Published in final edited form as:

Neuroscience. 2014 December 26; 0: 210–221. doi:10.1016/j.neuroscience.2014.04.036.

The role of the immune system in central nervous system plasticity after acute injury

Luca Peruzzotti-Jametti^{#1}, Matteo Donegá^{#1}, Elena Giusto¹, Giulia Mallucci^{1,4}, Bianca Marchetti^{5,6}, and Stefano Pluchino^{1,2,3}

¹John van Geest Centre for Brain Repair, Dept of Clinical Neurosciences

²NIHR Biomedical Research Centre

³Wellcome Trust-Medical Research Council Stem Cell Institute, University of Cambridge, CB2 0PY, UK

⁴Department of Brain and Behavioural sciences, National Neurological Institute C. Mondino, 27100 Pavia, Italy

⁵Department of Clinical and Molecular Biomedicine, Pharmacology Section, Medical School, University of Catania, 95125 Catania, Italy

⁶OASI Institute for Research and Care on Mental Retardation and Brain Aging, Neuropharmacology Section, 94018 Troina, Italy

These authors contributed equally to this work.

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 central nervous system (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

Correspondence to Stefano Pluchino, MD, PhD, Department of Clinical Neurosciences, John van Geest Centre for Brain Repair and Wellcome Trust-Medical Research Council Stem Cell Institute. 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, spp24@cam.ac.uk.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

cellular and molecular pathways that ultimately are associated to intrinsic repair, neuronal functional plasticity and facilitation of tissue reorganization.

Keywords

CNS plasticity; immune system; stroke; spinal cord injury

1. Introduction

Although considered for many years an immune privileged tissue, it is today well accepted that the central nervous systems (CNS) is engaged in an intense bidirectional communication with the immune system. The CNS physiologically controls peripheral immunity through complex humoral signalling 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 centres 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 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 remodelling 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), remodelling 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 Nikolic, 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).

2. 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 signalling pathways, such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), 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 dysfunction 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 favour the recruitment of blood-born 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 mediators and proinflammatory cytokines, which in turn recruit and promote the infiltration of more leukocytes. Activated mast cells (MCs) secrete MMP-2 and MMP-9 that further damage most of the protein constituents of the ECM (like 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 on 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 form (Zlokovic, 2006). Released growth factors, infiltrating immune cells and the accumulation of blood born 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 spinal cord injury. Within areas of BBB damage, astrocytic activation mainly ensues after SCI as a direct consequence of the local inflammatory reaction (Burda and Sofroniew, 2014). Activated macrophages and microglia start secreting leukaemia inhibitory factor (LIF) and IL-6, which promote astrocytic differentiation of progenitor cells (Nakanishi et al., 2007). MCs attract astroglial processes to elongate in their close proximity (Khalil et al., 2007) and 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 the early astrocytic reactive gliosis, thus hampering neurological recovery and increasing lesion 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 reduce further detrimental infiltration of immune cells into the adjacent CNS parenchyma. Besides their role in structural confinement, astrocytes can also directly repair the BBB

(Alvarez et al., 2013) to 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, which both participate in spinal cord glial scar formation, 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 are 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 astroglial activation has major positive features in the initial response to damage (mainly by prompting early stabilization of injured tissue), the glial scar represents a major impediment for axonal regrowth and other regenerative mechanisms in the following phases (Silver and Miller, 2004). A certain degree of astroglial modulation and ECM remodelling 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 once more fundamental. Mast cells can secrete mouse mast cell protease 4 (mMCP4), a chymase that is able to degrade inflammatory-associated cytokines and to reduce astrogliosis (Nelissen et al., 2014), while eosinophils might amplify complement-dependent cell-mediated cytotoxicity (CDCC) on astrocytes (Boulanger, 2009; Zhang and Verkman, 2013). Apoptotic neutrophils within the lesion border can affect nearby reactive microglia/macrophages by promoting a switch towards the alternative anti-inflammatory phenotype (M2) (Filardy et al., 2010). Once polarized, M2-like macrophages start producing anti-inflammatory IL-10 and increase the expression of MMP-13, which allows the remodelling of the scar matrix into a more permissive environment for axonal re-growth (Shechter et al., 2011). This polarization towards 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 mostly negligible and transient 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 even at chronic phase. This is in contrast with 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 in neutrophils, this consequently causes the recruitment of M2 macrophages that promotes tissue healing and brings the inflammatory process to an end. A similar M1 to M2 macrophage shift does not occur after SCI, and chronic inflammation is indeed a hallmark of spinal contusion/compression pathology. Interfering with the microglia/macrophages polarization by shifting the M1 pro-inflammatory activation towards an M2 pro-healing phenotype is currently one of the most promising approaches to increase tissue remodelling after SCI injury (Cusimano et al., 2012).

3. 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 (PIDs) (Dreier, 2011). PIDs propagate from the lesion core towards the surrounding ischemic penumbra (the region where intermediate perfusion prevails along with partially preserved energy metabolism). Every PID induces intermittent depolarizations of the neurons of the penumbra, 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 PIDs lead to progressive enhancement of cellular death because of energetic failure and ultimately cause the ischemic core to enlarge and match the whole penumbra (Dijkhuizen et al., 1999).

At this early time point, the major compensatory mechanism that can limit the spreading of these waves of depolarization are dendritic and synaptic pruning of the ischemic, but still viable, neurons (Mattson, 2008). These first synaptic rearrangements are very similar to those occurring during neurodevelopment to mediate excessive synapses elimination 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). These evidences suggest a possible reactivation of developmental pathways also 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 the first synaptic remodelling 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 by modulating 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). The role of the complement after ischemic stroke *in vivo* is yet to be fully elucidated, and the complexity of experimental animal studies suggests that complement activation could 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 dendritic arborizations, 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 *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

eventually increase the final sprouting response (Carmichael et al., 2005). Axonal fibre 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 enhanced. Fully differentiated neurons engage a neuronal growth program, elaborate 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 remodelling and contralesional plasticity (e.g. erythropoietin and VEGF administration) have shown to be extremely efficacious in promoting functional neurological recovery in the ischemic brain (Reitmeir et al., 2011; Reitmeir et al., 2012).

The role of immune cells (either of the 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 to overcome surrounding inhibitory environment (Silver and Miller, 2004). MCs attach to growing neurites (Furuno et al., 2005) where they can synthesize, store and release NGF, thus enhancing axonal sprouting of neuronal networks (Wilhelm et al., 2005). Similarly, eosinophils synthesize specific neurotrophins, including NGF, brain-derived neurotrophic factor (BDNF) and neurotrophin (NT)-3, that can be released upon stimulation (Kobayashi et al., 2002) and have major stimulatory effect on neurite outgrowth (Foster et al., 2011). Several *in vitro* and *in vivo* experiments have shown that also microglia/macrophages have a major role in axonal regeneration. While soon 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 period 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 stimulate 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 signalling (Yin et al., 2006).

The role of the adaptive immune response in modulating axonal sprouting after SCI injury is still not fully understood. Although it has been shown that T cells can significantly enhance the sprouting of calretinerergic fibres by promoting the removal of cell debris by microglia/macrophages (Hvilsted Nielsen et al., 2011), distinct T cell subsets could act in different (and somehow opposite) ways. So far, results coming 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 indeed that activated CD4^{+} T cells could promote neurite extension, while activated CD8^{+} T cells inhibit 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 damage. Clarifying the role 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.

4. Reparative regeneration

Precursor cells of the main neurogenic zones within the adult brain, as well as local progenitors, have a main 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, are responsible for 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 four months after damage (Thored et al., 2006). Although the extent of this proliferation 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 during the first two weeks after 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 survival and prevent neuronal differentiation by either direct cell-to-cell contact or through the secretion of soluble molecules (e.g. IFN- γ , IL-1 β , 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 a strong effect of minocycline (a drug that inhibits microglial activation) in preserving adult new 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 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 indeed their ability to support (or impair) the adult neurogenic response. In particular, TNF- α play a beneficial role in neurogenesis after ischemic injury, probably acting via its receptor TNF-R2, promoting the survival of stroke-generated hippocampal and striatal neurons (Heldmann et al., 2005). Interestingly, it has been shown that TNF α knockout 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 T helper-2

polarized T cells (Ziv and Schwartz, 2008), CD8⁺ T cells seem to have opposite effects on neurogenesis 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 blockade of C3a signalling 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 mediated in synergy with stromal cell-derived factor-1 α (SDF-1 α) to promote neural progenitor cell migration and differentiation (Shinjo et al., 2009). Interestingly, SDF-1 α 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 CNS, newly formed neurons and neuroblasts proliferate and migrate in chains towards the ischemic lesion along blood vessels, which provide an essential trophic support (Thored et al., 2007). As a consequence of this interaction, neurogenesis and neovascularization after CNS damage show interdependent processes that share common mediators and signals (Snayyan et al., 2009). Neovascularization in rodent models of cerebral ischemia comprises 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 showed an increase of pro-angiogenic genes already at 1 hour post-ischemia, while endothelial cells around the infarcted brain area start to proliferate as early as 12-24 hours (Beck and Plate, 2009). Both angiogenesis and vasculogenesis lead to an increase of vessel density in the peri-infarcted region, which is visible at three 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 towards the sites of 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 proangiogenic factors (such as VEGF, FGF-2, TGF- β , TNF- α , IL-8, MMPs, tryptases and chymases), suggest indeed a prominent role for MCs in the neo-angiogenetic response after ischemic damage (Bennett et al., 2009; Sayed et al., 2011; Ribatti et al., 2000; 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 macrophage/microglial cells can in turn secrete TGF- β , Galectin-3 (Gal-3) and VEGF, finally 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 remodelling after focal cerebral ischemia via mechanisms involving anti-inflammatory

actions, thus suggesting a link between immunosuppressive and plasticity-promoting actions of VEGF (Herz et al., 2011).

Although the role of dendritic cells (DCs) has raised great attention primarily in the context of T cell-mediated autoimmune diseases, recent evidences indicate that a profound activation of DCs is a common feature also 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 one hour after ischemia, and keep accumulating up to six 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 might polarize DCs towards an alternative activated (AA-DCs) phenotype (Riboldi et al., 2005). The AA-DCs phenotype is characterized by an 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 evidences suggest that mature DCs can 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 transfer remains unclear and 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).

5. 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 regeneration, the CNS retains a much lower regenerative capacity. The reasons behind this phenomenon are not completely understood, but it might well depend on the degree and timing of activation of the immune system.

In comparison to the robust immune reaction of peripheral nerve injury, the response of immune cells in the damaged CNS is indeed faint, and this *weakness* likely contributes to the delay in phagocytosis of debris and to the prolonged presence of inhibitors for axonal regrowth. Early immune activation after CNS damage is indeed interpreted by many authors as a fundamental part of the regenerative response, and enhancement of this *protective autoimmunity* would foster CNS repair after injury (Schwartz and Kipnis, 2001). Recent evidence on the possible protective function of B cells in the regenerating CNS might support this opinion: natural auto-reactive antibodies (NAAs) secreted by B cells seem to have profound effects on remyelination after inflammatory damage by increasing myelin debris clearance through Ig-dependent macrophages activation (Bieber et al., 2001).

Many authors have also indicated that the lower regenerative potential of the CNS might be related to a prolonged duration of the immune activation after damage (Horner and Gage, 2000; Mescher and Neff, 2005). The immune response in the CNS is indeed considerably more protracted 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 reported literature that inflammation in the damaged CNS cannot be seen as a unified event that is all 'degenerative' or 'regenerative'. These two aspects act in continuous interplay throughout the whole evolution of CNS damage, and both the innate and adaptive immunity strictly regulate the final regenerative outcome. Future therapies for CNS disorders must be then conceived to execute a fine immune-modulatory tuning in response to the diverse signals of the inflammatory microenvironment.

Acknowledgments

The authors thank Gillian Tannahill, Jayden A. Smith and Giulia Longoni for critically reviewing the article, and acknowledge the contribution of past and present members of the Marchetti and Pluchino laboratories, who have contributed to (or inspired) this manuscript. This work was supported by grants from the National Multiple Sclerosis Society (NMSS; RG-4001-A1), the Italian Multiple Sclerosis Foundation (FISM; RG 2010/R/31), the Italian Ministry of Health (GR08/7) the European Research Council (ERC) 2010-StG (RG 260511-SEM_SEM), the European Community (EC) 7th Framework Program (FP7/2007-2013; RG 280772-iONE), The Evelyn Trust (RG 69865), and The Bascule Charitable Trust (RG 75149). GM received a European Neurological Society (ENS) Training fellowship.

References

- Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood–brain barrier. *Nat Rev Neurosci.* 2006; 7:41–53. [PubMed: 16371949]
- Alexander JJ, Jacob A, Vezina P, Sekine H, Gilkeson GS, Quigg RJ. Absence of functional alternative complement pathway alleviates lupus cerebritis. *Eur J Immunol.* 2007; 37:1691–1701. [PubMed: 17523212]
- Aloisi F, Pujol-Borrell R. Lymphoid neogenesis in chronic inflammatory diseases. *Nat Rev Immunol.* 2006; 6:205–217. [PubMed: 16498451]
- Alvarez JI, Katayama T, Prat A. Glial influence on the blood brain barrier. *Glia.* 2013; 61:1939–1958. [PubMed: 24123158]
- An C, Shi Y, Li P, Hu X, Gan Y, Stetler RA, Leak RK, Gao Y, Sun B-L, Zheng P, Chen J. Molecular dialogs between the ischemic brain and the peripheral immune system: Dualistic roles in injury and repair. *Prog Neurobiol.* 2014;1–19.
- Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O. Neuronal replacement from endogenous precursors in the adult brain after stroke. *Nat Med.* 2002; 8:963–970. [PubMed: 12161747]
- Asahi M, Wang X, Mori T, Sumii T, Jung JC, Moskowitz MA, Fini ME, Lo EH. Effects of matrix metalloproteinase-9 gene knock-out on the proteolysis of blood-brain barrier and white matter components after cerebral ischemia. *J Neurosci.* 2001; 21:7724–7732. [PubMed: 11567062]
- Bacigaluppi M, Pluchino S, Peruzzotti-Jametti L, Kilic E, Kilic U, Salani G, Brambilla E, West MJ, Comi G, Martino G, Hermann DM. Delayed post-ischaemic neuroprotection following systemic neural stem cell transplantation involves multiple mechanisms. *Brain.* 2009; 132:2239–2251. [PubMed: 19617198]
- Baldus S, Eiserich JP, Mani A, Castro L, Figueroa M, Chumley P, Ma W, Tousson A, White CR, Bullard DC, Brennan M-L, Lusis AJ, Moore KP, Freeman BA. Endothelial transcytosis of myeloperoxidase confers specificity to vascular ECM proteins as targets of tyrosine nitration. *J Clin Invest.* 2001; 108:1759–1770. [PubMed: 11748259]
- Bao Dang Q, Lapergue B, Tran-Dinh A, Diallo D, Moreno J-A, Mazighi M, Romero IA, Weksler B, Michel J-B, Amarencu P, Meilhac O. High-density lipoproteins limit neutrophil-induced damage

- to the blood-brain barrier in vitro. *J Cereb Blood Flow Metab.* 2013; 33:575–582. [PubMed: 23299241]
- Barnabé-Heider F, Göritz C, Sabelström H, Takebayashi H, Pfrieger FW, Meletis K, Frisén J. Origin of new glial cells in intact and injured adult spinal cord. *Cell Stem Cell.* 2010; 7:470–482. [PubMed: 20887953]
- Beck H, Plate KH. Angiogenesis after cerebral ischemia. *Acta Neuropathol.* 2009; 117:481–496. [PubMed: 19142647]
- Bénard M, Raoult E, Vaudry D, Leprince J, Falluel-Morel A, Gonzalez BJ, Galas L, Vaudry H, Fontaine M. Role of complement anaphylatoxin receptors (C3aR, C5aR) in the development of the rat cerebellum. *Mol Immunol.* 2008; 45:3767–3774. [PubMed: 18635264]
- Ben-Hur T, Ben-Menachem O, Furer V, Einstein O, Mizrahi-Kol R, Grigoriadis N. Effects of proinflammatory cytokines on the growth, fate, and motility of multipotential neural precursor cells. *Mol Cell Neurosci.* 2003; 24:623–631. [PubMed: 14664813]
- Bennett JL, Blanchet MR, Zhao L, Zbytniuk L, Antignano F, Gold M, Kubes P, McNagny KM. Bone Marrow-Derived Mast Cells Accumulate in the Central Nervous System During Inflammation but Are Dispensable for Experimental Autoimmune Encephalomyelitis Pathogenesis. *J Immunol.* 2009; 182:5507–5514. [PubMed: 19380799]
- Besedovsky HO, Rey AD. Physiology of psychoneuroimmunology: a personal view. *Brain Behav Immun.* 2007; 21:34–44. [PubMed: 17157762]
- Bieber AJ, Warrington A, Pease LR, Rodriguez M. Humoral autoimmunity as a mediator of CNS repair. *TINS.* 2001; 24:S39–S44. [PubMed: 11881744]
- Boulanger LM. Immune Proteins in Brain Development and Synaptic Plasticity. *Neuron.* 2009; 64:93–109. [PubMed: 19840552]
- Bourbié-Vaudaine S, Blanchard N, Hivroz C, Roméo P-H. Dendritic Cells Can Turn CD4+ T Lymphocytes into Vascular Endothelial Growth Factor-Carrying Cells by Interleukin-1 Transfer. *J Immunol.* 2006; 177:1460–1469. [PubMed: 16849452]
- Brennan FH, Anderson AJ, Taylor SM, Woodruff TM, Ruitenberg MJ. Complement activation in the injured central nervous system: another dual-edged sword? *J Neuroinflammation.* 2012; 9:1–13. [PubMed: 22212381]
- Burda JE, Sofroniew MV. Reactive Gliosis and the Multicellular Response to CNS Damage and Disease. *Neuron.* 2014; 81:229–248. [PubMed: 24462092]
- Bush TG, Puvanachandra N, Horner CH, Polito A, Ostendorf T, Svendsen CN, Mucke L, Johnson MH, Sofroniew MV. Leukocyte infiltration, neuronal degeneration, and neurite outgrowth after ablation of scar-forming, reactive astrocytes in adult transgenic mice. *Neuron.* 1999; 23:297–308. [PubMed: 10399936]
- Butovsky O, Ziv Y, Schwartz A, Landa G, Talpalar AE, Pluchino S, Martino G, Schwartz M. Microglia activated by IL-4 or IFN-gamma differentially induce neurogenesis and oligodendrogenesis from adult stem/progenitor cells. *Mol Cell Neurosci.* 2006; 31:149–160. [PubMed: 16297637]
- Butti E, et al. Subventricular zone neural progenitors protect striatal neurons from glutamatergic excitotoxicity. *Brain.* 2012; 135:3320–35. [PubMed: 23008234]
- Cacci E, Ajmone-Cat MA, Anelli T, Biagioni S, Minghetti L. In vitro neuronal and glial differentiation from embryonic or adult neural precursor cells are differently affected by chronic or acute activation of microglia. *Glia.* 2008; 56:412–425. [PubMed: 18186084]
- Carmichael ST. Cellular and molecular mechanisms of neural repair after stroke: Making waves. *Ann Neurol.* 2006; 59:735–742. [PubMed: 16634041]
- Carmichael ST, Archibeque I, Luke L, Nolan T, Momiy J, Li S. Growth-associated gene expression after stroke: evidence for a growth-promoting region in peri-infarct cortex. *Exp Neurol.* 2005; 193:291–311. [PubMed: 15869933]
- Chamorro A, Meisel A, Planas AM, Urra X, van de Beek D, Veltkamp R. The immunology of acute stroke. *Nar Rev Neurol.* 2012; 8:401–410.
- Chu Y, Jin X, Parada I, Pesic A, Stevens B, Barres B, Prince DA. Enhanced synaptic connectivity and epilepsy in C1q knockout mice. *Proc Natl Acad Sci USA.* 2010; 107:7975–7980. [PubMed: 20375278]

- Cohen T, Nahari D, Cerem LW, Neufeld G, Levi BZ. Interleukin 6 Induces the Expression of Vascular Endothelial Growth Factor. *J Biol Chem*. 1996; 271:736–741. [PubMed: 8557680]
- Coull JAM, Beggs S, Boudreau D, Boivin D, Tsuda M, Inoue K, Gravel C, Salter MW, De Koninck Y. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature*. 2005; 438:1017–1021. [PubMed: 16355225]
- Cusimano M, Bizziato D, Brambilla E, Donega M, Alfaro-Cervello C, Snider S, Salani G, Pucci F, Comi G, Garcia-Verdugo JM, De Palma M, Martino G, Pluchino S. Transplanted neural stem/precursor cells instruct phagocytes and reduce secondary tissue damage in the injured spinal cord. *Brain*. 2012; 135:447–60. [PubMed: 22271661]
- Dijkhuizen RM, Beekwilder JP, van der Worp HB, Berkelbach van der Sprenkel JW, Tulleken KA, Nicolay K. Correlation between tissue depolarizations and damage in focal ischemic rat brain. *Brain Res*. 1999; 840:194–205. [PubMed: 10517971]
- Dirnagl U, Iadecola C, Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. *Trends Neurosci*. 1999; 22:391–397. [PubMed: 10441299]
- Doetsch F. A niche for adult neural stem cells. *Curr Opin Genet Dev*. 2003; 13:543–550. [PubMed: 14550422]
- Doyle KP, Simon RP, Stenzel-Poore MP. Mechanisms of ischemic brain damage. *Neuropharmacology*. 2008; 55:310–318. [PubMed: 18308346]
- Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. *Nat Med*. 2011; 17:439–47. [PubMed: 21475241]
- Ekdahl CT, Kokaia Z, Lindvall O. Brain inflammation and adult neurogenesis: The dual role of microglia. *Neuroscience*. 2009; 158:1021–1029. [PubMed: 18662748]
- Elali A, Doeppner TR, Zechariah A, Hermann DM. Increased Blood-Brain Barrier Permeability and Brain Edema After Focal Cerebral Ischemia Induced by Hyperlipidemia. *Stroke*. 2011; 44:3238–44. [PubMed: 21836084]
- Fang KC, Wolters PJ, Steinhoff M, Bidgol A, Blount JL, Caughey GH. Mast cell expression of gelatinases A and B is regulated by kit ligand and TGF-beta. *J Immunol*. 1999; 162:5528–5535. [PubMed: 10228034]
- Fernandez Pujol B, Lucibello FC, Zuzarte M, Lütjens P, Müller R, Havemann K. Dendritic cells derived from peripheral monocytes express endothelial markers and in the presence of angiogenic growth factors differentiate into endothelial-like cells. *Eur J Cell Biol*. 2001; 80:99–110. [PubMed: 11211940]
- Filardy AA, Pires DR, Nunes MP, Takiya CM, Freire-de-Lima CG, Ribeiro-Gomes FL, DosReis GA. Proinflammatory clearance of apoptotic neutrophils induces an IL-12(low)IL-10(high) regulatory phenotype in macrophages. *J Immunol*. 2010; 185:2044–2050. [PubMed: 20660352]
- Foster, EL.; Simpson, EL.; Fredrikson, LJ.; Lee, JJ.; Lee, NA.; Fryer, AD.; Jacoby, DB. Eosinophils Increase Neuron Branching in Human and Murine Skin and In Vitro. In: Tsokos, GC., editor. *PLoS ONE*. Vol. 6. 2011. p. 1-11.
- Furuno T, Ito A, Koma Y-I, Watabe K, Yokozaki H, Bienenstock J, Nakanishi M, Kitamura Y. The spermatogenic Ig superfamily/synaptic cell adhesion molecule mast-cell adhesion molecule promotes interaction with nerves. *J Immunol*. 2005; 174:6934–6942. [PubMed: 15905536]
- Gelderblom M, Leypoldt F, Steinbach K, Behrens D, Choe CU, Siler DA, Arumugam TV, Orthey E, Gerloff C, Tolosa E, Magnus T. Temporal and Spatial Dynamics of Cerebral Immune Cell Accumulation in Stroke. *Stroke*. 2009; 40:1849–1857. [PubMed: 19265055]
- Hammarberg H, Lidman O, Lundberg C, Eltayeb SY, Gielen AW, Muhallab S, Svenningsson A, Linda H, van der Meide PH, Cullheim S, Olsson T, Piehl F. Neuroprotection by encephalomyelitis: rescue of mechanically injured neurons and neurotrophin production by CNS-infiltrating T and natural killer cells. *J Neurosci*. 2000; 20:5283–5291. [PubMed: 10884312]
- Hanke ML, Kielian T. Toll-like receptors in health and disease in the brain: mechanisms and therapeutic potential. *Clin Sci*. 2011; 121:367–387. [PubMed: 21745188]
- Hao J, Liu R, Piao W, Zhou Q, Vollmer TL, Campagnolo DI, Xiang R, La Cava A, Van Kaer L, Shi FD. Central nervous system (CNS)-resident natural killer cells suppress Th17 responses and CNS autoimmune pathology. *J Exp Med*. 2010; 207:1907–1921. [PubMed: 20696699]

- Hasbani MJ, Schlieff ML, Fisher DA, Goldberg MP. Dendritic spines lost during glutamate receptor activation reemerge at original sites of synaptic contact. *J Neurosci.* 2001; 21:2393–2403. [PubMed: 11264313]
- Hauben E, Gothilf A, Cohen A, Butovsky O, Nevo U, Smirnov I, Yoles E, Akselrod S, Schwartz M. Vaccination with Dendritic Cells Pulsed with Peptides of Myelin Basic Protein Promotes Functional Recovery from Spinal Cord Injury. *J Neurosci.* 2003; 23:8808–8819. [PubMed: 14507981]
- Heldmann U, Thored P, Claassen J, Arvidsson A, Kokaia Z, Lindvall O. TNF- α antibody infusion impairs survival of stroke-generated neuroblasts in adult rat brain. *Exp Neurol.* 2005; 196:204–208. [PubMed: 16157335]
- Hermann DM, Chopp M. Promoting brain remodelling and plasticity for stroke recovery: therapeutic promise and potential pitfalls of clinical translation. *The Lancet Neurology.* 2012; 11:369–380. [PubMed: 22441198]
- Hermann DM, Elali A. The Abluminal Endothelial Membrane in Neurovascular Remodeling in Health and Disease. *Sci Signal.* 2012; 5:re4. [PubMed: 22871611]
- Herrmann JE, Imura T, Song B, Qi J, Ao Y, Nguyen TK, Korsak RA, Takeda K, Akira S, Sofroniew MV. STAT3 is a critical regulator of astrogliosis and scar formation after spinal cord injury. *J Neurosci.* 2008; 28:7231–7243. [PubMed: 18614693]
- Herz J, Reitmeier R, Hagen SI, Reinboth BS, Guo Z, Zechariah A, Elali A, Doeppner TR, Bacigaluppi M, Pluchino S, Kilic U, Kilic E, Hermann DM. Intracerebroventricularly delivered VEGF promotes contralesional corticorubral plasticity after focal cerebral ischemia via mechanisms involving anti-inflammatory actions. *Neurobiol Dis.* 2012; 5(3):1077–85. [PubMed: 22198574]
- Horiuchi T, Weller PF. Expression of Vascular Endothelial Growth Factor by Human Eosinophils: Upregulation by Granulocyte Macrophage Colony-stimulating Factor and Interleukin-5. *Am J Respir Cell Mol Biol.* 1997; 17:70–77. [PubMed: 9224211]
- Horner PJ, Gage FH. Regenerating the damaged central nervous system. *Nature.* 2000; 407:963–970. [PubMed: 11069169]
- Huehnchen P, Prozorovskii T, Klaissle P, Lesemann A, Ingwersen J, Wolf SA, Kupsch A, Aktas O, Steiner B. Modulation of adult hippocampal neurogenesis during myelin-directed autoimmune neuroinflammation. *Glia.* 2011; 59:132–142. [PubMed: 20967885]
- Hvilsted Nielsen H, Toft-Hansen H, Lambertsen KL, Owens T, Finsen B. Stimulation of Adult Oligodendrogenesis by Myelin-Specific T Cells. *Am J Pathol.* 2011; 179:2028–2041. [PubMed: 21872562]
- Imitola J, Raddassi K, Park KI, Mueller F-J, Nieto M, Teng YD, Frenkel D, Li J, Sidman RL, Walsh CA. Directed migration of neural stem cells to sites of CNS injury by the stromal cell-derived factor 1 /CXCR4 chemokine receptor 4 pathway. *Proc Natl Acad Sci USA.* 2004; 101:18117–18122. [PubMed: 15608062]
- Ishii H, Kubo T, Kumanogoh A, Yamashita T. Th1 cells promote neurite outgrowth from cortical neurons via a mechanism dependent on semaphorins. *Biochem Biophys Res Commun.* 2010; 402:168–172. [PubMed: 20946887]
- Ishii H, Jin X, Ueno M, Tanabe S, Kubo T, Serada S, Naka T, Yamashita T. Adoptive transfer of Th1-conditioned lymphocytes promotes axonal remodeling and functional recovery after spinal cord injury. *Cell Death Dis.* 2012; 3:1–10.
- Jacobsen EA, Taranova AG, Lee NA, Lee JJ. Eosinophils: Singularly destructive effector cells or purveyors of immunoregulation? *J Allergy Clin Immunol.* 2007; 119:1313–1320. [PubMed: 17481717]
- Jauneau A-C, Ischenko A, Chatagner A, Benard M, Chan P, Schouft M-T, Patte C, Vaudry H, Fontaine M. Interleukin-1 β and anaphylatoxins exert a synergistic effect on NGF expression by astrocytes. *J Neuroinflammation.* 2006; 3:1–10. [PubMed: 16426448]
- Joly E, Hudrisier D. What is trogocytosis and what is its purpose? *Nat Immunol.* 2003; 4:815–815. [PubMed: 12942076]
- Justicia C, Pan s JN, Sol SN, Cervera L, Deulofeu R, Chamorro N, Planas AM. Neutrophil Infiltration Increases Matrix Metalloproteinase-9 in the Ischemic Brain after Occlusion/Reperfusion of the

- Middle Cerebral Artery in Rats. *J Cereb Blood Flow Metab.* 2003;1430–1440. [PubMed: 14663338]
- Kamel H, Iadecola C. Brain-immune interactions and ischemic stroke: clinical implications. *Arch Neurol.* 2012; 69:576–581. [PubMed: 22782509]
- Khalil M, Ronda J, Weintraub M, Jain K, Silver R, Silverman A-J. Brain mast cell relationship to neurovasculature during development. *Brain Res.* 2007; 1171:18–29. [PubMed: 17764664]
- Kitayama M, Ueno M, Itakura T, Yamashita T. Activated microglia inhibit axonal growth through RGMa. *PLoS ONE.* 2011; 6:e25234. [PubMed: 21957482]
- Kitson RP, Appasamy PM, Nannmark U, Albertsson P, Gabauer MK, Goldfarb RH. Matrix metalloproteinases produced by rat IL-2-activated NK cells. *J Immunol.* 1998; 160:4248–4253. [PubMed: 9574526]
- Kobayashi H, Gleich GJ, Butterfield JH, Kita H. Human eosinophils produce neurotrophins and secrete nerve growth factor on immunologic stimuli. *Blood.* 2002; 99:2214–2220. [PubMed: 11877300]
- Kobayashi NR, Fan DP, Giehl KM, Bedard AM, Wiegand SJ, Tetzlaff W. BDNF and NT-4/5 prevent atrophy of rat rubrospinal neurons after cervical axotomy, stimulate GAP-43 and α -tubulin mRNA expression, and promote axonal regeneration. *J Neurosci.* 1997; 17:9583–9595. [PubMed: 9391013]
- Kostulas N, Li HL, Xiao BG, Huang YM, Kostulas V, HH L. Dendritic Cells Are Present in Ischemic Brain After Permanent Middle Cerebral Artery Occlusion in the Rat. *Stroke.* 2002; 33:1129–1134. [PubMed: 11935071]
- Lalancette-Hebert M, Gowing G, Simard A, Weng YC, Kriz J. Selective Ablation of Proliferating Microglial Cells Exacerbates Ischemic Injury in the Brain. *J Neurosci.* 2007; 27:2596–2605. [PubMed: 17344397]
- Lambertsen KL, Clausen BH, Babcock AA, Gregersen R, Fenger C, Nielsen HH, Haugaard LS, Wirenfeldt M, Nielsen M, Dagnaes-Hansen F, Bluethmann H, Faergeman NJ, Meldgaard M, Deierborg T, Finsen B. Microglia Protect Neurons against Ischemia by Synthesis of Tumor Necrosis Factor. *J Neurosci.* 2009; 29:1319–1330. [PubMed: 19193879]
- Langer HF, Chung K-J, Orlova VV, Choi EY, Kaul S, Kruhlak MJ, Alatsianos M, Deangelis RA, Roche PA, Magotti P, Li X, Economopoulou M, Rafail S, Lambris JD, Chavakis T. Complement-mediated inhibition of neovascularization reveals a point of convergence between innate immunity and angiogenesis. *Blood.* 2010; 116:4395–4403. [PubMed: 20625009]
- Lee TH. Vascular Endothelial Growth Factor Modulates Neutrophil Transendothelial Migration via Up-regulation of Interleukin-8 in Human Brain Microvascular Endothelial Cells. *J Biol Chem.* 2002; 277:10445–10451. [PubMed: 11784713]
- Leon A, Buriani A, Dal Toso R, Fabris M, Romanello S, Aloe L, Levi-Montalcini R. Mast cells synthesize, store, and release nerve growth factor. *Proc Natl Acad Sci USA.* 1994; 91:3739–3743. [PubMed: 8170980]
- Li S, Overman JJ, Katsman D, Kozlov SV, Donnelly CJ, Twiss JL, Giger RJ, Coppola G, Geschwind DH, Carmichael ST. An age-related sprouting transcriptome provides molecular control of axonal sprouting after stroke. *Nat Neurosci.* 2010; 13:1496–1504. [PubMed: 21057507]
- Liu Z, Fan Y, Won SJ, Neumann M, Hu D, Zhou L, Weinstein PR, Liu J. Chronic treatment with minocycline preserves adult new neurons and reduces functional impairment after focal cerebral ischemia. *Stroke.* 2007; 38:146–152. [PubMed: 17122429]
- Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. *Nat Rev Immunol.* 2011; 11:519–531. [PubMed: 21785456]
- Martino G, Pluchino S, Bonfanti L, Schwartz M. Brain regeneration in physiology and pathology: the immune signature driving therapeutic plasticity of neural stem cells. *Physiol Rev.* 2011; 91:1281–1304. [PubMed: 22013212]
- Mattson MP. Glutamate and Neurotrophic Factors in Neuronal Plasticity and Disease. *Ann N Y Acad Sci.* 2008; 1144:97–112. [PubMed: 19076369]
- Meisel C, Schwab JM, Prass K, Meisel A, Dirnagl U. Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci.* 2005; 6:775–786. [PubMed: 16163382]

- Mescher AL, Neff AW. Regenerative capacity and the developing immune system. *Adv Biochem Eng Biotechnol.* 2005; 93:39–66. [PubMed: 15791943]
- Mikami Y, Okano H, Sakaguchi M, Nakamura M, Shimazaki T, Okano HJ, Kawakami Y, Toyama Y, Toda M. Implantation of dendritic cells in injured adult spinal cord results in activation of endogenous neural stem/progenitor cells leading to de novo neurogenesis and functional recovery. *J Neurosci Res.* 2004; 76:453–465. [PubMed: 15114617]
- Mukherjee P, Thomas S, Pasinetti GM. Complement anaphylatoxin C5a neuroprotects through regulation of glutamate receptor subunit 2 in vitro and in vivo. *J Neuroinflammation.* 2008; 5:1–7. [PubMed: 18171484]
- Nakanishi M, Niidome T, Matsuda S, Akaike A, Kihara T, Sugimoto H. Microglia-derived interleukin-6 and leukaemia inhibitory factor promote astrocytic differentiation of neural stem/progenitor cells. *Eur J Neurosci.* 2007; 25:649–658. [PubMed: 17328769]
- Nelissen S, Vanganswinkel T, Geurts N, Geboes L, Lemmens E, Vidal PM, Lemmens S, Willems L, Boato F, Dooley D, Pehl D, Pejler G, Maurer M, Metz M, Hendrix S. Mast cells protect from post-traumatic spinal cord damage in mice by degrading inflammation-associated cytokines via mouse mastcell protease 4. *Neurobiol Dis.* 2014; 62:260–272. [PubMed: 24075853]
- Norrbj K. Mast cells and angiogenesis. Review article. *Apmis.* 2002; 110:355–371. [PubMed: 12076253]
- Okada S, Nakamura M, Katoh H, Miyao T, Shimazaki T, Ishii K, Yamane J, Yoshimura A, Iwamoto Y, Toyama Y, Okano H. Conditional ablation of Stat3 or Socs3 discloses a dual role for reactive astrocytes after spinal cord injury. *Nat Med.* 2006; 12:829–834. [PubMed: 16783372]
- Ousman SS, Kubes P. Immune surveillance in the central nervous system. *Nat Neurosci.* 2012; 15:1096–1101. [PubMed: 22837040]
- Pedersen ED, Waje-Andreassen U, Vedeler CA, Aamodt G, Mollnes TE. Systemic complement activation following human acute ischaemic stroke. *Clin Exp Immunol.* 2004; 137:117–122. [PubMed: 15196251]
- Penna G, Adorini L. 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J Immunol.* 2000; 164:2405–2411. [PubMed: 10679076]
- Perry VH, O'Connor V. The role of microglia in synaptic stripping and synaptic degeneration: a revised perspective. *ASN Neuro.* 2010; 2:281–291.
- Peruzzotti-Jametti L, Cambiaghi M, Bacigaluppi M, Gallizioli M, Gaude E, Mari S, Sandrone S, Corsi M, Teneud L, Comi G, Musco G, Martino G, Leocani L. Safety and Efficacy of Transcranial Direct Current Stimulation in Acute Experimental Ischemic Stroke. *Stroke.* 2013; 44:3166–3174. [PubMed: 23982710]
- Pool M, Rambaldi I, Darlington PJ, Wright MC, Fournier AE, Bar-Or A. Molecular and Cellular Neuroscience. *Mol Cell Neurosci.* 2012; 49:68–76. [PubMed: 21971580]
- Popa N, Cedile O, Pollet-Villard X, Bagnis C, Durbec P, Boucraut J. RAE-1 is expressed in the adult subventricular zone and controls cell proliferation of neurospheres. *Glia.* 2010; 59:35–44. [PubMed: 21046555]
- Rahpeymai Y, Hietala MA, Wilhelmsson U, Fotheringham A, Davies I, Nilsson A-K, Zwirner J, Wetsel RA, Gerard C, Pekny M, Pekna M. Complement: a novel factor in basal and ischemia-induced neurogenesis. *The EMBO Journal.* 2006; 25:1364–1374. [PubMed: 16498410]
- Reitmeir R, Kilic E, Kilic U, Bacigaluppi M, Elali A, Salani G, Pluchino S, Gassmann M, Hermann DM. Post-acute delivery of erythropoietin induces stroke recovery by promoting perilesional tissue remodelling and contralesional pyramidal tract plasticity. *Brain.* 2011; 134:84–99. [PubMed: 21186263]
- Reitmeir R, Kilic E, Reinboth BS, Guo Z, Elali A, Zechariah A, Kilic U, Hermann DM. Vascular endothelial growth factor induces contralesional corticobulbar plasticity and functional neurological recovery in the ischemic brain. *Acta Neuropathol.* 2012; 123:273–284. [PubMed: 22109109]
- Rhodes KE, Fawcett JW. Chondroitin sulphate proteoglycans: preventing plasticity or protecting the CNS? *J Anat.* 2004; 204:33–48. [PubMed: 14690476]

- Ribatti D, Ranieri G, Nico B, Benagiano V, Crivellato E. Tryptase and chymase are angiogenic in vivo in the chorioallantoic membrane assay. *Int J Dev Biol.* 2011; 55:99–102. [PubMed: 21425085]
- Ribatti D, Vacca A, Marzullo A, Nico B, Ria R, Roncali L, Dammacco F. Angiogenesis and mast cell density with tryptase activity increase simultaneously with pathological progression in B-cell non-Hodgkin's lymphomas. *Int J Cancer.* 2000; 85:171–175. [PubMed: 10629073]
- Riboldi E, Musso T, Moroni E, Urbinati C, Bernasconi S, Rusnati M, Adorini L, Presta M, Sozzani S. Cutting edge: proangiogenic properties of alternatively activated dendritic cells. 2005; 175:2788–2792.
- Rossini PM, Calautti C, Pauri F, Baron J-C. Post-stroke plastic reorganisation in the adult brain. *Lancet Neurol.* 2003; 2:493–502. [PubMed: 12878437]
- Saarinen J, Kalkkinen N, Welgus HG, Kovanen PT. Activation of human interstitial procollagenase through direct cleavage of the Leu83-Thr84 bond by mast cell chymase. *J Biol Chem.* 1994; 269:18134–18140. [PubMed: 8027075]
- Sabelström H, Stenudd M, Réu P, Dias DO, Elfineh M, Zdunek S, Damberg P, Göritz C, Frisén J. Resident neural stem cells restrict tissue damage and neuronal loss after spinal cord injury in mice. *Science.* 2013; 342:637–640. [PubMed: 24179227]
- Sayed BA, Walker ME, Brown MA. Cutting Edge: Mast Cells Regulate Disease Severity in a Relapsing-Remitting Model of Multiple Sclerosis. *J Immunol.* 2011; 186:3294–3298. [PubMed: 21325623]
- Scapini P, Morini M, Tecchio C, Minghelli S, Di Carlo E, Tanghetti E, Albin A, Lowell C, Berton G, Noonan DM, Cassatella MA. CXCL1/macrophage inflammatory protein-2-induced angiogenesis in vivo is mediated by neutrophil-derived vascular endothelial growth factor-A. *J Immunol.* 2004; 172:5034–5040. [PubMed: 15067085]
- Schwartz M, Kipnis J. Protective autoimmunity: regulation and prospects for vaccination after brain and spinal cord injuries. *Trends Mol Med.* 2001; 7:252–258. [PubMed: 11378514]
- Schwartz M, Shechter R. Protective autoimmunity functions by intracranial immunosurveillance to support the mind: The missing link between health and disease. *Mol Psychiatry.* 2010; 15:342–354. [PubMed: 20332793]
- Shechter R, Raposo C, London A, Sagi I, Schwartz M. The glial scar-monocyte interplay: a pivotal resolution phase in spinal cord repair. *PLoS ONE.* 2011; 6:1–13.
- Shinjo N, St hlberg A, Dragunow M, Pekny M, Pekna M. Complement-Derived Anaphylatoxin C3a Regulates In Vitro Differentiation and Migration of Neural Progenitor Cells. *Stem Cells.* 2009; 27:2824–2832. [PubMed: 19785034]
- Silver J, Miller JH. Regeneration beyond the glial scar. *Nat Rev Neurosci.* 2004; 5:146–156. [PubMed: 14735117]
- Snayyan M, Lemasson M, Brill MS, Blais M, Massouh M, Ninkovic J, Gravel C, Berthod F, Gotz M, Barker PA, Parent A, Saghatelian A. Vasculature Guides Migrating Neuronal Precursors in the Adult Mammalian Forebrain via Brain-Derived Neurotrophic Factor Signaling. *J Neurosci.* 2009; 29:4172–4188. [PubMed: 19339612]
- Solerte SB, Ferrari E, Cuzzoni G, Locatelli E, Giustina A, Zamboni M, Schifino N, Rondanelli M, Gazzaruso C, Fioravanti M. Decreased Release of the Angiogenic Peptide Vascular Endothelial Growth Factor in Alzheimer's Disease: Recovering Effect with Insulin and DHEA Sulfate. *Dement Geriatr Cogn Disord.* 2005; 19:1–10. [PubMed: 15383738]
- Stephan AH, Barres BA, Stevens B. The complement system: an unexpected role in synaptic pruning during development and disease. *Annu Rev Neurosci.* 2012; 35:369–389. [PubMed: 22715882]
- Stevens B, Allen NJ, Vazquez LE, Howell GR, Christopherson KS, Nouri N, Micheva KD, Mehalow AK, Huberman AD, Stafford B, Sher A, Litke AM, Lambris JD, Smith SJ, John SWM, Barres BA. The classical complement cascade mediates CNS synapse elimination. *Cell.* 2007; 131:1164–1178. [PubMed: 18083105]
- Stirling DP, Liu S, Kubes P, Yong VW. Depletion of Ly6G/Gr-1 Leukocytes after Spinal Cord Injury in Mice Alters Wound Healing and Worsens Neurological Outcome. *J Neurosci.* 2009; 29:753–764. [PubMed: 19158301]
- Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell.* 2010; 140:805–20. [PubMed: 20303872]

- Tchougounova E, Lundquist A, Fajardo I, Winberg J-O, Abrink M, Pejler G. A key role for mast cell chymase in the activation of pro-matrix metalloprotease-9 and pro-matrix metalloprotease-2. *J Biol Chem*. 2005; 280:9291–9296. [PubMed: 15615702]
- Thored P, Arvidsson A, Cacci E, Ahlenius H, Kallur T, Darsalia V, Ekdahl CT, Kokaia Z, Lindvall O. Persistent Production of Neurons from Adult Brain Stem Cells During Recovery after Stroke. *Stem Cells*. 2006; 24:739–747. [PubMed: 16210404]
- Thored P, Heldmann U, Gomes-Leal W, Gisler R, Darsalia V, Taneera J, Nygren JM, Jacobsen S-EW, Ekdahl CT, Kokaia Z, Lindvall O. Long-term accumulation of microglia with proneurogenic phenotype concomitant with persistent neurogenesis in adult subventricular zone after stroke. *Glia*. 2009; 57:835–849. [PubMed: 19053043]
- Thored P, Wood J, Arvidsson A, Cammenga J, Kokaia Z, Lindvall O. Long-Term Neuroblast Migration Along Blood Vessels in an Area With Transient Angiogenesis and Increased Vascularization After Stroke. *Stroke*. 2007; 38:3032–3039. [PubMed: 17901386]
- Van Beek J, Nicole O, Ali C, Ischenko A, MacKenzie ET, Buisson A, Fontaine M. Complement anaphylatoxin C3a is selectively protective against NMDA-induced neuronal cell death. *Neuroreport*. 2001; 12:289–293. [PubMed: 11209937]
- Walther M, Kuklinski S, Pesheva P, Guntinas-Lichius O, Angelov DN, Neiss WF, Asou H, Probstmeier R. Galectin-3 is upregulated in microglial cells in response to ischemic brain lesions, but not to facial nerve axotomy. *J Neurosci Res*. 2000; 61:430–435. [PubMed: 10931529]
- Wang J, Yang Z, Liu C, Zhao Y, Chen Y. Activated microglia provide a neuroprotective role by balancing glial cell-line derived neurotrophic factor and tumor necrosis factor- α secretion after subacute cerebral ischemia. *Int J Mol Med*. 2013; 31:172–178. [PubMed: 23151666]
- Wang T, Lee M-H, Johnson T, Allie R, Hu L, Calabresi PA, Nath A. Activated T cells Inhibit Neurogenesis by Releasing Granzyme B: Rescue by Kv1.3 blockers. *J Neurosci*. 2010; 30:5020–5027. [PubMed: 20371822]
- Warrington AE, Bieber AJ, Van Keulen V, Ciric B, Pease LR, Rodriguez M. Journal of Neuropathology and Experimental Neurology 2004 Warrington. *J Neuropathol Exp Neurol*. 2004; 63:461–473. [PubMed: 15198125]
- Weerth SH, Rus H, Shin ML, Raine CS. Complement C5 in experimental autoimmune encephalomyelitis (EAE) facilitates remyelination and prevents gliosis. *Am J Pathol*. 2003; 163:1069–1080. [PubMed: 12937147]
- Wieloch T, Nikolich K. Mechanisms of neural plasticity following brain injury. *Curr Opin Neurobiol*. 2006; 16:258–264. [PubMed: 16713245]
- Wilhelm M, Silver R, Silverman AJ. Central nervous system neurons acquire mast cell products via transgranulation. *Eur J Neurosci*. 2005; 22:2238–2248. [PubMed: 16262662]
- Wright BR, Warrington AE, Edberg DE, Rodriguez M. Cellular Mechanisms of Central Nervous System Repair by Natural Autoreactive Monoclonal Antibodies. *Arch Neurol*. 2009; 66:1456–1459. [PubMed: 20008649]
- Xie L, Poteet EC, Li W, Scott AE, Liu R, Wen Y, Ghorpade A, Simpkins JW, Yang S-H. Modulation of polymorphonuclear neutrophil functions by astrocytes. *J Neuroinflammation*. 2010; 7:53. [PubMed: 20828397]
- Yang H, Feng G-D, Liang Z, Vitale A, Jiao X-Y, Ju G, You S-W. In vitro beneficial activation of microglial cells by mechanically-injured astrocytes enhances the synthesis and secretion of BDNF through p38MAPK. *Neurochem Int*. 2012; 61:175–186. [PubMed: 22561407]
- Yin Y, Henzl MT, Lorber B, Nakazawa T, Thomas TT, Jiang F, Langer R, Benowitz LI. Oncomodulin is a macrophage-derived signal for axon regeneration in retinal ganglion cells. *Nat Neurosci*. 2006; 9:843–852. [PubMed: 16699509]
- Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain Behav Immun*. 2011; 25:181–213. [PubMed: 20970492]
- Zhang H, Verkman AS. Eosinophil pathogenicity mechanisms and therapeutics in neuromyelitis optica. *J Clin Invest*. 2013; 123:2306–2316. [PubMed: 23563310]
- Ziv Y, Schwartz M. Immune-based regulation of adult neurogenesis: implications for learning and memory. *Brain Behav Immun*. 2008; 22:167–176. [PubMed: 17905567]
- Zlokovic BV. Remodeling after stroke. *Nat Med*. 2006; 12:390–391. [PubMed: 16598283]

Zuo J, Neubauer D, Dyess K, Ferguson TA, Muir D. Degradation of chondroitin sulfate proteoglycan enhances the neurite-promoting potential of spinal cord tissue. *Exp Neurol*. 1998; 154:654–662. [PubMed: 9878200]

Highlights

- Early immune activation after acute CNS injury might have neuroprotective effects.
- Sustained inflammation profoundly shapes functional and structural plasticity within the CNS
- Modulation of the innate or adaptive immune responses represents a promising approach to treat acute CNS disorders.

Figure 1. Evolution of plasticity processes and immune cells activation after acute CNS damage
 Innate and adaptive components of the immune system have been shown to play a crucial role in CNS plasticity mechanisms upon injury/inflammation. The role played by these components during the pro-inflammatory and the pro-tissue healing phases are incredibly strict, overlapped and still far from being completely elucidated. Increasing evidence has demonstrated an indispensable role for immune system components in CNS plasticity events including brain blood barrier (BBB) and extracellular matrix (ECM) remodelling (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 grey bars represent the dynamic accumulation and activation of immune cells within the injured CNS. The horizontal arrow represents the time after injury.

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

Abbreviations: nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase; radical oxygen species (ROS); interleukin (IL); brain-derived neurotrophic factor (BDNF); nerve growth factor (NGF); neurotrophin (NT); matrix metalloprotease (MMP); myeloperoxidase (MPO), vascular endothelial growth factor (VEGF); transforming growth factor (TGF); platelet-derived growth factor (PDGF); tumor necrosis factor (TNF); leukemia inhibitory factor (LIF); eosinophil-derived neurotoxin (EDN); interferon (IFN); mouse mast cell protease (mMCP); fibroblast growth factors (FGFs); endothelial-like cells (ELCs); insulin-like growth factor (IGF) ribonucleic acid export (RAE); semaphorin-4A (Sema4a); sonic hedgehog homolog (SHH); neurogenin (NGN); natural autoantibodies (NAA); hydrogen peroxide (H₂O₂).

	Complement	Neutrophils	Eosinophils	Mast cells	Dendritic cells	Microglia/ Macrophages	NK cells	T cells	B cells
ECM remodelling	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 (Nakanishy et al., 2007)		Increased TNF signalling (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 (Warrington et al., 2004; Yin et al., 2006), BDNF (Coull et al., 2005; Kobayashi et al., 1997)	IFN-γ (Rahpeymai et al., 2006; Hao et al., 2010), BDNF, NT-3 (Hammarberg et al., 2000; Shinjiyo et al., 2009)	Sema4A, NT-3 (Bénard et al., 2008; Ishii et al., 2012)	NAA (modulation of H₂O₂-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 et al., 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 (Solerie et al., 2005)		
Neurogenesis	C3 (Mikami et al., 2004; Rahpeymai et al., 2006; Shinjiyo et al., 2009), C5 (Benard et al., 2008; Popa et al., 2010).	BDNF, NGF, NT-4 (Schwartz and Shechter, 2010; Mantovani, 2011)	EDN, TNF-α, IFN-γ	Serotonin, NGF	NT-3 (Mikami, 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)	