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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 crosstalk 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, thus bringing the inflammatory reaction to a close. In the chronic phase, a sustained immune activation has been described in many CNS disorders, and the degree of this prolonged response has variable effects on spontaneous brain regenerative processes. The challenge for treating acute CNS damage is to understand how to optimally engage and modify these immune responses, thus providing new strategies that will compensate for tissue lost to injury. Herein we have reviewed the available information regarding the role and function of the innate and adaptive immune responses in influencing CNS plasticity during the acute and chronic phases of after injury. We have examined how CNS damage evolves along the activation of main cellular and molecular pathways that are associated with 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 to be an immune privileged tissue, it is now 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

*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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brain, a large percentage of 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 the occurrence of focal CNS damage, the lesioned area undergoes acute loss of function and neurodegeneration, which are later followed by a regenerative response aimed at restoring both structure and function. As the first line of defense in the CNS, the immune system provides the earliest responses against acute brain injury, which consist 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 during the regenerative phase within the CNS has yet to be 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, the first phase of functional plasticity characterized by dendritic reorganization and axonal sprouting is followed by the second phase of structural neuroanatomical plasticity (e.g. 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 has become increasingly clear that many of the events that characterize the acute neurodegeneration are linked (directly or indirectly) with the following regenerative phase, and that the immune activation within the CNS must be interpreted as 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 responses 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 evidence related to the innate and adaptive immune responses after damage has been derived from CNS focal-sterile injuries, we focus mainly 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 composed of 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 are comprised of the failure of ion pumps, overaccumulation of intracellular sodium and calcium, loss of membrane integrity and subsequent 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 site of 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, contributes to the further down-regulation of junctional proteins and together represent the main contributors to the initial derangement of the BBB (Bao Dang et al., 2013; Peruzzotti-Jametti et al., 2013). This initial BBB disruption is soon enhanced by ECM degradation, which participates in secondary ischemic brain damage by permitting serum elements to enter the

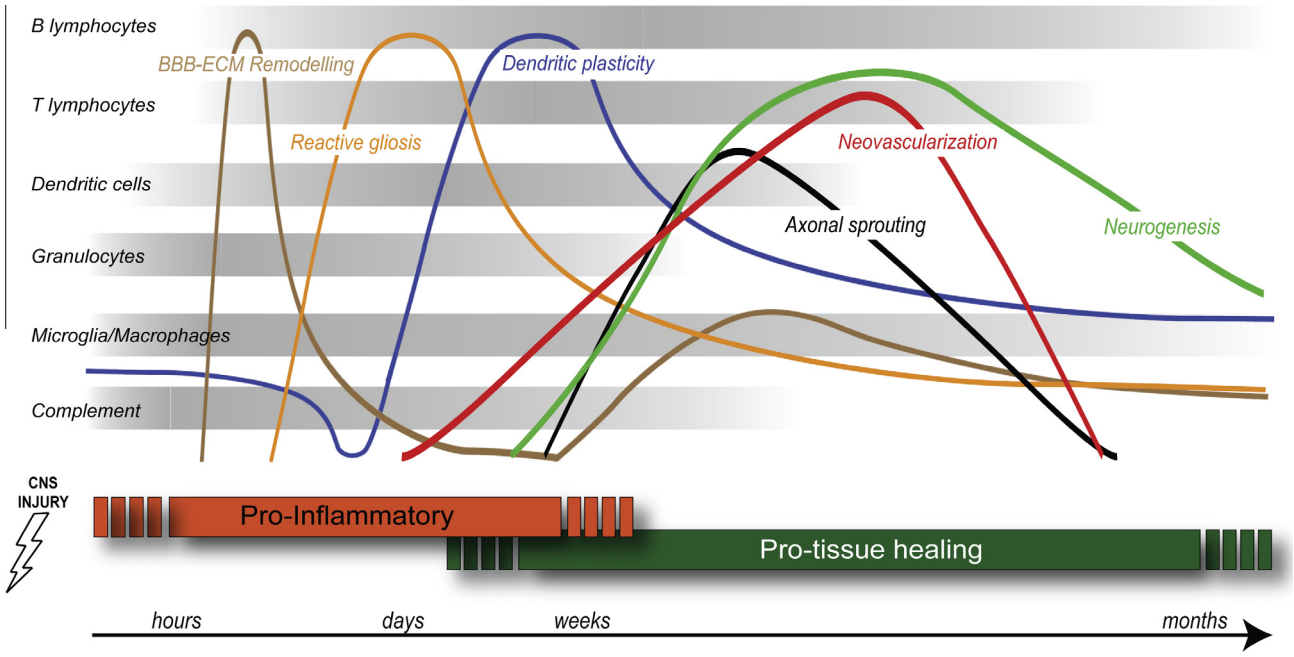

Fig. 1. Evolution of plasticity processes and immune cell activation after acute CNS damage. Innate and adaptive components of the immune system have been shown to play a crucial role during the pro-inflammatory and the pro-tissue healing phases after acute CNS damage. Increasing evidence has indeed demonstrated an indispensable role of the immune system in brain–blood barrier (BBB) and extracellular matrix (ECM) remodeling (in brown), reactive gliosis (in orange), dendritic plasticity (in blue), axonal sprouting (in black), neovascularization (in red) and neurogenesis (in green). The height of the curves represents the magnitude of the event. The gray bars represent the dynamic accumulation and activation of immune cells within the injured CNS. The horizontal arrow represents the time after injury.

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 mediators and proinflammatory cytokines, which in turn recruit and promote the infiltration of more leukocytes. Activated MCs secrete MMP-2 and MMP-9 that further damage the majority of the protein constituents within the ECM (e.g. collagen, elastin, fibronectin, vitronectin and gelatin), while MCs-derived tryptases and chymases cleave and activate fibronectin, procollagenases (Saarinen et al., 1994), pro-MMP-2 and pro-MMP-9 (Tchougounova et al., 2005). Likewise, eosinophils have a major role in enhancing BBB and ECM disruption after ischemic injury through the secretion of eosinophil-derived MMPs and elastases (Jacobsen et al., 2007). Once degraded, the ECM releases growth factors, such as the vascular endothelial growth factor (VEGF) and the transforming growth factor (TGF)-β, that are normally bound to the ECM in their zymogen forms (Zlokovic, 2006). Released growth factors, infiltrating immune cells and the accumulation of blood-borne soluble mediators within the perivascular space finally activate CNS astrocytes at the lesion border.

The role of these 'reactive astrocytes' has been extensively investigated in mouse models of SCI. Within areas of BBB damage, astrocytic activation mainly ensues as a direct consequence of the local inflammatory reaction (Burda and Sofroniew, 2014). Activated macrophages and microglia start secreting leukemia inhibitory factor (LIF) and IL-6, which promote astrocytic differentiation of progenitor cells (Nakanishi et al., 2007). MCs attract astroglial processes and stimulate their elongation (Khalil et al., 2007), while neutrophils induce early astroglial activation through the production of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, TGF-α, ROS, IL-1 and IL-6 (Silver and Miller, 2004). This early immune-mediated activation of astrocytes is of pivotal importance for the final outcome after SCI. As a matter of fact, the treatment of mice with anti-Ly6G/Gr-1 (an antibody that results in a profound loss of neutrophils) reduces this early astrocytic reactive gliosis, thus hampering neurological recovery and increasing lesional area (Stirling et al., 2009).

Following acute CNS damage, activated astrocytes increase the expression of intermediate filament proteins, such as vimentin and glial fibrillary acidic protein (GFAP), and secrete chondroitin sulfate proteoglycans (CSPGs), such as neurocan, phosphacan and versican (Rhodes and Fawcett, 2004). Reactive astrocytes and CSPGs form an insuperable barrier (the glial scar), which restricts extravasated leukocytes to perivascular clusters and thereby reduces further detrimental infiltration of immune cells into the adjacent CNS parenchyma. Beyond their role in structural confinement, astrocytes can also directly repair the BBB (Alvarez et al., 2013) and in so doing prevent an overwhelming inflammatory response (Bush et al., 1999). Interestingly, it has been recently shown that resident astrocytes and ependymal neural stem cells (NSC)-derived astrocytes, both participate in spinal cord glial scar formation, yet have different functions. Resident astrocytes form the peripheral part of the scar, while ependymal NSC-derived astrocytes constitute its central part (Barnabé-Heider et al., 2010). Moreover, while the former is implicated in restricting the infiltration of inflammatory cells (Okada et al., 2006;

Herrmann et al., 2008) and in inhibiting the degranulation of neutrophils (Xie et al., 2010), the latter is required to reinforce the injured spinal cord (Sabelström et al., 2013).

Despite the fact that astroglial activation plays a major positive role in the initial response to damage (mainly by prompting early stabilization of injured tissue), the glial scar represents a significant impediment for axonal regrowth and spontaneous regenerative mechanisms (Silver and Miller, 2004). A certain degree of astroglial modulation and ECM remodeling is therefore needed to initiate pro-regenerative adaptive responses within the damaged CNS (Zuo et al., 1998). The role of the immune cells in this phase is yet again fundamental. MCs can secrete mouse mast cell protease 4 (mMCP4), a chymase that is able to degrade inflammatory-associated cytokines and concurrently reduce astrogliosis (Nelissen et al., 2014), while eosinophils amplify complement-dependent cell-mediated cytotoxicity (CDCC) targeting astrocytes (Boulanger, 2009; Zhang and Verkman, 2013). Apoptotic neutrophils within the lesion border can affect nearby reactive microglia/macrophages by promoting a switch toward the alternative anti-inflammatory phenotype (M2) (Filardy et al., 2010). Once polarized, M2-like macrophages begin producing anti-inflammatory IL-10 and increase the expression of MMP-13, which allows the remodeling of the scar matrix into a more permissive environment for axonal re-growth (Shechter et al., 2011). This polarization toward the IL-10^{hi}IL-12^{low} M2-like anti-inflammatory phenotype is also dependent on IL-6 secretion by astrocytes and on the direct interaction of CSPGs with microglia/macrophages.

Unfortunately, this M2-like response is negligible and transient as compared to the durable pro-inflammatory (M1) polarization of microglia/macrophages after CNS damage. The short M2 response dissipates within 3–7 days post-SCI, while M1 macrophages dominate the lesion site and the surrounding tissue during both the acute and chronic phases. This is in stark contrast to the typical dynamics following cutaneous wound healing processes, where a well-defined shift in macrophage effector functions takes place. In this case the initial M1 phenotype ensures the sterility of the wound and induces apoptosis of neutrophils, that consequently causes the recruitment of M2 macrophages thereby promoting tissue healing and the conclusion of the inflammatory process. A similar M1 to M2 macrophage shift does not occur after SCI, and thus chronic inflammation is indeed a hallmark of spinal contusion/compression pathology. Interfering with the microglia/macrophages polarization by shifting the M1 pro-inflammatory activation toward an M2 pro-healing phenotype currently represents one of the most promising approaches to increase tissue remodeling after SCI injury (Cusimano et al., 2012).

NEURONAL FUNCTIONAL PLASTICITY

Upon acute ischemic damage, neurons in the ischemic core (the region of low perfusion in which cells have lost their membrane potential terminally) release excitatory neurotransmitters (e.g. glutamate) and intracellular solutes (e.g. potassium) that trigger waves of peri-infarct depolarizations (PID) (Dreier, 2011). PID propagate from the lesion core toward the surrounding ischemic penumbra (the region where intermediate perfusion prevails along with partially preserved energy metabolism). Every PID induces intermittent depolarizations of the neurons within the penumbra, thereby increasing the request of metabolic substrates (e.g. oxygen and glucose) in a zone that has reduced viability by definition (Doyle et al., 2008). Subsequent PID lead to the progressive enhancement of cellular death primarily due to energetic failure and ultimately cause the expansion of the ischemic core to match the whole penumbra (Dijkhuizen et al., 1999).

At this early time point, the major compensatory mechanism that can limit the spreading of PID are dendritic and synaptic pruning of the ischemic, but still viable, neurons (Mattson, 2008). These initial synaptic rearrangements are very similar to those occurring during neurodevelopment which mediate elimination of excessive synapses through the activation of the complement system and microglia (Rossini et al., 2003). It is known from post-natal studies that complement proteins mediate microglia-dependent pruning of synapses within neuronal circuits. As such, C1q-deficient mice display abnormal neocortical excitatory synaptic connectivity, as well as enhanced epileptiform activity (Chu et al., 2010). Such evidence suggests a possible reactivation of developmental pathways in adult CNS disorders (Stevens et al., 2007). After ischemic injury, complement proteins become profoundly upregulated within the lesion (Pedersen et al., 2004) and, together with microglia (Hasbani et al., 2001), mediate synaptic remodeling aimed at protecting vulnerable penumbral neurons from excessive excitotoxicity (Perry and O'Connor, 2010; Stephan et al., 2012). It has also been shown that both C3a and C5a are neuroprotective against glutamate analogs and function via the modulation of the caspase cascade and the expression of glutamate receptor subunit 2 (GluR2) *in vitro* and *in vivo* (Mukherjee et al., 2008). In particular, C3a protects neurons against *N*-methyl-D-aspartate (NMDA)-induced excitotoxicity in a dose- and astrocyte-dependent manner (Van Beek et al., 2001), while C5a exposure causes upregulation of nerve growth factor (NGF) in astrocytes, with similar neuroprotective effects *in vitro* (Jauneau et al., 2006). Although the role of complement after ischemic stroke *in vivo* has yet to be fully defined, the complexity of experimental animal studies suggests that complement activation may be a ''dual edged sword'' exerting beneficial or detrimental effects depending on its timing and context (Brennan et al., 2012).

After the initial synaptic depletion of the dendritic arborizations referenced above, spine turnover undergoes a profound secondary up-regulation that is paralleled by an increase in axonal regeneration. This period of increased plasticity (also referred to as the *critical period*) is the preferential target of current rehabilitative therapies, and is mainly characterized by the preponderant expression of pro-plasticity (over growth-inhibitory) genes (Carmichael, 2006). During this

limited period, the transitory expression of growth-promoting molecules (e.g. small proline rich protein-1, myristoylated alanine-rich C-kinase substrate and growth-associated protein-GAP-43) is coupled by a reduction of CSPGs (in the form of peri-neuronal nets) that ultimately increasing the final sprouting response (Carmichael et al., 2005). Axonal fiber tracts and dendrites start to reorganize along the infarct rim, and regenerative mechanisms, even in distant part of the brain (e.g. the contralateral side) are also enhanced. Fully differentiated neurons engage in a neuronal growth program, form a growth cone, extend an axon (or an axon collateral) and re-innervate unmatched targets via axonal sprouting. Interestingly, therapeutic approaches aimed at increasing perilesional tissue remodeling and contralesional plasticity (e.g. erythropoietin and VEGF administration) have been shown to be extremely efficacious in promoting functional neurological recovery in the ischemic brain (Reitmeir et al., 2011, 2012).

The role of immune cells (both innate and adaptive immunity) in modulating axonal sprouting and regrowth has been extensively studied in mouse models of SCI. Growth-promoting molecules secreted by innate immune cells stimulate the intrinsic growth machinery of neurons and help overcome surrounding inhibitory environments (Silver and Miller, 2004). MCs attach to growing neurites (Furuno et al., 2005) where they can synthesize, store and release NGF, thus enhancing the axonal sprouting of neuronal networks (Wilhelm et al., 2005). Similarly, eosinophils synthesize specific neurotrophins (NTs), including NGF, brain-derived neurotrophic factor (BDNF) and NT-3, that can be released upon stimulation (Kobayashi et al., 2002) and have a major stimulatory effect on neurite outgrowth (Foster et al., 2011). Several *in vitro* and *in vivo* experiments have shown that microglia/macrophages also have a major role in axonal regeneration. While immediately after damage adhesion molecules expressed by microglial cells (e.g. Slit, Netrin-1, and RGMa) are responsible for the early inhibition of neurite growth (Kitayama et al., 2011), in the following phases microglial cells may release neuroprotective and neurotrophic factors, such as glial cell-derived neurotrophic factor (GDNF) (Wang et al., 2013) and insulin-like growth factor 1 (IGF-1), that promote axonal re-growth (Lalancette-Hebert et al., 2007). Microglial cells also secrete BDNF (Yang et al., 2012), a key player in neuronal plasticity, which is capable of modulating *ex vivo* synaptic potentials (Coull et al., 2005) and stimulates regeneration of spinal cord-injured neurons via GAP-43 expression (Kobayashi et al., 1997). Interestingly, part of the regenerative potential of microglia/macrophages has also been attributed to the release of oncomodulin, a small Ca^{2+}-binding protein that promotes axonal regeneration via downstream Ca^{2+}/calmodulin kinase signaling (Yin et al., 2006).

The role of the adaptive immune response in modulating axonal sprouting after SCI injury is still unfolding. Although it has been shown that T cells can significantly enhance the sprouting of calretinergic fibers by promoting the removal of cell debris via microglia/macrophages (Hvilsted Nielsen et al., 2011), distinct T cell subsets may act in different (and potentially opposite) ways. So far, results from *in vitro* conditions show that neurite outgrowth is positively modulated by T helper (TH)-1 cells and negatively affected by $CD8^+$ T cells and natural killer cells. Co-cultures of peripheral blood mononuclear cells (PBMCs) with neurons obtained from the cortex, the cerebellum or the hippocampus of rats, demonstrated that activated $CD4^+$ T cells could promote neurite extension, while activated $CD8^+$ T cells inhibited axonal outgrowth (Pool et al., 2012). Interestingly, co-cultures of cortical neurons with either naïve $CD4^+$ T cells or polarized (TH1 vs. TH2) $CD4^+$ T cells, showed that only TH-1 cells can efficiently enhance neurite outgrowth, mainly through the expression of semaphorin (Sema)-4A (Ishii et al., 2010). Future *in vivo* experiments should be aimed at confirming the relevance of these interesting findings after CNS insult/injury. Clarifying the roles of the different subpopulations of immune cells and their specific mediators on axon viability, will substantially enhance the development of immunomodulatory therapies aimed at improving CNS regeneration.

REPARATIVE REGENERATION

Precursor cells of the main neurogenic zones within the adult brain, as well as local progenitors, have a major role in the recovery after CNS injury in mice (Butti et al., 2012). Classically, two fundamental brain regions, i.e. the subventricular zone (SVZ) and the subgranular zone (SGZ) of the hippocampus, have been demonstrated to be responsible for the majority of neurogenesis in adult mammals (Doetsch, 2003). Upon ischemic injury, neurogenesis in these areas is rapidly increased and a pool of progenitors is continuously generated up to 4 months after damage (Thored et al., 2006). While the extent of this proliferative response is massive, the overall neurogenic response after stroke is insufficient in terms of (a) survival of immature or mature neurons and (b) their mobilization from the neurogenic niches.

The survival rate of adult NSC in the ischemic brain is very poor and about 80% of the newly-generated striatal neurons die within the first 2 weeks of their formation (Arvidsson et al., 2002). Activated microglial cells are one of the main determinants of NSC survival in the ischemic environment (Ekdahl et al., 2009). It has been shown that activated microglia can reduce NSC viability and prevent neuronal differentiation by either direct cell-to-cell contact or through the secretion of soluble molecules (e.g. IFN-γ, IL-1β, IL-6 and TNF-α) (Ben-Hur et al., 2003; Cacci et al., 2008). The detrimental role of microglia on post-stroke neurogenesis is supported by several *in vivo* experiments that have demonstrated the strong effect of minocycline (a drug that inhibits microglial activation) in preserving new adult neurons, enhancing neurogenesis, and promoting functional recovery after focal cerebral ischemia (Liu et al., 2007). Similarly, other therapeutic approaches (including the transplantation of NSC) have been shown to be effective in inducing restorative effects in a mouse model of stroke by reducing excessive microglial activation (Bacigaluppi et al., 2009).

It is becoming increasingly clear that the role of microglia in CNS neurogenesis cannot be identified as detrimental per se. The phenotype (and cytokine production) of differently activated microglial subpopulations affects their ability to support (or impair) the adult neurogenic response. In particular, TNF-α plays a beneficial role in neurogenesis after ischemic injury, and probably acts via its receptor TNF-R2, thereby promoting the survival of stroke-generated hippocampal and striatal neurons (Heldmann et al., 2005). Interestingly, it has been shown that TNFα knock-out mice have a 50% increase in the final ischemic damage (Lambertsen et al., 2009). Microglial activation in the perilesional area might also positively regulate post-stroke neurogenesis by increasing the expression of the neuroprotective mediator IGF-1 in the SVZ (Thored et al., 2009). It has indeed been demonstrated that microglial cells (activated *in vitro* with IL-4 or IFN-γ) are able to promote neurogenesis from adult NSC via IGF-1 upregulation (Butovsky et al., 2006). While a local secretion of BDNF by resident microglia can be also induced by the production of IL-4 from TH-2-polarized T cells (Ziv and Schwartz, 2008), $CD8^+$ T cells seem to have opposite effects on neurogenesis as mediated by the release of granzyme B (Wang et al., 2010).

Besides its role in modulating NSC survival, the immune system is a key player in the mobilization of newly formed neuroblasts from the neurogenic niches to the sites of damage. NSC of the main murine neurogenic brain regions express both C3a and C5a receptors, and as such blockade of C3a signaling with a non-specific C3a receptor antagonist has been shown to attenuate basal and ischemia-induced neurogenesis in the adult mouse brain (Rahpeymai et al., 2006). The effects of C3a on basal neurogenesis are synergetic with stromal cell-derived factor-1α (SDF-1α) to promote neural progenitor cell migration and differentiation (Shinjyo et al., 2009). Interestingly, SDF-1α is strongly upregulated in the perilesional area after stroke, and behaves as an inflammatory stimulus that enhances progenitor proliferation and chain migration (Imitola et al., 2004).

In the regenerating murine CNS, newly formed neurons and neuroblasts proliferate and migrate in chains toward the ischemic lesion along blood vessels, which provide essential trophic support (Thored et al., 2007). As a consequence of this interaction, neurogenesis and neovascularization after CNS damage are interdependent processes that share common mediators and signals (Snapyan et al., 2009). Neovascularization in rodent models of cerebral ischemia is comprised of both angiogenesis (i.e. the out-growth of pre-existing vasculature) and vasculogenesis (i.e. the differentiation of endothelial progenitor cells into endothelial cells *in situ*). Both these mechanisms are rapidly induced upon brain stroke. Gene expression analysis of mouse brains have shown an increase of pro-angiogenic genes at 1 h post-ischemia, while endothelial cells around the infarcted brain area start to proliferate as early as 12–24 h (Beck and Plate, 2009). Both angiogenesis and vasculogenesis lead to an increase in vessel density in the peri-infarcted region. This effect is visible at 3 days following the ischemic injury and results in vessel proliferation for more than 21 days following experimental cerebral ischemia.

Immune cells regulate the complex neovascularization in response to CNS damage in several ways. Infiltrating neutrophils are the first to be attracted toward the sites of the deranged BBB where they contribute to further proteolysis of ECM proteins, thus increasing tissue-bound VEGF in a positive loop that ultimately promotes focal angiogenesis (Lee, 2002). VEGF, the most important mitogen in the process of angiogenesis, is also secreted by infiltrating eosinophils and MCs (Horiuchi and Weller, 1997). The occurrence of MCs on the vasculature wall, their location at the branch points of vessels, their production of pro-angiogenic factors (such as VEGF, FGF-2, TGF-β, TNF-α, IL-8, MMPs, tryptases and chymases), indeed suggests a prominent role for MCs in the neo-angiogenetic response after ischemic damage (Ribatti et al., 2000, 2011; Bennett et al., 2009; Sayed et al., 2011). MCs further contribute to neo-vascularization after ischemia through the promotion of VEGF production from non-mast cell sources (e.g. via monocyte chemotactic protein-1 mediated recruitment of circulating macrophages) (Cohen et al., 1996). Activated microglia/macrophages can in turn secrete TGF-β, Galectin-3 (Gal-3) and VEGF, thereby enhancing the formation of new blood vessels within the ischemic region (Walther et al., 2000). Interestingly, VEGF production by immune cells may be also important for successful brain remodeling after focal cerebral ischemia via anti-inflammatory actions, thus suggesting a link between immunosuppressive and plasticity-promoting actions of VEGF (Herz et al., 2012).

Although the role of dendritic cells (DCs) has generated vast interest primarily in the context of T cell-mediated autoimmune diseases, recent evidence indicates that a profound activation of DCs is a common feature after ischemic stroke. DCs positive for OX62 (a marker of rat lymph node-DCs) are present in the brains of rats subjected to permanent middle cerebral artery occlusion (MCAo) as early as 1 hour after ischemia, and continue accumulating up to 6 days post-injury (Kostulas et al., 2002). DCs have been shown to be involved in the complex process of neovascularization, especially during the resolution of inflammation, when IL-10 polarizes DCs toward an alternative activated (AA-DCs) phenotype (Riboldi et al., 2005). This AA-DCs phenotype is characterized by increased VEGF secretion, and it may contribute to neovascularization via a concomitant down-regulation of the anti-angiogenic IL-12 (Penna and Adorini, 2000). Recent evidence suggests that mature DCs can also affect angiogenesis by transferring membrane-bound molecules to T cells in the context of immune-synapsis (ISs), a process called "trogocytosis" (Joly and Hudrisier, 2003). Although the mechanism of such a transfer remains unclear and has yet to be confirmed in CNS disorders, trogocytosis may permit the acquisition of proteins usually not expressed by T cells (like Neuropilin-1, Sema-3A and VEGF receptor), and ultimately enhance angiogenesis within the ischemic tissue (Bourbié-Vaudaine et al., 2006).

Table 1. Potential immune mediators and pathways modulating recovery in the injured CNS

	Complement	Neutrophils	Eosinophils	Mast cells	Dendritic cells	Microglia/ macrophages	NK cells	T cells	B cells
ECM remodeling	Factor B Tchougounova et al. (2005), Alexander et al. (2007)	MMP-9, collagenase, gelatinase, elastase Fang et al. (1999), Bao Dang et al. (2013), MPO Baldus et al. (2001), Shechter et al. (2011)	Elastase Kitson et al. (1998), Jacobsen et al. (2007)	Tryptase chymase Weerth et al. (2003), Tchougounova et al. (2005), MMP-2, MMP-9 Fang et al. (1999), Stirling et al. (2009)		MMP-3, MMP-9, MMP-13 Shechter et al. (2011), Nelissen et al. (2014)	MMP-2, MMP-9 Kitson et al. (1998), Hvilsted Nielsen et al. (2011)		
Astroglial activation	C5 Weerth et al. (2003), Wright et al. (2009)	NADPH oxidase, ROS Stirling et al. (2009), Li et al. (2010), IL-6	ROS, TGF-β, IL-6, IL-4	mMCP-4 Stevens et al. (2007), Nelissen et al. (2014), IL-6		IL-6, LIF Nakanishi et al. (2007)		Increased TNF signaling Hvilsted Nielsen et al. (2011), Mantovani et al. (2011)	NAA (Clearance of myelin debris) Kobayashi et al. (2002), Wright et al. (2009)
Neuronal plasticity	C3 Leon et al. (1994), Li et al. (2010), C1q Hauben et al. (2003), Stevens et al. (2007)	BDNF, NGF, NT-4 Yin et al. (2006), Mantovani et al. (2011)	NGF, BDNF, NT-3 Kobayashi et al. (2002), Hao et al. (2010), IFN-γ	Serotonin, NGF Leon et al. (1994), Hammarberg et al. (2000)	NT-3 Hauben et al. (2003), Ishii et al. (2012)	Oncomodulin Yin et al. (2006) BDNF Coull et al. (2005), Kobayashi et al. (2002)	IFN-γ Rahpeymai et al. (2006), Hao et al. (2010), BDNF, NT-3 Hammarberg et al. (2000), Shinjyo et al. (2009)	Sema4A, NT-3 Bénard et al. (2008), Ishii et al. (2012)	NAA (modulation of H_2O_2-induced apoptosis) Warrington et al. (2004), Mantovani et al. (2011)
Angiogenesis	C5 Norrby (2002), Langer et al. (2010)	VEGF Scapini et al. (2004), Ribatti et al. (2011), MMP-9 Justicia et al. (2003), Riboldi et al. (2005)	PDGF, TNF-α and VEGF Horiuchi and Weller (1997)	VEGF, TNF-α and β, FGF, MMP Norrby (2002) tryptase and chymase Ribatti et al. (2011)	VEGF Riboldi et al. (2005), TNF-α, trans-differentiation in ELCs Fernandez Pujol et al. (2001), trogocytosis of VEGF receptor Bourbié-Vaudaine et al. (2006)	Galectin-3 Walther et al. (2000)	VEGF Solerte et al. (2005)		
Neurogenesis	C3 Mikami et al. (2004), Rahpeymai et al. (2006), Shinjyo et al. (2009), C5 Bénard et al. (2008), Popa et al. (2010)	BDNF, NGF, NT-4 Schwartz and Shechter (2010), Mantovani et al. (2011)	EDN, TNF-α, IFN-γ	Serotonin, NGF	NT-3 Mikami et al. (2004), Ziv and Schwartz (2008)	IGF-1 Thored et al. (2007), Huehnchen et al. (2011)	RAE1-NKG2D interaction Langer et al. (2010), Popa et al. (2010)	IL-4, IGF-1 Scapini et al. (2004), Schwartz and Shechter (2010) BDNF Justicia et al. (2003) SHH, NeuroD6, Ngn-1, Ngn-2 Horiuchi and Weller (1997), Huehnchen et al. (2011)	

Abbreviations: NADPH, nicotinamide adenine dinucleotide phosphate-oxidase; ROS, radical oxygen species; IL, interleukin; BDNF, brain-derived neurotrophic factor; NGF, nerve growth factor; NT, neurotrophin; MMP, matrix metalloprotease; MPO, myeloperoxidase, VEGF, vascular endothelial growth factor; TGF, transforming growth factor; PDGF, platelet-derived growth factor; TNF, tumor necrosis factor; LIF, leukemia inhibitory factor; EDN, eosinophil-derived neurotoxin; IFN, interferon; mMCP, mouse mast cell protease; FGFs, fibroblast growth factors; ELCs, endothelial-like cells; IGF, insulin-like growth factor, RAE, ribonucleic acid export; Sema4a, semaphorin-4A; SHH, sonic hedgehog homolog; NGN, neurogenin; NAA, natural autoantibodies; H_2O_2, hydrogen peroxide.

CONCLUSIONS

Damage to the central or peripheral nervous system results in the activation of complex immunological reactions that profoundly affect recovery after injury (Table 1). However, while the peripheral nervous system holds a certain degree of spontaneous regeneration after damage, the CNS retains a much lower regenerative capacity. While the myriad of factors governing the aforementioned phenomenon are not completely understood, the timing and pathophysiologic context of immune activation certainly play critical roles.

In comparison to the robust acute immune reaction following peripheral nerve injury, the response of immune cells in the damaged CNS is indeed faint. This insufficient response likely contributes to the delayed phagocytosis of debris and to the prolonged presence of inhibitors of axonal regrowth. Early immune activation after CNS damage is indeed of paramount importance for the regenerative response, and enhancement of this *protective autoimmunity* may foster CNS repair after injury (Schwartz and Kipnis, 2001). Recent evidence supporting the putative protective function of B cells in the regenerating CNS lends credence to the aforesaid: natural auto-reactive antibodies (NAAs) secreted by B cells seem to have profound effects on remyelination after inflammatory damage via an increase in myelin debris clearance through Ig-dependent macrophage activation (Bieber et al., 2001).

Many authors have also suggested that the decreased regenerative potential of the CNS might be related to a prolonged immune activation after damage (Horner and Gage, 2000; Mescher and Neff, 2005). The immune response in the CNS is considerably more protracted as compared to peripheral nerve injuries, and sustained meningeal inflammation (e.g. in the form of ectopic lymphoid-like structures) has been suggested to play a prominent detrimental role in many chronic CNS diseases (Aloisi and Pujol-Borrell, 2006). Shedding light on the mechanisms by which the sustained innate and adaptive immune activation interferes with CNS regeneration might lead to the identification of valuable targets for novel therapeutic treatments.

It is evident from the literature that inflammation in the damaged CNS cannot be regarded as an event that is either ‘degenerative’ or ‘regenerative’. These aspects of inflammation act in dynamic interplay throughout the course of unfolding CNS injury. Future therapies for CNS disorders should be therefore conceived to execute a timed immune-modulatory tuning in response to the pathophysiological microenvironment.

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