Interaction Between Neurons and Glia in Aging and Disease
Interaction Between Neurons and Glia in Aging and Disease

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Preface

João O. Malva, Ana C. Rego, Rodrigo A. Cunha, and Catarina R. Oliveira

Recent years witness the amazing and enthusiastic growth of research activity dedicated to understand the complex mechanisms of interaction between neurons and glia in brain physiology and the involvement of these processes in brain dysfunction and pathology. Neuroscientists and neuroimmunologists face the major challenge of bringing to light new knowledge about the functional interplay of brain cellular partners. There is now a better understanding of the basic physiopathological processes of many diseases of the nervous system, including the role of inflammation and immune mechanisms. New powerful tools were shown to interfere with the “recital” of cytokines, chemokines and inflammatory molecules and their dynamic effects on neurons, glia, vascular cells and cells of the immune system that invade the brain parenchyma in response to injury. The ultimate goal of this area of research is to develop new therapeutical approaches and to find a cure for the devastating disorders of the nervous system to which inflammation and immune contributions were demonstrated to be key players.

This project was born after joining efforts from expert contributors in neuron–glial cross-talk in health and disease. We are grateful for the efforts of the contributors in this book. The aim of editors is to foster understanding on the mechanisms of brain injury and how they can be modulated to overcome irreversible damage resulting in a better quality of life. There is still much work to be done, but there are reasons to be optimistic.

We hope you will find this book interesting and informative.

Welcome to “Interaction Between Neurons and Glia in Aging and Disease”

The Editors

University of Coimbra, December 1, 2006
Special thanks to
All colleagues contributing to the present book.

The colleagues working at “Neuroprotection and Neurogenesis in Brain Repair”,
“Mitochondrial dysfunction” and “Purines at CNC” groups.

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Bruno Manadas for his enthusiastic collaboration with figures and animations in the accompanying DVD.
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Evidence exists showing a clear interaction between neurons, glia, and cells of the immune system, which is highly dynamic and highly regulated, playing a key role in brain homeostasis. There is increasing support for the contribution of the disruption of this interaction to the inflammatory (neuroinflammatory) and immune (neuroimmunity) responses associated to many diseases of the nervous system. In the present section, the major molecular and cellular players in neuroinflammation are introduced and their role in neuronal death/protection and brain repair is discussed.

In Chap. 1, Bernardino and Malva introduce neuroimmunity and neuroinflammation in health and disease, highlighting the close interaction between the innate immune response and excitotoxicity. The key proinflammatory cytokines, chemokines, receptors, and mechanisms involved in IL-1β and TNF-α receptors-mediated signaling transduction are reviewed. The central role of microglia activation in the innate immune response of the brain and its impact in neuronal death/survival is discussed. The authors introduce in this chapter many of the recurrent concepts used in other sections/chapters of the book.

In Chap. 2, by Bente Finsen’s group (Wirenfeldt et al.,) the authors revise and discuss the developmental origin and diversity of microglial cells and their response to injury. The highly dynamic plasticity of microglial populations in response to injury is explored and deeply discussed. The readers are invited to understand microglial diversity as a natural resource of brain development and defence against aggression.

Chapter 3 by Cunha, Chen, and Sitkovsky discuss the role of ATP in brain and peripheral response to injury. The shortcut between protection and toxicity and the ambiguous role of adenosine and adenosine receptors is dissected. Clearly, the next years will contribute to recognize the purinergic system as one of the key mediators/modulators of the inflammatory response in periphery and in the central nervous system.

Agasse, Bernardino, and Malva (Chap. 4) discuss the potential of subventricular zone cells as a resource for brain repair. Detailed information about subventricular zone niche of stem/progenitor cells, factors contributing to migration, differentiation, and survival of new neurons is provided. A special attention was given on the impact of brain injury and inflammatory mediators in the migration, differentiation, and survival of subventricular zone cells as endogenous/grafted resources for brain repair. The potential use (at the long-term) of adult brain stem/progenitor cells in the repair of injured central nervous system tissue is envisioned and discussed. Clearly, the stem/progenitor cells research is endowed with...
enormous potential for the future therapy of the major diseases affecting the central nervous system. The future years will assist to the enthusiastic expansion in stem/progenitor cell research and hopefully to the outcome of new strategies for brain repair.

In Sect. 2, “Signaling and Inflammation in Aging,” and Sect. 3, “Neurodegeneration and Inflammation in Age-Related Diseases,” the concepts introduced in Sect. 1 will be used in the context of inflammatory reactions and signaling transduction in aging and disease.
INFLAMMATION AND NEURONAL SUSCEPTIBILITY TO EXCITOTOXIC CELL DEATH

Liliana Bernardino and João O. Malva

1. ABSTRACT

The fast growing research field of Neuroinflammation is challenging the traditional view of the Brain as an immune privileged organ. Our increasing understanding of the mechanisms involved in the close functional interaction between neurons and glia in health and disease is contributing to shed new light into the cellular and molecular mechanisms of neurodegeneration. The response of microglia and astrocytes to injury, releasing signaling molecules (specially, cytokines, chemokines, growth factors, reactive oxygen and nitrogen species), is central in neuroinflammation and in neuron death/survival.

At long-term, our better knowledge of the functional crosstalk between neurons and glia in health and disease and the bidirectional flux of immune cells from the peripheral blood to the brain parenchyma through the blood–brain barrier will allow the build-up of new tools for the treatment of the major diseases afflicting the human brain. In this chapter we review and discuss the immune response of the brain to injury, on the basis of the close interaction between excitotoxicity and inflammation.

2. INFLAMMATION IN THE CENTRAL NERVOUS SYSTEM

Until recently, the brain was considered as an immune privileged organ mostly because it was assumed that blood–brain barrier (BBB) should be completely impermeable to entrance of immune system cells into the brain parenchyma. In this way, the central nervous system (CNS) was considered unable to respond with an immune reaction when challenged by neurodegeneration or by infection. However, in the last decade the immune privileged status of the brain was questioned mostly because in pathological conditions molecules and cells of the immune system enter the brain via the BBB and target the brain parenchyma (Huber et al., 2001; Nguyen et al., 2002). Yet, inflammatory response in the CNS shows some peculiarities when compared with inflammation in other organs. This is most evident in response to acute insults because lymphocyte recruitment is rapid and pronounced in many systemic organs, but modest and delayed in the CNS. Accordingly, the number of patrolling lymphocytes in
the healthy CNS is also lower when compared with other tissues. Moreover, in normal resting conditions, the resident immune effector cells in the brain, the microglia cells (Perry and Gordon, 1991), show a resting phenotype, with a low or absent expression of immunological molecules and their receptors (Neumann and Wekerle, 1998; Neumann, 2001, 2004). Although, besides these peculiarities, following an injury, the brain may initiate and develop by itself a local and rapid immune response resulting in the activation (within minutes or hours after the insult) of brain microglia and the release of inflammatory mediators (Lucas et al., 2006). These reactions induce a rapid and efficient clearance of pathogens and cell debris from the damaged CNS (Schwartz et al., 1999; Becher et al., 2000; Nguyen et al., 2002; Elward and Gasque, 2003). The efficient regulation of the inflammatory cascade results from a fine-tune equilibrium of events that promotes both immune privilege in health and effective responses in injury or disease.

In general, acute inflammation is beneficial to the organism in limiting the survival and proliferation of invading pathogens and promoting regeneration of the tissue. However, prolonged, excessive inflammation is highly detrimental, leading to the onset and/or to the exacerbation of cell damage in neurodegenerative diseases.

2.1. Innate Immunity in the CNS

Among the first line of defense of the body, the innate immunity is responsible for the immediate response to insults and pathogens and plays an essential role in survival of the organism. It is characterized by the rapid and relatively generic recognition of pathogens by immune cells that either kill the invaders directly or activate phagocytic cells to ingest and remove them (Rivest, 2003). Phagocytic cells (including macrophages and microglia cells) are the principal effector cells of innate immunity response in the brain. These cells produce and release substantial amounts of pro-inflammatory cytokines, specially tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 that facilitate the recruitment and enhance the activity of other immune players, thus improving the overall immune response (Simard and Rivest, 2005).

**Pathogen-Associated Molecular Patterns (PAMPs)**

Phagocytic cells of the innate immune system express receptors that detect the presence of infectious agents (e.g. bacteria, fungi) by recognizing specific and highly conserved structures produced by these pathogens, which are not expressed by eukaryotic organisms (Anderson, 2000). These elements are called pathogen-associated molecular patterns (PAMPs) and are recognized specially by macrophages and microglial cells that put in motion a rapid response to infection (Medzhitov and Janeway, 2000). The endotoxin lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria, is one of the most characterized PAMP, able to stimulate the innate immune system phagocytic cells and to trigger a robust innate inflammatory response (Wright, 1999). These immune cells can also recognize disease-associated molecules, such as modified endogenous molecules or cell debris from damaged cells, leading to tissue remodeling and tissue repair (Devitt et al., 1998; Elward and Gasque, 2003).

**Toll-Like Receptors (TLR)**

The Toll-like receptors (TLRs) are signaling receptors present in immune cells that recognize PAMPs, and represent the first element of contact between pathogens and the host
The Toll protein was originally described as a receptor involved in dorsoventral polarization of the *Drosophila* embryo (Anderson et al., 1985; Belvin and Anderson, 1996) with a vital role in the antifungal immunity of adult flies (Lemaitre et al., 1996). The TLRs are mammalian homologues of the Toll protein, both characterized by multiple leucine-rich repeats in extracellular domains and cytoplasmic domains resembling the cytoplasmic portion of the IL-1 receptor (IL-1R), commonly known as Toll/IL-1R motif (TIR) (Wright, 1999; Anderson, 2000). The broad spectrum of ligands recognized by these receptors depends not only from the high diversity of the extracellular domains, but also from the complex pattern of recognition of the ligand by the receptor, including dimerization of some TLRs (Ozinsky et al., 2000; Rivest, 2003).

### 2.2. Adaptive Immunity in the CNS

Innate immunity is sometimes sufficient to counteract a simple infection, and in these cases the response of the host with an adaptive response is not required. However, sometimes innate immune response cannot eliminate the infectious organisms. In these conditions, following TLRs/PAMPs interaction, glial cells and neurons begin to produce inflammatory cytokines, chemokines, and adhesion molecules, which activate and stimulate the traffic of immune cells with a role in adaptive immune system, such as T and B lymphocytes, to the sites of lesion in the brain (Kielian et al., 2002; Olson and Miller, 2004, Simard and Rivest, 2005). In this sense, TLRs as well as these inflammatory mediators (cytokines and chemokines) play a pivotal role between the innate immune response and the adaptive immunity of the CNS.

One of the characteristic features of acquired immunity in the response to the pathogen is plasticity and development of memory signals. Some viruses and bacterial antigens do not stimulate T lymphocytes directly. In these cases a specific group of highly specialized immune cells, antigen presenting cells (APCs), process and expose the antigens bound to the major histocompatibility complex (MHC) molecules on their cell surface, making these antigens recognizable by specific T lymphocytes (Nguyen et al., 2002). APCs include microglia, macrophages, and dendritic cells. After an injury, T lymphocytes interact with APCs, become activated and develop immune memory. The latter process depends specifically on the recognition of the antigen peptide fragments bound to MHC and on co-stimulatory signals on the APCs, leading ultimately to the clonal selection of lymphocytes. So, after acquiring memory and clonal selection, the lymphocytes better contribute to provide more versatile mechanisms of defense specially when the host is repetitively infected by the same pathogen (Neumann, 2004). Besides T lymphocytes, B lymphocytes are also cellular players with major role in acquired immunity, responsible for the humoral defense. Despite increasing evidences showing that B lymphocytes can enter the CNS in pathological conditions, differentiate into plasma cells and secrete antibodies (Knopf et al., 1998), the ability of B lymphocytes to patrol the neural parenchyma is less understood.

Brain inflammation involves a bidirectional communication between the immune system and the CNS. As indicated before, even in the presence of intact BBB, the CNS is routinely surveyed by blood immune cells (e.g. T lymphocytes) in search for pathogens (Flügel et al., 2001). However, in normal healthy conditions, only few activated T lymphocytes can pass the BBB and most of these cells cannot find antigens and are committed to die by apoptosis (Bauer et al., 1998). Under pathological conditions, T cells accumulate and can reach relatively high density in inflammatory sites in brain parenchyma (Neumann and Wekerle, 1998; Raivich et al., 1998; Yeager et al., 2000; Flügel et al., 2001; Hickey, 2001; Engelhardt,
When a strong inflammatory reaction occurs in the body, even if the CNS is not itself directly involved, patrolling T cells can be found in the CNS. Moreover, systemic inflammation often does not induce evident CNS lesions but contributes to cerebral vulnerability and exacerbate cell damage (Perry, 2004; Cunningham et al., 2005). This crosstalk between periphery immunomodulators of blood and CNS cells occurs directly at regions lacking BBB, which include circumventricular organs (CVOs), the choroid plexus and leptomeninges. These structures are characterized by a rich vascular plexus where the junctions between capillary endothelial cells are absent or modified, allowing the diffusion of molecules such as pro-inflammatory cytokines, but also infectious agents into brain parenchyma (Nguyen et al., 2002; Schulz and Engelhardt, 2005). Another mechanism by which circulating cytokines may communicate with CNS is through direct interaction with BBB endothelial cells. These cells constitutively express receptors for several molecules of the immune system. In the presence of a challenge, the receptor’s expression is rapidly up-regulated and, following activation, can induce the release of immunomodulatory molecules across the brain parenchyma. Moreover, several factors such as the intercellular adhesion molecule 1 (ICAM-1), vascular endothelial growth factor (VEGF), IL-1β, TNF-α, IL-6 and some chemokines such as macrophage inflammatory protein-1α (MIP-1α), CCL19, CCL21 and CCL2, can induce transient alterations in the stability and permeability of the BBB and ultimately facilitate the entry of immunomodulators from the blood into the CNS (Dobrogowska et al., 1998; Mark and Miller, 1999; Huber et al., 2001; Engelhardt, 2006; Mahad et al., 2006; Man et al., 2006).

Therefore, in both models, systemic cytokines interact directly or indirectly with the CNS parenchyma and can trigger a series of events leading to the activation of transduction pathways, generating an inflammatory state in the CNS (Zhang and Rivest, 2003). Furthermore, cytokines amplify the immune response, and lead to the expression of other cytokines and chemokines, contributing to recruit other immune cells such as T and B lymphocytes to the inflammation site and by this way put in motion the onset of the adaptive immune response. So, both innate and acquired immunity are not separate entities, but they are functionally interconnected (Medzhitov and Janeway, 1997; Bailey et al., 2006).

3. MEDIATORS OF INFLAMMATION

The inflammatory response in the CNS comprises a complex and integrated interplay between different cellular types of the immune system (macrophages, T and B lymphocytes, dendritic cells) and resident cells of the CNS (microglia, astrocytes, oligodendrocytes, neurons) as well as a complex orchestra of cytokines, adhesion molecules, chemokines and their receptors. In normal resting conditions, most inflammatory mediators produced by these cells are expressed at very low, or undetectable, levels. However, they are rapidly upregulated in response to infection or tissue injury (Rothwell and Luqueshi, 2000; Chavarria and Alcocer-Varela, 2004). In this section we will focus on both the cell component of the BBB and the resident parenchymal immune cells of the CNS, and the interaction between them, in health and disease.

3.1. BBB as a Key Immune Sentinel of the Brain

Immune surveillance at the BBB is ensured by endothelial cells of the brain capillaries and by perivascular cells surrounding cerebral vessels (Thomas, 1999; Williams et al., 2001).