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REVIEW

THE ROLE OF THE IMMUNE SYSTEM IN CENTRAL NERVOUS SYSTEM PLASTICITY AFTER ACUTE INJURY

L. PERUZZOTTI-JAMETTI,[a†] M. DONEGÁ,[a†] E. GIUSTO,[a] G. MALLUCCI,[a,d] B. MARCHETTI[e,f] AND S. PLUCHINO[a,b,c*]

[a] *John van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, Cambridge CB2 0PY, UK*

[b] *NIHR Biomedical Research Centre, University of Cambridge, Cambridge CB2 0PY, UK*

[c] *Wellcome Trust-Medical Research Council Stem Cell Institute, University of Cambridge, Cambridge CB2 0PY, UK*

[d] *Department of Brain and Behavioural Sciences, National Neurological Institute C. Mondino, 27100 Pavia, Italy*

[e] *Department of Clinical and Molecular Biomedicine, Pharmacology Section, Medical School, University of Catania, 95125 Catania, Italy*

[f] *OASI Institute for Research and Care on Mental Retardation and Brain Aging, Neuropharmacology Section, 94018 Troina, Italy*

Abstract—Acute brain injuries cause rapid cell death that activates bidirectional crosstalks between the injured brain and the immune system. In the acute phase, the damaged CNS activates resident and circulating immune cells via the local and systemic release of soluble mediators. This early immune activation is necessary to confine the injured tissue and foster the clearance of cellular debris, which would ultimately bring the inflammatory reaction to a close. In the chronic phase, a sustained immune activation is described in many CNS disorders, and the degree of this prolonged response has variable effects on the spontaneous brain regenerative processes. The challenge for treating acute CNS damages is to understand how to optimally engage and modify these immune responses, thus providing new strategies that will compensate for tissue lost to injury. Here we have reviewed the available information about the role and function of the innate and adaptive immune responses in influencing CNS plasticity during the acute and chronic phases of recovery after injury. We have examined how CNS damage evolves along the activation of main cellular and molecular pathways that ultimately are associated to intrinsic repair, neuronal functional plasticity and facilitation of tissue reorganization.

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Key words: CNS plasticity, immune system, stroke, spinal cord injury.

Contents

INTRODUCTION

Although considered for many years an immune privileged tissue, it is today well accepted that the CNS is engaged in an intense bidirectional communication with the immune system. The CNS physiologically controls peripheral immunity through complex humoral signaling and via the direct activation of neuronal pathways that include the hypothalamic–pituitary–adrenal axis and the autonomic nervous system (An et al., 2014). The hypothalamus normally suppresses the release of pro-inflammatory cytokines from T cells, monocytes and macrophages, while promoting the systemic release of anti-inflammatory cytokines, such as interleukin (IL)-10 (Chamorro et al., 2012). Similarly, the release of noradrenaline from the autonomic centers and peripheral organs (including the adrenal medulla, liver and spleen) induces a constitutive anti-inflammatory phenotype in circulating immune cells (Meisel et al., 2005). The immune system is in turn responsible for CNS development, surveillance and response to damage. In the developing brain, a large percentage of

*Correspondence to: S. Pluchino, John van Geest Centre for Brain Repair, Department of Clinical Neurosciences, University of Cambridge, E.D. Adrian Building, Robinson Way, CB2 0PY Cambridge, UK. Tel: +44-1223-331163 (office), +44-778-6012508 (mobile); fax: +44-1223-331174.
E-mail address: spp24@cam.ac.uk (S. Pluchino).
† These authors contributed equally.

Abbreviations: BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CSPG, chondroitin sulfate proteoglycans; DC, dendritic cells; ECM, extracellular matrix; GAP, growth- associated protein; IFN, type 1 interferon; IGF, insulin-like growth factor; IL, interleukin; MC, mast cells; MMP, matrix metalloproteinases; MPO, myeloperoxidase; NGF, nerve growth factor; NSC, neural stem cells; NT, neurotrophins; NVU, neurovascular unit; PID, peri-infarcts depolarizations; PRR, pattern recognition receptors; ROS, reactive oxygen species; SCI, spinal cord injury; SDF-1α, stromal cell-derived factor-1α; TGF, transforming growth factor; SVZ, subventricular zone; TH, T helper; VEGF, vascular endothelial growth factor.

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the processes underlying neurogenesis and dynamic pruning (i.e. the selective degeneration of whole or parts of dendrites and axon collaterals) is mediated by resident immune cells (Besedovsky and Rey, 2007; Boulanger, 2009). Later in adulthood, both resident and circulating immune cells function as primary guardians of the CNS and their sentinel duties contribute to the maintenance of normal homeostasis (Chamorro et al., 2012; Ousman and Kubes, 2012). Immune mechanisms are indeed responsible for the constant remodeling of neural circuits, memory consolidation, hippocampal long-term potentiation and neurogenesis in response to everyday environmental stimuli (Meisel et al., 2005; Yirmiya and Goshen, 2011).

After focal damage, the lesioned area undergoes acute loss of function and neurodegeneration, which are later followed by a regenerative response finalized at restoring both structures and functions. As the first line of defense in the CNS, the immune system provides the earliest responses against acute brain injury, consisting of both physical and chemical barriers created by innate immune cells (microglia/macrophages, neutrophils, and natural killer cells) and the complement system (Gelderblom et al., 2009). In this acute phase immune cells actively participate in the disruption of the blood–brain barrier (BBB), remodeling of the extracellular matrix (ECM), and activation of glial cells (reactive gliosis), while protecting neurons from increasing excitotoxicity, calcium release and free radicals (Dirnagl et al., 1999). This first intense systemic immune activation orchestrates the clearance of necrotic debris and the containment of the initial damage (Kamel and Iadecola, 2012).

The role of the immune system in the following regenerative phase within the CNS is however far from being fully elucidated. The CNS copes with injury and loss of function by enacting a variety of functional and structural changes in neural pathways and synapses, which are commonly referred to as *CNS plasticity*. In particular, a first phase of functional plasticity characterized by dendritic reorganization and axonal sprouting is followed by a second phase of structural neuroanatomical plasticity (generation of new neurons and vessels) ultimately leading to the formation of novel connections within the damaged brain (Wieloch and Nikolich, 2006). The components of both the innate and adaptive (T and B lymphocytes) immune responses profoundly shape functional and structural plasticity of the injured CNS by priming (or hindering) brain recovery via modulation of *intrinsic* growth properties and *extrinsic* growth-regulatory cues (Martino et al., 2011).

It is increasingly clear that many of the events that characterize the first acute neurodegeneration are linked (directly or indirectly) with the following regenerative phase, and that the immune activation within the CNS must be interpreted in a *continuum* between degenerative and reparative processes (Hermann and Chopp, 2012). In this review we focus on the role exerted by the innate and the adaptive immune response in regulating CNS plasticity through the different phases of acute injury and subsequent recovery. In particular, we explore the ability of the immune system to modulate the initial BBB damage and glial activation, the following functional plasticity of neurons, and the final reparative regeneration of the injured CNS (Fig. 1). Since most of currently available evidences related to the innate and adaptive immune responses after damage derive from CNS focal sterile injuries, we mainly focus on describing the pathophysiology and the evolution of acute (focal) damage after experimental ischemic stroke and spinal cord injury (SCI).

BBB DAMAGE AND REACTIVE GLIOSIS

The BBB is made by endothelial cells, pericytes, astrocytes and ECM that, together with neurons, are organized in a complex cellular system called the *neurovascular unit* (NVU) (Abbott et al., 2006). Upon ischemic brain injury, the NVU undergoes intense early changes that comprise failure of ion pumps, overaccumulation of intracellular sodium and calcium, loss of membrane integrity and necrotic cell death. Release of damage-associated molecular patterns (DAMPs) from necrotic cells activates pattern recognition receptors (PRRs) of the resident immune cells (microglia) that include Toll-like receptors (TLRs), RIG-1-like receptors (RLRs), NOD-like receptors (NLRs), AIM2-like receptors (ALRs) and C-type lectin receptors (Hanke and Kielian, 2011; Chamorro et al., 2012). Activation of PRRs on microglial cells triggers downstream signaling pathways, such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), the mitogen-activated protein kinase (MAPK) and type 1 interferon (IFN) pathway, which in turn upregulate proinflammatory cytokines, chemokines, costimulatory signals and reactive oxygen species (ROS) (Takeuchi and Akira, 2010). Excessive oxidative damage leads to dysfuntion of endothelial cells, degradation of tight junctions and modification of integrins on the abluminal endothelial membrane (Hermann and Elali, 2012). Cell adhesion molecules (CAMs), such as the intercellular cell adhesion molecule (ICAM-1) or the vascular cell adhesion molecule (VCAM-1), and P-selectins are then upregulated on the endothelium and ultimately favor the recruitment of blood-borne leukocytes to the ischemic damage.

Infiltrating neutrophil granulocytes are the first circulating immune cells to appear within the ischemic lesion and they virtually overwhelm the ischemic hemisphere by 3 days post-reperfusion (Gelderblom et al., 2009). Upon infiltration, neutrophils start producing inducible nitric oxide synthase (iNOS), an enzyme that generates toxic amounts of nitric oxide (NO), and release both matrix metalloproteinases (MMPs) and myeloperoxidase (MPO) (Justicia et al., 2003). Release of MMP-9, as well as the upregulation of MPO within the ischemic tissue, contribute to the further down-regulation of junctional proteins and are the main contributors to the first derangement of the BBB (Bao Dang et al., 2013; Peruzzotti-Jametti et al., 2013). Initial BBB disruption is soon enhanced by ECM degradation, which participates in the secondary ischemic brain damage by permitting serum elements to enter the perivascular space (Asahi et al., 2001; Elali et al., 2011). Resident macrophages and mast cells (MCs) become further activated, leading to the release of vasoactive media-

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