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REVIEW ARTICLE

The role of the microglia in acute CNS injury

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Abstract Microglia are considered the brain's resident immune cell involved in immune defense, immunocompetence, and phagocytosis. They maintain tissue homeostasis within the brain and spinal cord under normal condition and serves as its initial host defense system. However, when the central nervous system (CNS) faces injury, microglia respond through signaling molecules expressed or released by neighboring cells. Microglial responses are dual in nature. They induce a nonspecific immune response that may exacerbate CNS injury, especially in the acute stages, but are also essential to CNS recovery and repair. The full range of microglial mechanisms have yet to be clarified, but there is accumulating knowledge about microglial activation in acute CNS injury. Microglial responses require hours to days to fully develop, and may present a therapeutic target for intervention with a much longer window of opportunity compare to other neurological treatments. The challenge will be to find ways to selectively suppress the deleterious effects of microglial activation without compromising its beneficial functions. This review aims to provide an overview of the recent progress relating on the deleterious and beneficial effect of microglia in the setting of acute CNS injury and the potential therapeutic intervention against microglial activation to CNS injury.

Keywords Microglia · Inflammation · Brain · Spinal cord · Stroke · Trauma

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Introduction

Microglia represent anywhere from 5 to 20 % of the total glial population and are key modulators of the immune response in the brain (Kreutzberg 1996). Under normal physiological conditions, these highly dynamic and motile cells are spread throughout the brain and spinal cord and constantly survey their microenvironment for noxious agents and injurious processes (Nimmerjahn et al. 2005). They respond to extracellular signals and are responsible for clearing debris and toxic substances by phagocytosis, thereby maintaining normal cellular homeostasis in the central nervous system (CNS) (Hanisch and Kettenmann 2007). Therefore, under non-pathological conditions there is continuous low-level microglial activity in the CNS which is primarily involved in activity-dependent synaptic pruning and repair (El Khoury et al. 1998).

However, in the event of infection, inflammation, trauma, ischemia, and neurodegeneration, microglia quickly respond and can undergo morphologic transformation from a resting state referred to as "ramified" to an active "amoeboid" state, where they become virtually indistinguishable from circulating macrophages (Kreutzberg 1996; Thomas 1992). Therefore, activated microglia are often called "resident brain macrophages". This is also stems from the fact that microglia are of mesodermal origin as are macrophages. The origin of brain microglia and whether microglia are renewed in situ or are replenished by precursors originating outside of the CNS is the subject of controversy (Lawson et al. 1992; Priller et al. 2001; Simard et al. 2006; Ajami et al. 2007; Mildner et al. 2007). The current thinking is that embryonic hemoatopoietic waves of microglial recruitment and differentiation occur in the CNS, and that maintenance and local expansion of microglia are solely dependent on the self-renewal of CNS resident cells (Ajami et al. 2007; Ginhoux et al. 2010), rather than continuous replenishment from the periphery.

Microglial normally display a ramified appearance, but when activated, microglia become amoeboid and it are indistinguishable from macrophages and circulating monocytes, not only morphologically, but also with regard to surface markers and function (Saijo and Glass 2011; Appel et al. 2011). Despite the many similarities between microglia and macrophages, there are a few reports regarding cell type specific gene transcription mechanisms in these tow cell types (Durafourt et al. 2012; Lee et al. 2014). There are also several reports using bone marrow chimera model obtained by transplantation of lethally irradiated recipients to distinguish the microglia to macrophages (Tang et al. 2012b; Evans et al. 2014). However, due to technical issues, such as BBB disruption by irradiation permitting influx of circulating myeloid cells, limit the interpretation of data generated by this approach (Ajami et al. 2007; Ginhoux et al. 2010).

Accumulating evidence now indicates that activated microglial responses can be detrimental as well as beneficial after CNS injury (Fig. 1). Once activated, microglia are thought to release a variety of inflammatory and cytotoxic mediators contributing to cell damage and cell death leading to exacerbated damage (Wood 1995; Lai and Todd 2006). Deleterious effects seem to be predominated especially in the acute stages of CNS injury, while beneficial activities characterize later stages. Recent studies demonstrated that microglia and macrophages can be activated into two major phenotypes: classically activated (M1) and alternatively activated (M2) (Chawla 2010; Gordon and Taylor 2005; Geissmann et al. 2010). Lipopolysaccharide (LPS) and the pro-inflammatory cytokine IFNγ promote M1 phenotype, which produces high levels of pro-inflammatory cytokines and oxidative metabolites such as IL-12, TNF-α, IL-6, IL-1β, and nitric oxide (NO), factors previously shown to cause additional damage. In contrast, M2 cells are activated in response to IL-4 or IL-13 (Nair et al. 2006; Nguyen et al. 2011), which are thought to suppress inflammation, tissue repair, and promote wound healing (Colton 2009). Hu et al. and Wang et al. recently reported that local microglia and recruited macrophages assume a M2 phenotype at an early stage, peaking at around 5 days from injury, gradually transforming into a M1 phenotype at the sites of injury in ischemic stroke and traumatic brain injury. The M1 phenotype seems to be primed by ischemic neurons and leads to exacerbated neuronal damage, whereas M2 protects against it (Hu et al. 2012; Wang et al. 2013). This raises the importance of the understanding of different phenotype and their function of microglia (Mantovani et al. 2004; Mosser and Edwards 2008).

Microglia require longer time windows to fully develop as described later, and thus presents a good target for therapeutic intervention with a much longer window of opportunity compare to other neurological treatment. The challenge will be to find ways to selectively suppress the deleterious effects of microglial activation after CNS injury without compromising repair and remodeling.

In this review, the authors will focus on the deleterious and beneficial effect of microglia in the setting of acute CNS injury and the potential therapeutic intervention against microglial activation to the CNS injury.

Mechanisms of microglial cytotoxicity and cellular protection

Microglia, like macrophages, respond to invading pathogens by facilitating rapid sequestration and killing of microorganisms and limit the effects of damage and cell necrosis

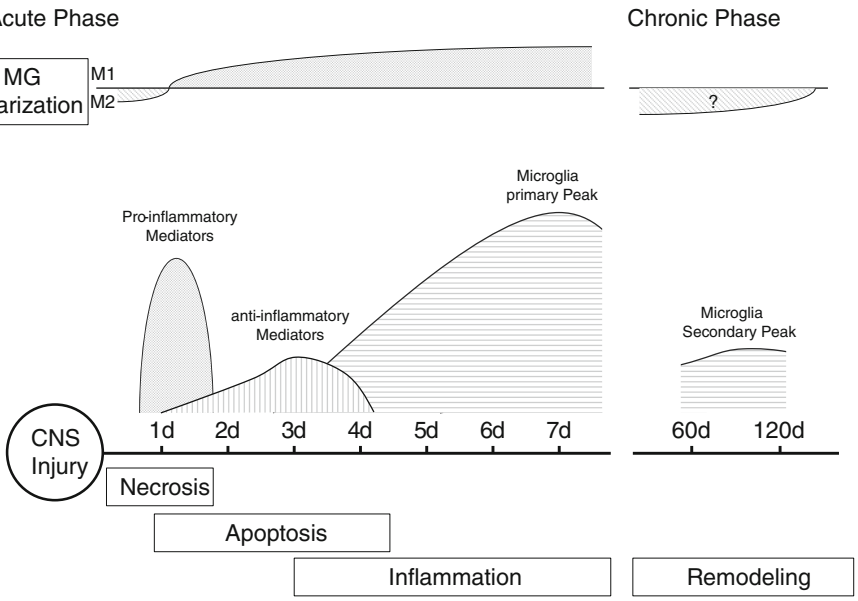

Fig. 1 Schematic of the time course of microglial activation after CNS injury. Temporal evolution of M1 and M2 microglial polarization ratios is indicated

(Ransohoff and Perry 2009). These responses include rapid migration, proliferation, and release of superoxide, nitric oxide (NO), proteases, cytokines, and phagocytosis of the damaged cells. However, some of these reactions may lead to deleterious effects to the CNS.

Superoxide and nitric oxide

Superoxide, produced by the partial reduction of molecular oxygen, is a reactive species which interacts with other molecules to produce more highly reactive oxygen species, such as peroxynitrite, hypochlorous acid, carbonyl radical, and hydroxyl radical, all of which are directly cytotoxic to neurons and other cells. Superoxide and other reactive species are also pro-inflammatory signaling molecules which promote microglial activation in a feed-forward manner (Mander et al. 2006; Kauppinen et al. 2008). The production of superoxide in microglia occurs primarily by NADPH oxidase (NOX), of which several isoforms have been characterized (Groemping and Rittinger 2005; Lambeth 2004). The major isoform found in immune cells including microglia is NOX2, or professional NOX. Activation of NOX through has been demonstrated in brain ischemia and related disorders, and its inhibition or deficiency has been shown to be protective (Tang et al. 2012a). While NOX2 is present in both microglia and circulating immune cells, one study using a bone marrow chimera model suggested that the detrimental effects of NOX-generated superoxide was due to NOX present in brain cells (Walder et al. 1997). However, work from our own group using a similar approach indicated that while superoxide generated by NOX in both microglia and circulating immune cells contributed to ischemic brain injury (Tang et al. 2011; Yenari et al. 2006), NOX in circulating immune cells contributed more to injury.

Nitric oxide (NO) is another major reactive species produced by immune cells. Activated microglia produce NO through inducible nitric oxide synthase (iNOS). The cytotoxicity of NO is thought to be due primarily to its reactive metabolite, peroxynitrite, which is formed by reaction with superoxide (Beckman and Koppenol 1996). However, like superoxide, NO is also a powerful signaling molecule, and also promotes pro-inflammatory responses in a feed forward manner.

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are proteases that can break down extracellular proteins, such as collagen, and are involved in extracellular matrix remodeling. MMPs are normally found in the microglial cytosol as an inactivated state, they are cleaved by proteases such as plasmin or other MMPs to their active state (Rosenberg 2002). Some MMPs, notably MMP-2 also have direct cytotoxic effects and can disrupt the blood–brain barrier (Candelario-Jalil et al. 2009). Microglia are the major source of MMP, especially MMP-3 and -9 (Rosenberg et al. 2001; del Zoppo et al. 2007). Recent work has indicated that fibronectin and vitronectin, substances typically found in the plasma, can activate microglial cells to generate pro-MMP-9 (del Zoppo et al. 2012). Bone marrow chimera models, where bone marrow of host animals is transplanted with marrow from host marrow, have shown that MMPs derived from immune cells contribute to worsened ischemic injury, although the contribution from leukocytes appears more significant that that contributed by microglia (Gidday et al. 2005; Wang et al. 2009).

Chemokines, cytokines, and trophic factors

Resting microglia release a variety of chemokines and cytokines, and pattern of this release is dramatically altered after CNS injury (Lucas et al. 2006). These factors function primarily as intercellular signaling molecules, and many have feed-forward effects in driving the inflammatory response. Some, such as tumor necrosis factor-α (TNFα), can also have direct cytotoxic effects and promote disruption of the blood–brain barrier (Shohami et al. 1999; Vexler et al. 2006). On the other hand, microglia also release a number of neurotrophic factors, such as TGFβ1, BDNF, and GDNF, and these are thought to be important in maintaining neuronal integrity after CNS injury (Lehrmann et al. 1998; Suzuki et al. 1999; Lee et al. 2002; Batchelor et al. 1999).

Phagocytosis

Microglia and macrophages phagocytose injured cells, thereby clearing necrotic debris and setting the stage for recovery. A few signals that lead to phagocytosis have been recently identified. One model proposes that necrotic cells release nucleic acid remnants into the extracellular space where they can bind appropriate receptors on phagocytes. Some of these phagocytosis initiating signals have been referred to as DAMPs, or danger associated molecular patterns (An et al. 2013). Those identified in stroke and related injury models include purines such as UTP, ADP and ATP, and signal through purinergic receptor systems to lead to phagocytosis (Koizumi et al. 2007). However, phagocytosis through these signaling systems, while leading to the clearance of injured cells, may also worsen cell death either by causing microglia to phagocytose viable cells or generate neurotoxic substances (Emmrich et al. 2013; Neher et al. 2013). Our laboratory has recently begun to study a recently characterized microglial receptor, triggering receptor expressed on myeloid cells (TREM2). TREM2 was originally characterized by its ability to bind pathogens such as bacteria and initiate phagocytosis (N'Diaye et al. 2009). It has been described on activated macrophages and microglia (Sessa et al. 2004; Takahashi

et al. 2005; Daws et al. 2001), and binds to one or more ill-defined ligands on eukaryotic cells including neurons and astrocytes (Hsieh et al. 2009; Stefano et al. 2009; Daws et al. 2003). TREM2 has been shown to mediate phagocytosis of apoptotic neurons without stimulating a typical inflammatory response (Hsieh et al. 2009). Conversely, loss of TREM2 impairs phagocytosis and promotes inflammation (Takahashi et al. 2005). In a model of neuroprotection by therapeutic hypothermia, our group found that while therapeutic cooling led to decreased activated microglia and other pro-immune responses, TREM2 was actually increased on microglia of brains protected from ischemia, suggesting that TREM2 was correlated to improved stroke outcome (Kawabori et al. 2013). Thus, some phagocytic pathways of microglia may potentiate damage, while other pathways may ameliorate it. Preliminary work in our lab suggests that preventing phagocytosis by deleting TREM2 may exacerbate functional neurological recovery (Kawabori et al., International Stroke Conference 2014 abstract).

Phagocytic activities of microglia are also shown to regulate the numbers of synapses and affect the structural plasticity of the CNS. Microglia are engaged in the regulation and remodeling of synapses both in perinatal and postnatal periods (Ji et al. 2013; Paolicelli et al. 2011). These observations highlight the fact that microglial activities are crucial not only under pathological condition, but also under physiological condition.

Microglial activation in stroke

Stroke is a leading cause of death and disability in the industrialized world (Onwuekwe and Ezeala-Adikaibe 2012; Towfighi and Saver 2011). Stroke is a heterogeneous condition consisting of several subtypes. Regardless, stroke can be broadly categorized into ischemic and hemorrhagic types. Microglia have been documented to play an important role in both, contributing to inflammatory responses both negatively and positively.

Microglia in ischemic stroke

Ischemic stroke constitutes 87 % of all strokes and is caused by the occlusion of a blood vessel due to either embolism or thrombus. As a result, brain tissue is deprived of blood glucose and oxygen. This leads to neuronal death, release of reactive oxygen species and other substances. Many of these molecules are shown to activate microglia and causes secondary damage to the injured and alive cells that escaped the damage (Yenari and Han 2012; Taylor and Sansing 2013). Accumulating data shows that TNF-α, glutamate, heat shock protein (HSP), Adenosine triphosphate (ATP), CD14 receptors, followed by toll-like receptor 4 (TRL4) have been documented in activated microglia in the infarct brain (Saito et al. 2000; Beschorner et al. 2002b; Lehnardt et al. 2003).

Activated microglia can be detected as early as 2 h after ischemia, whereas blood-derived macrophages do not enter the brain before 10 h. By 22–46 h after the insult, activated microglia and macrophages are distributed throughout the entire lesion and are detectable up to 1 week after the insult (Zhang et al. 1995; Nilupul Perera et al. 2006; Stoll et al. 1998; Dirnagl et al. 1999; Clausen et al. 2008).

Direct evidence supporting a damaging role of microglia/macrophages was demonstrated when their direct application potentiated neuron cell death (Giulian et al. 1993; Lehnardt et al. 2003; Zhang et al. 1997; Huang et al. 2010), and microglia were also shown to express and release various kind of inflammatory mediators as described above, most of which are cytotoxic. Recent work has shown that microglia can potentiate injury to blood–brain barrier constituents (astrocytes and endothelial cells) via NOX-mediated superoxide in cell culture models of ischemia (Yenari et al. 2006). Several groups also show that mice deficient in the gp91 subunit of NOX2 have smaller infarcts than do wild-type mice (Kahles et al. 2007; Walder et al. 1997; Chen et al. 2009), and that outcomes from experimental cerebral ischemia reperfusion are improved with early administration of the pharmacological NOX inhibitor, apocynin (Chen et al. 2009; Tang et al. 2007; Tang et al. 2005; Tang et al. 2008). Pharmacological inhibition of iNOS reduces infarct volume (Iadecola et al. 1995), and iNOS null mice have smaller infarcts and better neurological outcomes than wild-type control animals (Zhao et al. 2000). Therapeutic hypothermia after ischemia likewise reduces microglial iNOS expression and NO production (Han et al. 2002). Inhibition of MMP at the acute stage of ischemia are also shown to reduce infarct size, brain edema, and recombinant tissue plasminogen activator-induced hemorrhage (Pfefferkorn and Rosenberg 2003), and mice deficient in MMP-9 or MMP-3 have reduced ischemic injury compare to wild-type (Asahi et al. 2000; Walker and Rosenberg 2009). However, because of the neurovascular remodeling function of the protease, prolonged inhibition of MMPs after ischemia may have deleterious effects on function recovery (Zhao et al. 2006). Of translational relevance, the widely used antiplatelet agent, clopidogrel, is also an antagonist of the P2Y12 purinergic receptor. P2Y12 is known to mediate microglial chemotaxis under conditions of injury. P2Y12 deletion or its inhibition by clopidogrel led to reduced microglial migration to areas of injury, and also protected the brain from global cerebral ischemia (Webster et al. 2013).

In addition to the pro-inflammatory aspects of microglia, microglia have also been shown to have anti-inflammatory properties, which are neuroprotective. Microglia produce the growth factor TGF-β1 (Watanabe et al. 2000; Lai and Todd 2006). When microglial proliferation was inhibited in transgenic mice, infarct size was increased following ischemia, and

suggests that proliferating microglia cells exert a beneficial role (Lalancette-Hebert et al. 2007). There are some possible mechanisms underlying these observations. First, microglia produce neurotrophic factors which stimulate neurogenesis and plasticity. Secondly, phagocytosis of neutrophils by activated microglia may prevent the release of toxic mediators (Weston et al. 2007; Frank-Cannon et al. 2009). Finally, resident macrophages scavenge and remove necrotic debris and other potentially harmful substances (Frank-Cannon et al. 2009).

Minocycline, a tetracycline family antibiotic, was shown to provide significant protection against brain ischemia by inhibiting microglial activation and proliferation (Yrjanheikki et al. 1998; Yrjanheikki et al. 1999), and minocycline has shown to protect against permanent cerebral ischemia in wild-type but not in MMP-9 deficient mice (Koistinaho et al. 2005). Edaravone, a novel free radical scavenger, significantly reduced infarct volume and improved neurological deficit scores for ischemic mice by reducing microglial activation (Zhang et al. 2005). In spontaneously hypertensive rats with permanent MCAO, repetitive hyperbaric oxygen (HBO) treatment reduced infarct volume by suppressing microglia activation (Gunther et al. 2005). Protection by hypothermia has been shown to be related, in part, to inhibiting microglial activation and reducing elaboration of many pro-inflammatory immune molecules (Yenari and Han 2012; Han et al. 2002). However, as mentioned above, hypothermic neuroprotection has also been associated with the upregulation of the pro-phagocytic molecule, TREM2 (Kawabori et al. 2013).

Recombinant human tissue plasminogen activator (rt-PA) is the only approved thrombolytic treatment of ischemic stroke at the current medical practice. Beside from its thrombolytic aspect, recent evidence shows that t-PA and its substrate plasmin enhances microglial cell activation and recruitment to the injured site through several chemokines. Activated microglia are shown to exacerbate the neurological damage after ischemic stroke (Sheehan et al. 2007; Lenglet et al. 2014).

Microglia in intracerebral hemorrhage (ICH)

Intracerebral hemorrhage occurs when a blood vessels in the brain parenchyma ruptures, most commonly due to hypertension and accounts for 10–15 % of all strokes (Manno 2012). ICH has a high mortality rate: 30–50 % of patients die within the first 30 days (Qureshi et al. 2009). Despite the recent advances in the intracerebral hemorrhage research, no specific treatment for this currently exists (Morgenstern et al. 2010). The introduction of blood components, including thrombin, heme, and leukocytes and platelets, into the brain creates the basis for a secondary injury due to microglial activation and neuroinflammation resulting in the recruitment of leukocytes into a normally immune privileged site (Keep et al. 2012).

Microglial activation may also have a dual role after ICH. While some microglial activities may be beneficial, microglia have also been shown to play a role in the secondary injury that occurs after ICH (Keep et al. 2012). A major role of microglial cells after ICH is to phagocytose the debris and red blood cells left in the brain after hemorrhage. They have been shown to endocytose heme and hemoglobin. These processes are mediated through scavenger receptors, such as CD36 (Aronowski and Zhao 2011). As in the case of ischemic stroke, microglia also produce proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, in models of ICH (Wang 2010; Aronowski and Zhao 2011; Wang and Dore 2007b).

The activation of microglia/macrophage occurs early following ICH. Activated microglia have been observed within the peri-hematomal region as early as 1 h following in the collagenase model ICH (where collagenase disrupts extracellular matrix proteins and causes primary brain hemorrhage) and within 4 h in the ICH model where whole blood is directly injected into the brain (Wang and Dore 2007a; Xue and Del Bigio 2000). Microglial production of IL-1β in rats can be seen as early as 6 h and can persist up to 24 h (Wasserman et al. 2007). The numbers of the activated microglia/macrophages reaches peak at around 72 h in the peri-hematomal region, and returns to basal levels between 3 and 4 weeks (Wang 2010; Yabluchanskiy et al. 2010).

Mediators of microglial activation after ICH have also been studied and some candidates have been found to activate the microglia (Donovan et al. 1997). Thrombin, a serine protease necessary for coagulation, has been shown to play a pivotal role. Direct injection of thrombin into the striatum led to upregulation of CD11b in microglia, and microglia changed from the resting, ramified to activated morphology to an amoeboid shape within 4 h. Activated microglia were also immunopositive for iNOS by 24 h and the number of microglia/macrophages were increased by 72 h (Fujimoto et al. 2007). The effect of thrombin on microglial proinflammatory cytokine and MMPs has also been described. Microglia express thrombin receptors and produce IL-1β, TNF-α, and MMP-9 when stimulated with thrombin (Wu et al. 2008; Xue et al. 2006). Product of red blood cell lysis, including heme and iron, are also active initiators of microglial activation and neuroinflammation (Wu et al. 2008).

Microglia in subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH), especially aneurysmal SAH, is often a catastrophic condition of CNS. Although accounting for only 5 % of all strokes, SAH imposes a significant burden on society and economy, as it affects mainly middle-aged patients, leading to high mortality and disability rates (Venti 2012). Early and delayed brain injury after

SAH have been well documented, but the underlying mechanisms especially the effect of neuroinflammation have not been well elucidated. Recent findings have highlighted a strong contribution of neuroinflammation to the early brain injury, the vasospasm after SAH (Fassbender et al. 2001; Pradilla et al. 2010). A total of 30 to 40 % of aneurysmal SAH patients will have delayed cerebral ischemia from vasospasm, anywhere from 4 to 14 days after the insult, resulting in increased morbidity and mortality. A recent report from Hanafy showed that microglia and the TLR4 signaling pathway play important roles in the development of vasospasm and also in the acute phase of neuronal apoptosis after SAH (Hanafy 2013). Deficiency of TLR4 downstream adaptor molecules MyD88 and TRIF reduced vasospasm as well as neuronal apoptosis. Conversely, another group showed that administration of the TLR4 agonist, lipopolysaccharide (LPS) worsened vasospasm (Smithason et al. 2012).

Microglial activation in trauma

Traumatic brain injury (TBI) and spinal cord injury (SCI) are the leading cause of morbidity and mortality in the younger generations, and have substantial direct, and indirect cost to society (Potts et al. 2006). TBI and SCI are a highly complex disorders caused by both primary and secondary injury mechanisms (Kumar and Loane 2012). Primary injury mechanisms result from the mechanical damage that occurs at the time of trauma to neurons, axons, glia and blood vessels as a result of shearing, tearing, or stretching, consequently these damages induce secondary injury mechanisms that evolve over minutes to days after the initial traumatic insult and result from delayed neuronal damage (McIntosh et al. 1996). The secondary injury includes delayed events, such as ischemia, lipid degradation, free radical formation, excitotoxity, and protease release (Bao et al. 2005; Hausmann 2003), leading to demyelination, axonal degeneration, neuronal death, cavitation, and glial scarring surrounding the area of initial damage (Fitch et al. 1999; Dusart and Schwab 1994; Koshinaga and Whittemore 1995). Inflammation by microglia is thought to play an important role in these expanded secondary damage (Potts et al. 2006; Hausmann 2003), as they not only release proinflammatory cytokines, but rapidly recruit other immune cells and exacerbate injury (Dusart and Schwab 1994; Kigerl et al. 2009). However, as described before, these microglial responses are thought to have not only harmful effects, but beneficial effects as shown in stroke models.

Similar to the response in stroke, microglia have been shown to react within a few hours with a migratory response toward the lesion site following CNS trauma. In fact, in vivo two-photon microscopy imaging studies of microglia following laser-induced injury documented rapid proliferation and movement of ramified microglial cells to the site of injury in response to extracellular ATP released by the injured tissue (Davalos et al. 2005; Haynes et al. 2006). Microglial processes then coalesce to form an area of containment between healthy and injured tissues, suggesting that microglia may represent the first line of defense following injury (Davalos et al. 2005). In human TBI, microglial activation has been reported as early as 72 h after injury (Engel et al. 2000), and can remain elevated for months after injury as well as in the rodent model of TBI (Beschorner et al. 2002a; Gentleman et al. 2004; Csuka et al. 2000; Maeda et al. 2007).

Previous studies have shown that microglia and blood-derived macrophages release potentially neurotoxic agents after spinal cord injury (reactive oxygen species; NO and peroxynitrite, cytokines; TNF-α and IL-1β) (Satake et al. 2000; Bao et al. 2004). Activation of microglia/macrophages through Toll-like receptors (TLRs) induces neuronal cell death and neurite degeneration (Fitch et al. 1999; Lehnardt et al. 2002; Popovich et al. 2002). White matter is also quite sensitive to these immune molecules, and treatments aimed at reducing the microglial/macrophage response and subsequent neurotoxicity are often protective (Blight 1994; Popovich et al. 1999; Park et al. 2004; Byrnes et al. 2009). These interventions may be expected to prevent the second late phase of axonal dieback (Stirling et al. 2004; Horn et al. 2008). IL-1β, and TNF-α levels are also elevated in both the serum and CSF of patients with severe TBI (Ross et al. 1994; Goodman et al. 1990). TNF-a expression after experimental TBI is detectable after 1 h, peaks between 3 and 8 h, and returns to normal level at 24 h after injury (Stover et al. 2000; Shohami et al. 1994; Fan et al. 1996).

Also in the chronic stage of the injury, activated microglia surround the lesion and remain chronically activated for weeks and months after the initial brain trauma (Maeda et al. 2007). Persistent long-term microglial activation was observed in the traumatized cortex 3 months after experimental brain injury and was associated with increased expression of proinflammatory cytokines, IL-1β and TNF-α (Holmin and Mathiesen 1999). In humans, long-term microglial activation and chronic inflammation after injury may persist for many years in brain injury survivors (Gentleman et al. 2004). These long-term persistent inflammatory changes may cause post-traumatic neurodegeneration, which could form the basis of the cognitive decline that is often observed in long-term survivors of TBI.

Anti-inflammatory cytokine levels are also modulated by TBI. In humans, IL-10 and TFG-b levels are elevated acutely after injury (Morganti-Kossmann et al. 1999; Csuka et al. 1999), and experimental studies have shown that IL-10 has beneficial effects following trauma (Knoblach and Faden 1998). Injection of the anti-inflammatory cytokine TGF-β after injury in rodents reduces damaged lesion size, improves function, and reduces iNOS expression (Tyor et al. 2002; Hamada et al. 1996). Intravenous administration of IL-10 after experimental TBI in rats improved neurological recovery and

significantly reduced TNF-α and IL1β expression in the traumatized cortex and hippocampus. These neuroprotective effects may be the result of suppressed microglial activation, in that IL-10 treatment has been shown to decrease production of proinflammatory cytokines (Kremlev and Palmer 2005).

Conclusions

Inflammation following acute CNS injury is increasingly recognized as a key element in its progression. In this review we have focused on several elements which are involved in inflammatory responses following ischemic stroke, intracerebral hemorrhage, SAH, and traumatic injury. Although, early inflammatory responses may potentiate ischemic injury, late responses may be important in recovery and repair. The precise mechanisms of the inflammatory responses are still to be elucidated. And future work and better understanding against this field will shed light on new therapeutic methods to these injuries.

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