This chapter aims at providing readers the updated knowledge of the immune regulatory functions of the CNS residential cells: glia and neurons (Table 1). Since immune functions of glia are much better known than those of neurons [4, 5, 9], we will emphasize more on the latter ones in this review.

ROLE OF MICROGLIA AS INNATE IMMUNE MODULATOR IN THE BRAIN DEVELOPMENT

Although the CNS is relatively secluded from the peripheral immune system, it has its own residential immune network, in which glial cells (mainly microglia and astrocytes) not only serve supportive and nutritive roles for neurons, but also defend the CNS from stress and pathogenic insults by transiently up-regulating inflammatory processes [9]. These processes are usually kept in check by other endogenous anti-inflammatory and neuroprotective responses that return the CNS back into homeostasis. However, excessive or prolonged glial activation results in a more severe and chronic neuronal damage that eventually propagates neuroinflammation and

neurodegeneration, suggesting the delicacy of tipping the balance between neuroprotection and neurotoxicity [10].

Microglia comprises 5-20% of all glial cells in various brain regions. As commonly known, they are the major phagocytic cells that provide the first line of defense for the CNS [11].

Table 1. Pro- and anti-inflammatory molecules expressed by glia and neurons

Properties	Promotion of inflammation	Inhibition of inflammation
Microglia		
Soluble factors	TNF, IFN-γ, IL-1β; [15, 16, 18, 94] CXCL1,2,12, CCL2,5,10,19; [41] Glutamate; NO, ATP; [15, 16, 18, 94]MMPs; [95] Complements; [16, 20] HMGB1, heat-shock proteins [90-93]	IL-4, IL-10, IFN-β, TGF-β;[15, 16, 18, 94]BDNF, GDNF;[41]TIMPs[95]
Membrane proteins	TLRs, RAGE, LFA-1, MAC-1, CRs, FcRβ; [15, 16, 18, 90–94, 96]	CD45, CD91, CD200R, CD172a, [16, 68] CX3CR1, [46] TREM-2, [73]FasL, Fas [86, 87]
Astrocytes		
Soluble factors	TNF, IFN-γ, IL-1β; [10, 27, 30] CXCL1,2,12, CCL2,5,10,19; [27, 41] Glutamate; NO, ATP; MMPs; [10, 27, 30] Complements; [16, 20, 27] HMGB1, heat-shock proteins [90-93]	IL-4, IL-10, IFN-β, TGF-β;[10, 27, 30]Complement inhibitors; [27] BDNF, GDNF; [41, 52, 53]TIMPs [95]
Membrane proteins	TLRs, RAGE, ICAM-1, CRs [91, 92, 96]	FasL[85, 86]
Neurons		
Soluble factors	CXCL10, CCL21; [8, 39, 41] Glutamate, dopamine; [39] NO, ATP; Substance P; [39] MMPs; [95]HMGB1, heat-shock proteins [90-93]	TGF-β;[43, 44] CX3CL1;[45, 46] GABA;[57, 58] VIP; [42, 55] NE,[60, 61]Proteoglycans; [97, 98] NGF, BDNF, NT3, GDNF, CNTF[41, 52, 53]
Membrane proteins	TLRs[96]	CD22,[65] CD47,[66, 67] CD200,[68] ICAM-5,[78, 79] FasL[85, 86]

It was long thought that microglia differentiate from peripheral macrophages that enter the brain shortly after birth. But a recent mouse study found that the majority of resident microglia derive from yolk sac

macrophages formed during primitive hematopoiesis at very early embryonic stage (E7.5) [12]. These primitive macrophages migrate to the developing nervous system and reside throughout life. Local progenitors replenish the microglial population and proliferate in response to stimuli during adulthood. In contrast, other CNS macrophages, found in the perivascular space, meninges, and choroid plexus, derive from infiltrated blood monocytes and are replenished by hematopoietic stem cells in bone marrow. The embryonic engagement of microglial ontogenesis provides a timely basis for them to interact with neurons and affect neurogenesis and differentiation during development [11, 13].

Microglia acquires a ramified but nevertheless active morphology normally, with minimal expression of myeloid-monocytic markers such as Fc receptors-cluster of differentiation (CD) 32 and CD64, complement receptors (CR)-3 and -4, (also named as CD11b and CD11c integrins, respectively), major histocompatibility complex (MHC) class I and II and CD45 [14]. But once challenged by inflammation, it becomes rapidly amoeboid and up-regulates a variety of cell surface receptors involved in innate immune responses. These receptors include pattern recognition receptors, such as toll-like receptors and receptor for advanced glycation end products, and phagocytic receptors, such as CR-3, -4 and triggering receptor expressed on myeloid cells (TREM) [15, 16].

In respect to neuroimmune crosstalk, microglia plays the most direct, and perhaps also the most important, role in sensing and modulating neuronal activities. Phagocytosis is an important mechanism for microglia to control neuronal apoptosis. When apoptosis of neurons occurs, for example, at the early developmental stage, or due to neurodegeneration, clearance of apoptotic cell debris in time through phagocytosis is vital for the reminiscent neurons to avoid collateral inflammation-induced damage [17, 18]. Apoptotic cells express cell surface molecular patterns that act as "eat me" signals. These signals are recognized by microglial PRRs, which rapidly initiate clearing processes [16]. On the other hand, insufficient phagocytic clearance of cell debris following neuronal injury is an important pathogenic factor in propagation of neurodegeneration, as illustrated by numerous studies on Alzheimer's disease (AD) [18].

Besides controlling neuronal apoptosis, microglia secrete a wide variety of cytokines, complements and growth factors that have been implicated in regulating synaptic formation and plasticity [17]. With the help of the complement system, unwanted synapses are efficiently removed by phagocytosis under both developmental and pathological conditions [19].

Mice deficient in complement C1q or C3 exhibited sustained defects in elimination of the CNS synapses [20]. More importantly, the orthodox view that microglial activity is only relevant for the pathological processes of neuronal pruning has been overturned by the recent evidences showing that they are highly sensitive for the neighboring neuronal activities and control dendritic spine density under physiological conditions [21, 22]. Furthermore, a recent elegant work by Derecki et al. demonstrated that microglia from bone marrow of wild type mice attenuated Rett syndrome, an X-linked autism spectrum disorder [23]. Undoubtedly, emerging evidences with the help of modern imaging and analytical technologies will shed light into the physiological functions of microglia in the coming years.

Another important function of microglia is the presentation of foreign antigens to T lymphocytes. In the normal CNS, antigen presenting cells (APC) are mainly confined to dendritic cells and macrophages located in the meninges, choroid plexuses and perivascular spaces [24]. MHC class I and II molecules are expressed at low levels by microglia, as they are actively down-regulated by the immune-quiescent microenvironment of the CNS. However, upon activation, these molecules are up-regulated together with the costimulatory receptors CD40, CD80 (B7-1), CD86 (B7-2) and leukocyte function-associated antigen-1 (LFA-1, CD11a/CD18 integrin), which subsequently induces optimal APC functions and T-cell activation [15, 24].

INNATE IMMUNE FUNCTIONS OF ASTROCYTES

Astrocytes have been traditionally viewed as supportive cells for neurons, which are responsible for the CNS homeostasis and neuronal functions [25] (Fig 1A). Their functions as innate immune cells are somehow less appreciated as compared to microglia. Nevertheless, astrocytes have been known to form the glia limitans around blood vessels, thereby restricting the entry of immune cells through the blood-brain barrier into the CNS parenchyma [26]. Emerging evidences have highlighted the importance of this cell population in the regulation of local innate and adaptive immune responses [27].

Astrocytes express a variety of PRRs involved in innate immunity, including toll-like receptors, scavenger receptors, mannose receptors and CRs [27] (Table 1 & 2). Following PRR engagement, astrocytes secrete cytokines, chemokines and neurotrophins that target neighboring glial cells and neurons [10, 27]. Released cytokines also promote the leakage of BBB, resulting in the recruitment of immune cells from the blood circulation into the CNS

parenchyma. These altogether amplify both the initial innate immune responses and the upcoming adaptive immune responses, which can result in the elimination of infectious or injurious insults and restoration of tissue integrity or scar formation [28].

Astrocytes are active players in the AD and multiple sclerosis (MS) [29, 30]. Under pathological conditions, astrocytes undergo a series of structural and functional changes collectively referred to as astrogliosis. Amyloid β-peptide (A-β) plays an important role in astrocyte stimulation [31]. Accumulation of astrocytes around the senile plaques and neurofibrillary tangles is one of the hallmarks of the AD [29]. Upon A-β stimulation, astrocytes secrete various chemokines that recruit microglia and monocyte/macrophages to the plaques with the concomitant release of neurotoxins and pro-inflammatory cytokines that contribute in concert to neurodegeneration [29]. Astrocytes are also involved in the MS disease through release of pro-inflammatory cytokines, matrix metalloproteinases and free radicals that result in recruitment of autoimmune cells, oligodendrocyte destruction and demyelination [30].

Another interesting, yet controversial, property of astrocytes is their antigen-presenting ability. In vitro studies have shown that astrocytes express low levels of MHC and costimulatory molecules upon stimulation by cytokines, and are capable of processing and presenting myelin protein epitopes to T cells, inferring that they can also be APCs [32, 33]. However, given the more efficient antigen presentation capabilities of microglia and other infiltrating APCs in the CNS, the in vivo significance of this function of astrocytes is unclear [9, 24, 30].

Despite of these controversies, the ability of astrocytes to regulate the antigen-presenting activities of other APCs and T-cell activation has been clearly established. The fact that the expression levels of MHC and costimulatory molecules are low even after stimulation in vitro suggests that astrocytes may be prone to induce T helper (Th) 2 rather than Th1 responses. Indeed, earlier studies showed that while microglial cells seem to be efficient in activating both Th1 and Th2 cells, astrocytes stimulate only Th2 cells [34]. Microglia and astrocytes also produce chemokines that differentially affect the recruitment of Th1 and Th2 cells [35].

Additionally, astrocytes have been shown to induce anergy of Th cells via cytotoxic T-lymphocyte antigen 4 (CTLA-4, CD152) [36] or promote recruitment and proliferation of regulatory T cells (Treg) via the anti-inflammatory cytokine transforming growth factor β (TGF-β) [37] and chemokine CXCL12 (stromal cell-derived factor-1) [38]. Astrocytes can also