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Traumatic Brain Injury and Inflammation: Emerging Role of Innate and Adaptive Immunity

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1. Introduction

Traumatic brain injury (TBI) has long been recognized as a leading cause of mortality and permanent neurological disability worldwide and has been described as a silent epidemic of modern societies. It is most common amongst young individuals, in their productive years of life, thereby causing a significant social and financial burden for them, their families and the public health system (Maas et al., 2008).

The pathophysiology of TBI is complex and multifactorial with several pathways involved in the damage of the brain. TBI has been classified into primary and secondary injury. The primary injury is the result of the external mechanical force at the moment of trauma leading to skull fractures, brain contusions, lacerations, diffuse axonal injuries, vascular tearing and intracranial hemorrhages (Maas et al., 2008). The initial impact damages directly the neuronal tissue via excitatory amino acids release and massive ionic influx referred to as traumatic depolarization (Katayama et al., 1995).

Secondary neuronal damage is induced immediately after primary injury and is mediated through several pathophysiologic mechanisms including raised intracranial pressure, disruption of blood brain barrier, brain edema, decreased cerebral blood flow, altered tissue perfusion, cerebral hypoxia, ischemia and reperfusion injury (Graham et al., 2000). Furthermore, a cascade of molecular, neurochemical, cellular and immune processes contribute to secondary damage such as disruption of calcium homeostasis, oxidative stress, excitatory mediators release, cytoskeletal and mitochondrial dysfunction, Ab-peptide deposition, inflammatory cell infiltration and neuronal cell apoptosis and death (Greve & Zink, 2009). Gene expression studies have demonstrated that several genes are implicated in the pathophysiology of secondary brain damage (Lei et al., 2009). Secondary cascade of events were found to dramatically aggregate primary neuronal damage and given that primary injury is unavoidable and irreversible, secondary processes are the targets of current therapeutic strategies and trials on neuroprotective agents (Jain, 2008).

Extensive research has indicated that cellular and humoral inflammation after TBI play a key role in the extent of brain injury and repair processes. The initiation, progression and resolution of inflammation in TBI is multifaceted involving leukocyte infiltration, activation of resident immune cells and secretion of inflammatory mediators such as pro- and anti-inflammatory cytokines, chemokines, adhesion molecules, complement factors, reactive oxygen species and other factors. Several lines of evidence support a dual role for the neuroinflammation either detrimental or beneficial depending on the extent, time and site of induction. Elucidation of the inflammatory cascade in the injured brain would offer the possibility of novel therapies.
The present article will focus on the TBI induced neuroinflammation and on the current knowledge regarding the involvement of innate and adaptive immune system in the inflammation and repair following TBI.

2. Neuroinflammation

The normal central nervous system (CNS) limits the entry of immune components and is traditionally regarded as an immune privileged organ separated from the peripheral immune system by the blood-brain-barrier (BBB). However, this concept of limited immune intervention in the CNS has been questioned, since under physiological conditions, resident brain cells are capable of immune surveillance and expression of immune mediators within the CNS. In addition, T-lymphocytes are known to enter the healthy brain parenchyma to perform surveillance in the absence of inflammatory stimulus (Hickey, 1999; Becher et al., 2000). During inflammatory brain insults the immune privileged status is compromised with an activation of innate immune cells and mobilization of specific adaptive immune responses.
A growing body of evidence suggests a pivotal role of TBI induced cerebral inflammation, including activation of resident cells, migration and recruitment of leukocytes and release of inflammatory mediators, in the extent of neuronal injury and repair. Inflammation after TBI is believed to be triggered by several factors such as extravasated blood products, tissue debris, intracellular components, complement fragments, prostaglandins, reactive oxygen and nitrogen species. The BBB is disrupted after TBI resulting in invasion of neutrophils, monocytes and lymphocytes from the periphery and activation of microglia and other resident cells and thus initiating a potent inflammatory response. A biphasic BBB breakdown after TBI has been reported with a first opening occurring immediately after the primary impact reaching a maximum permeability within a few hours and then being declined. A second-delayed opening as a result of secondary injury cascades was found to peak around 3-7 days following TBI and can last from days to years (Baskaya et al., 1997; Shlosberg et al., 2010).
The accumulation of leukocytes into the injured brain area is crucial to the extent of inflammation and secondary brain damage. Leukocytes migrate out of blood vessels into the injured brain parenchyma via binding to the endothelial selectins P and E and the intercellular adhesion molecules (ICAMs). Chemokines from the injured brain tissue contribute to the expression of these endothelial molecules in the local vasculature. Chemokines are produced by resident cells including microglia, astrocytes and neurons in response to local inflammation (Ransohoff, 2002). For instance, the chemokine CXCL8 (IL8) interacts with leukocytes, triggering the activation of the integrins LFA-1 and CR3 (Mac-1) in the surface of leukocytes. These integrins consequently interact with endothelial ICAM-1 and ICAM-2 leading to a firm adhesion, conformational changes and extravasation of

leukocytes between endothelial cells. Finally, these leukocytes migrate along the concentration gradient of chemokines to the site of TBI. Neutrophil accumulation peaks within 2 days after TBI whereas monocytes accumulate slightly later (Rhodes, 2011).

Leukocytes are believed to be important in the initiation and progression of inflammation following TBI because they contain and release a significant number of inflammatory mediators that injure neurons. Increased leukocyte infiltration has been linked to increased brain damage. Leukocytes release pro-inflammatory cytokines, proteases, prostaglandins, complement factors, free oxygen and nitrogen species which damage neuronal population and brain microvasculature and contribute to the disruption of BBB and formation of vasogenic edema (Nguyen et al., 2007). Studies in vitro have shown that mixed cultures of hippocampal neurons and neutrophils contributed to increased neuronal loss and excitotoxic damage (Dinkel et al., 2004). Also, leukocyte accumulation seemed to mediate the detrimental effects of chemokines. It was shown that increased intrathecal levels of CXCL8 were correlated to the extent of posttraumatic BBB dysfunction and mortality (Kossmann et al., 1997; Whalen et al., 2000). However, these effects were attenuated by prior depletion of the circulating leukocytes (Bell et al., 1996). Leukocytes also contribute to oxidative damage in the injured brain tissue. Free oxygen radicals released by leukocytes induce lipid and protein peroxidation, mitochondrial and DNA damage and neuronal apoptosis (Tyurin et al., 2000).

It has been hypothesized that inhibition of neutrophil function or migration would reduce the injury size and improve the functional outcome after TBI. This notion has already been proved in experimental models of ischemic brain injury. However, the beneficial role of leukocyte inhibition is less convincing in TBI experiments. Studies in animal models and humans with severe TBI have shown increased expression of the adhesion molecules selectin E and ICAM-1 in the early period following TBI (Carlos et al., 1997; McKeating et al., 1998; Pleines et al., 1998) indicating that these molecules are important in the neutrophil recruitment in the injured brain. Administration of monoclonal antibodies directed against the leukocyte adhesion molecules CD11b (aM subunit of integrin CR3) and ICAM-1 resulted in decreased neutrophil migration (Carlos et al., 1997; Weaver et al., 2000; Knoblach & Faden, 2002) and better clinical recovery (Knoblach & Faden, 2002) after experimental brain trauma. However, in the latter study the beneficial effect of anti-ICAM-1 treatment was also achieved, although to a lesser extent, with the administration of a nonspecific IgG, indicating that part of the effects may be attributed to the general properties of the antibodies. Moreover, ICAM-1 gene deficient mice with TBI did not demonstrate evidence of improved neurological function, reduced lesion volume or neutrophil accumulation compared to wild type control mice (Whalen et al., 1999), suggesting that other adhesion molecules may also play a significant role in the recruitment of neutrophils. Inhibition of neutrophil infiltration was also tested by blocking chemokine expression. Mice deficient in CXC receptor 2 which interacts with chemokines CXCL8, CXCL1 and CXCL2 and mediates the neutrophil transmigration across the BBB were reported to demonstrate significant attenuation of neutrophil infiltration, reduced tissue damage and neuronal loss, especially in the delayed phase post injury (Semple et al., 2010a). In a similar study, deletion of monocyte chemokine CCL2 gene resulted in improved neurological function, delayed reduction in lesion volume and macrophage accumulation (Semple et al., 2010b). Both the latter studies support the notion that late inhibition of leukocyte recruitment in TBI may be beneficial for the extent of brain trauma and the clinical outcome. These results were not achieved when neutrophil depletion was applied early in the course of TBI (Whalen et al., 1999), indicating that leukocyte infiltration in the early phase post injury may mediate some beneficial

physiologic processes and only delayed and prolonged leukocyte recruitment may be deleterious to the neuronal survival.

Apart from leukocyte infiltration, the humoral components of neuroinflammation were also found to play an important role in the initiation, maintenance and resolution of inflammation following TBI. The primary traumatic impact and the ensuing injury triggers the release of several cytokines which facilitate the migration of inflammatory cells, the activation of resident cells, the expression of vascular endothelial molecules and chemokines. Cellular sources of cytokines include leukocytes, lymphocytes, microglia, astrocytes, endothelial cells and neurons. Cytokines are induced shortly after primary insult and this early increase is mediated by resident brain cells. Cytokines have multiple actions and targets, and often overlapping biological effects. Cytokines exert their function either through binding to their receptors, which are expressed by both glial and neuronal cells, or through diverse pathways such as modulation of neurotransmitter receptor function, induction of nitric oxide synthase, secretion of chemokines and proteolytic enzymes (Allan & Rothwell, 2001).

Interleukin-1 (IL-1) is a pro-inflammatory cytokine that has been identified as an important mediator of the inflammation following TBI. The IL-1 family has three main members: the pro-inflammatory cytokines IL-1a and IL-1b, which exert their action by binding to the cell surface receptor IL-1RI, and the anti-inflammatory cytokine IL-1 receptor antagonist (IL-1ra) (Rothwell & Luheshi, 2000). The pro-inflammatory cytokines IL-1a and IL-1b have pleiotropic effects which are mediated by binding to the IL-1RI. IL-1 triggers inflammatory reactions, leads to recruitment of leukocytes, disruption of BBB and formation of edema, induces other interleukins, prostagladins, histamine, thromboxane, chemokines and adhesion molecules and exerts multiple effects in neuronal, glial and endothelial cells (Hopkins & Rothwell, 1995; Rothwell & Hopkins, 1995). IL-1ra is a naturally occurring competitive and highly selective inhibitor of IL-1a and IL-1b which binds to the IL-1RI without initiating signal transduction. IL-1ra plays an important role in the regulation of the inflammatory response and the balance between proinflammatory and anti-inflammatory cytokines (Arend, 1991; Dinarello, 1991).

In experimental TBI a rapid induction of IL-1b (mRNA expression and protein levels) was observed in the very early period following TBI (Fan et al., 1995; Wang & Shuaib, 2002). Similarly, IL-1ra was upregulated in response to head injury but shortly after the induction of IL-1b (Gabellec et al., 1999). Elevated levels of IL-1b were also detected intrathecally in patients with head injury (Winter et al., 2002). Moreover, these elevated levels were correlated to poorer clinical outcome (Chiaretti et al., 2005; Shiozaki et al., 2005). The proinflammatory cytokines IL-1a and IL-1b are believed to initiate inflammation and to contribute to neurodegeneration after various brain insults including TBI, whereas IL-1ra seemed to be neuroprotective. In experimental animal models, intracerebral or intraventricular administration of exogenous IL-1b markedly exacerbates brain injury (Patel et al., 2003). In contrast, administration or overexpression of IL-1ra significantly attenuates neuronal damage and inflammation (Toulmond & Rothwell, 1995; Sanderson et al., 1999; Tehranian et al., 2002). Apart from acute neuroinflammation, TBI induces long-term and persistent inflammation with elevation of IL-1 and other cytokines and increased expression of beta-amyloid protein and phosphorylated tau protein. This long-term inflammation may be the causative link between TBI and traumatic dementia (Hoshino et al., 1998; Holmin & Mathiesen, 1999). These data highlight the important role of IL-1 in the acute and chronic neuroinflammation following TBI and the possibility of beneficial effects that may ensue after its therapeutic inhibition. However, many studies have underlined the complexity of

inflammatory processes, the lack of meaningful effects after blocking a single inflammatory mediator and the duality of inflammation which means that inflammation may have either detrimental or beneficial effects depending on the site, the time of induction, the concentration of mediators and the microenvironment (Morganti-Kossmann et al., 2002). This duality was demonstrated for IL-1 which aside from its pro-inflammatory effects also seems to participate in tissue repair processes, especially when induced at later stages, via stimulation of neurotrophic factors synthesis (Spranger et al., 1990; DeKosky et al., 1994; Herx et al., 2000), astrocyte proliferation (Appel et al., 1997) and involvement in synaptic plasticity (Fagan & Gage, 1990; Bellinger et al., 1993; Ide et al., 1996).

IL-6 is another cytokine that has been studied in TBI. IL-6 was found to have also a dual role in inflammation with either regulatory, anti-inflammatory or inflammatory effects depending on the time course and extent of expression (Allan & Rothwell, 2001; Morganti-Kossmann et al., 2002). The neurotrophic properties of IL-6 are mediated by inhibition of TNFa synthesis, induction of IL-1ra and nerve growth factor and attenuation of oxidative stress (Morganti-Kossmann et al., 2001). On the contrary, IL-6 promotes inflammatory processes by stimulating the production of chemokines and adhesion molecules and the recruitment of leukocytes (Romano et al., 1997). Elevated levels of IL-6 were observed in the cerebrospinal fluid (CSF) and in the serum of patients with TBI and this increase was correlated with a favorable neurological outcome (Singhal et al., 2002; Chiaretti et al., 2008). In contrast, other studies demonstrated that IL-6 levels were correlated to the clinical severity of TBI patients (Arand et al., 2001; Minambres et al., 2003). Studies in animal models provide evidence for a neuroprotective effect of IL-6. IL-6 was found at elevated levels in experimental TBI (Shohami et al., 1994). Mice deficient for IL-6 had increased numbers of apoptotic neurons, increased oxidative stress and delayed healing of the tissue (Penkowa et al., 2000), whereas the same group demonstrated that IL-6 transgenic mice exhibited increased reduction of oxidative stress and apoptotic cell death after a cryogenic brain injury (Penkowa et al., 2003).

Tumor necrosis factor-a (TNFa) is another cytokine with a well-documented role in TBI. TNFa mRNA and protein is elevated in the early period after experimental TBI and before the infiltration of leukocytes suggesting that the early source of TNFa production are the resident cells (Riva-Depaty et al., 1994). Elevated levels were also observed in the clinical setting of TBI patients (Goodman et al., 1990; Csuka et al., 1999). TNFa has pro-inflammatory properties similar to that of IL-1 and exacerbates inflammation and secondary brain damage after TBI (Allan & Rothwell, 2001). Early upregulation of neuronal TNFa expression after TBI was found to contribute to subsequent neurological dysfunction (Knoblach et al., 1999). Inhibition of TNFa by the HU-211 compound (a novel TNFa production inhibitor), pentoxyfilline and TNF-binding protein resulted in improved neurological outcome after closed head injury (Shohami et al., 1997). However, in a phase III clinical trial, administration of the HU-211 compound in patients with TBI failed to show improved outcome 6 months after the injury, compared to the placebo group (Maas et al., 2006). These data indicate that neurodegeneration is mediated through various pathological pathways and neuroprotection cannot be achieved by blocking a single mediator as other alternative pathways may be activated leading to neuronal loss. Furthermore, as reported with IL-1, TNFa also has neuroprotective effects and can enhance recovery processes. In a very interesting study, knockout mice for the TNFa gene exhibited milder behavioral deficits compared to the wild-type mice during the acute period post-injury. However, in the long term period (4 weeks post-injury) knockout mice did not recover as well as the wild-type mice, had persistent motor deficits and greater cortical tissue loss (Scherbel et al.,

1999). These results suggest that the time, concentration and the site of TNFa induction may determine the driving of inflammatory processes towards neurodegeneration or neuroprotection.

3. Innate immunity

Microglia, the brain's resident macrophages, are the main cell type of the innate immune system of the brain. Microglia, although debatable, seem to originate from bone marrow monocytic cells which invade the CNS during embryonic development (Chan et al., 2007). Microglia provide a first line of regional defense in the CNS against various pathological insults. They are scattered throughout the CNS although some regional differences in their localization have been reported as they are more densely distributed in the gray than in the white matter and in structures like hippocampus, basal ganglia and substantia nigra (Block et al., 2007).

While resting, microglia have a highly ramified morphology with symmetrically extended, motile processes that form a network, which continuously monitor the local microenvironment of the brain parenchyma being the most susceptible sensors of brain pathology (Nimmerjahn et al., 2005; Kettenmann et al., 2011). In physiological conditions they provide surveillance of the CNS homeostasis and they sense neuronal and astrocytic activity and other physiological changes such as pH shifts, ion currents and neurotransmitter release (Farber & Kettenmann, 2005). This is achieved by the expression of numerous receptors by the microglia establishing a delicate neuron-microglia communication (McCluskey & Lampson, 2000). In an in vitro study the normal neuronal activity was found to inhibit the effects of microglia activators such as interferon-γ signifying the importance of cell to cell interactions (Neumann et al., 1996).

Various brain insults including bacterial lipopolysaccharide (LPS), cytokines, b-amyloid peptide and damaged tissue can result in activation of microglia (Nakamura, 2002). Upon activation, the cell size increases and the morphology dramatically changes to an amoeboid structure which facilitates the migration of microglial cells towards the lesion site and the phagocytosis of cellular debris and toxic substances (Raivich, 2005). In response to noxious stimuli microglia also proliferate and migrate to the lesion site. The rapidly chemotactic convergence to the site of injury is mediated by ATP, glutamate and other chemotactic agents released by the injured cells (Davalos et al., 2005; Liu et al., 2009). At this point the morphology of activated microglia cannot be discriminated from that of infiltrating macrophages using standard immunohistochemical techniques (Streit et al., 1999; Loane & Byrnes, 2010).

A significant part in the activation of microglia after inflammatory stimuli is the expression of constitutive and inducible surface receptors. Activated microglia express pattern recognition receptors, cytokine and chemokine receptors, phagocytic receptors, Fc and complement receptors, receptors for glutamate, growth factors and several other molecules (Gebicke-Haerter et al., 1996; Cho et al., 2006; Kettenmann et al., 2011). Activated microglia also express on their surface MHC class I and II molecules, making them able to present antigenic peptides and thus modulating T cell responses (Aloisi, 2001).

The specific profile of the surface receptors determine the phenotype of microglia and their functional properties. In line with macrophages phenotype, activated microglia may be neurotoxic (M1) due to the secretion of pro-inflammatory cytokines and reactive oxygen and nitrogen species. In contrast, activation of microglia may enable them to maintain and

enhance neuronal survival (M2) through the release of anti-inflammatory cytokines and neurotrophic factors. However, it is possible that M1 and M2 phenotypes may represent the two extremes of a wide spectrum of phenotypes that microglia can have in response to the type, intensity, persistence of the stimuli and the microenvironment interactions (Mantovani et al., 2004). In fact, microglia have plastic properties and at different stages of the disease can acquire diverse phenotypes and functions that can be either detrimental or beneficial.

The activation process begins when resting microglia detect the noxious stimuli or the sub-products of tissue damage. Microglia become activated, release inflammatory mediators, express surface molecules and remove cellular debris by phagocytosis. Once the toxic factors are eliminated and under the influences of the invading immune cells and the normal CNS cells activated microglia acquire a neurotrophic phenotype and release anti-inflammatory cytokines and neurotrophic factors. After a certain period of time inflammation is resolved and the activating microglia return to a resting-surveying state retaining some kind of memory of the processes. However, under not fully elucidated conditions, this delicate balance between activation-termination and neurotoxic-neurotrophic phenotype can be disrupted leading to excessive, uncontrolled or prolonged activation of microglia with destructive consequences in neuronal survival. Excessive and dysregulated microglia activation were elicited after intense and severe CNS insults. Moreover, insufficient recruitment of systemic immune cells to the CNS site of lesion may result in an inability to suppress and terminate the microglia activation or to turn them into a neuroprotective phenotype (Kempermann & Neumann, 2003; Hanisch & Kettenmann, 2007; Popovich & Longbrake, 2008; Rivest, 2009; Schwartz & Shechter, 2010). Thus, dysregulation of the innate or adaptive immune system may mediate excessive inflammatory damage following brain insults. It is obvious that a better understanding of the interaction mechanisms between immune cells may facilitate the introduction of novel therapies.

Several studies have investigated the microglia function after TBI. The release of various mediators in the extracellular space after the injured site alters the expression profile of local microglia. In a very interesting imaging study of fluorescent labeled microglia it was shown that microglia from the intact brain that are nearby the injured site extend their processes which reach the damaged site. There the processes and without cell body movement, converge and fuse together to form a spherical area of containment that separate the healthy from the injured tissue. In other words fused microglial processes act as a barrier that contains the tissue debris. This highly dynamic movement of microglial processes is under the chemotactic influence of extracellular ATP (Davalos et al., 2005).

The time of induction and the duration of microglia activation after TBI were found to be different from other brain insults such as cerebral ischemia. Studies in humans with TBI have revealed a striking delay of microglial activation and proliferation. Markers of microglial activation and proliferation were not detected until 3 days post TBI (Beschorner et al., 2000; Engel et al., 2000) whereas the same markers were expressed early in cerebral ischemia (Postler et al., 1997). This observation although in line with some findings in experimental models (Aihara et al., 1995; Holmin et al., 1997) cannot be fully understood. It is possible to reflect different activation cascades of microglia after TBI compared to other brain insults. However this window delay of microglial activation after TBI may provide a therapeutic opportunity when the target would be the microglial activation.

Several studies in TBI have also demonstrated that inflammation can persist for long period of time after the primary traumatic brain insult. Studies in rodents have revealed reactive astrocytosis for over a year following brain injury resulting in chronic progressive neuronal

tissue loss (Smith et al., 1997; Holmin & Mathiesen, 1999). In primates, microglia activation was found to persist for at least 12 months (Nagamoto-Combs et al., 2007). Post-mortem studies in humans have shown persistent elevated microglial activity several years after TBI (Gentleman et al., 2004). In addition, a recent PET imaging study in humans using a ligand that binds to activated microglia revealed increased microglial activation for up to 17 years after TBI (Ramlackhansingh et al., 2011). Persistent microglial activation is believed to underline both chronic neuroprotective and destructive processes. The precise mechanisms for the persistence of inflammatory processes after TBI are not fully understood. It is believed that a severe initial neuronal injury with excessive cytokine signals may lead to enhanced activation of microglia that further aggravate brain damage feeding a self-sustaining and self-propelling prolonged vicious circle of neurotoxicity and progressive degeneration (Gao & Hong, 2008). This dysregulated and uncontrolled microglial activation may be the key for chronic, long-lived and destructive inflammatory processes. The long-term microglia activation may also provide insights into a potential causative link between head injury and Alzheimer's disease.

4. Adaptive immunity

Adaptive immunity refers to an antigen-specific response either cell-mediated or humoral aiming at elimination of pathogenic factors. Adaptive immunity is mediated by B and T lymphocytes. In experiment TBI, T cells were found to infiltrate the brain parenchyma in a biphasic manner: immediately after the primary impact as a result of disruption of BBB and in a delayed phage with increased numbers of T cells which represents an active infiltration of specific targeting T-cells (Czigner et al., 2007). In other studies it was shown that T cell infiltration in the damaged tissue occurred 3-14 days after CNS trauma and persisted for 6 months (Kigerl et al., 2006; Beck et al., 2010). In post-mortem human studies $CD4^+$ and $CD8^+$ were identified in the injured tissue after spinal cord injury (Fleming et al., 2006).

It is known that the transformation of naive T cells into effector T cells requires an initial antigen presentation in secondary lymphoid organs and a re-activation after re-exposure to their antigen. However, the exact mechanics of adaptive immune response after brain injury have not been fully elucidated and some aspects remain obscure. It is known that naive T cells against CNS antigens are circulating in the periphery. After brain insults the cerebral auto-antigens are exposed to the peripheral blood cells. The activation of naive T cells can take place in the peripheral lymph nodes as a result of BBB disruption and release of cerebral antigens into the bloodstream alone or in conjunction with the brain APCs (Lenzlinger et al., 2001; Ling et al., 2003; Karman et al., 2004). After activation, T cells traffic to the CNS under the influence of chemokine gradient. Microglia are already activated as a result of brain tissue damage and release of inflammatory mediators. Activated microlgia release at the site of injury cytokines and chemokines, express various surface molecules including complement components and induce the expression of adhesion molecules by the endothelial cells. These alterations induce the recruitment of the T cells into the injury site. Within the CNS, T cells become re-activated against their antigen which is presented to them by local microglia and macrophages.

As already mentioned MHC expression is almost absent in normal brain parenchyma. After brain trauma activated microglia upregulate the expression of MHC class I and class II and the expression of adhesion molecules and costimulatory factors. Activated microglia can act as antigen-presenting cells to T cells by phagocytosis of the tissue debris,

processing of the relevant antigen and its subsequent presentation on class I or class II MHC (Ankeny et al., 2006).

Another hypothesis that has been introduced is that the initial activation of T cells takes place within CNS. However, data have shown that the interaction between microglia and T cells is incomplete and insufficient to support a full activation and proliferation of T cells. In an ex vivo study this interaction resulted in increased T cell apoptosis which may reflect a regulatory function of microglia upon T cell responses (Ford et al., 1996). It seems possible that activated microglia may influence the function and maintenance of auto-reactive T cells in the CNS either directly by presenting the antigen causing re-activation of the T cells or indirectly by determining the local inflammatory/anti-inflammatory microenvironment and the recruitment of T cells.

The peripheral activation of T cells against cerebral antigens is supported by a number of studies. Several studies have provided evidence for a traveling of the antigen from the CNS to the peripheral lymph nodes. Fluorescent substances injected into the CNS of animal models were detected in the cervical lymph nodes in a few hours after the injection. In addition, intracerebrally infused protein antigen was found to elicit the accumulation of antigen-specific CD8+ T cells 3 days after the injection (Ling et al., 2003). Moreover, experimental and human studies of CNS trauma have revealed the presence of auto-reactive T cells against cerebral antigens. Isolated T cells from an animal model of spinal cord injury when injected intravenously into naive recipients were found to induce spinal cord neuroinflammation and transient hind limb paralysis and ataxic gait (Popovich et al., 1996). Additionally auto-reactive T cells against myelin basic protein were found in increased frequencies in patients with spinal cord injury compared to multiple sclerosis patients and normal controls (Kil et al., 1999).

Adaptive immunity may mediate either pathogenic or reparative processes based of the inflammatory conditions of the microenvironment during activation of T-cells. It has been hypothesized that Th1 immune response may aggravate brain damage by pro-inflammatory actions whereas Th2 response may alleviate brain damage by anti-inflammatory and neurotrophic effects. In a study of freeze cerebral injury activated T cells were found to exacerbate brain damage when transferred to rats 24h before the injury (Fee et al., 2003). In contrast, in an very intriguing study in animals with injury in the optic nerve it was shown that intraperitoneally injected anti-myelin basic protein specific T cells prevented the secondary degeneration of retinal ganglion cells (Moalem et al., 1999). These significant data were also replicated in an animal model of spinal cord injury. It was shown that autoreactive T cells against myelin basic protein or active immunization with myelin basic protein improved the recovery by promoting neuroprotective and regenerative processes (Hauben et al., 2000). Furthermore, it was showed that Th2 cells specific for myelin basic protein had protective effects on neuronal survival. This neuroprotective effect of the antigen-specific T cells was influenced by the extent of non-specific activation of the T cells (Wolf et al., 2002). In another study of peripheral facial nerve injury $CD4^+$ T cells were found to mediate facial motor neurons survival (Serpe et al., 2003).

These observations of beneficial effects of autoreactive T cells led to the introduction of the term "protective autoimmunity" implying that the recognition of an exposed self antigen by T cells can result in protection, repair and maintenance of the functional integrity of a tissue rather than the initiation of an autoimmune process. (Schwartz et al., 2003; Schwartz & Shechter, 2010). Regulatory T cells ($CD4^+CD25^+Foxp3^+$) that suppress autoimmune activity seem to play a central role in protective autoimmunity. The concept of protective

autoimmunity raises some interesting therapeutics options. A vaccination with weak CNS specific antigens or a modulation of regulatory T cells activity that enhance protective autoimmunity would be a novel approach for neuroprotection and repair after CNS trauma (Schwartz et al., 2009).

In conclusion, neuroinflammation seems to play a key role in the pathophysiology of brain damage following TBI. A complex interaction between several components and mediators of the innate and adaptive immunity appear to determine the extent of inflammation and its nature, either destructive or reparative. A better understanding of these mechanisms that are implicated in the initiation, progression and termination of the inflammation and the communication between immune cells is required for the development of new and effective therapeutic strategies.

5. References

Aihara, N., et al. (1995). Altered immunoexpression of microglia and macrophages after mild head injury. *J Neurotrauma*, 12, 1, pp. 53-63.

Allan, S. M. and Rothwell, N. J. (2001). Cytokines and acute neurodegeneration. *Nat Rev Neurosci*, 2, 10, pp. 734-44.

Aloisi, F. (2001). Immune function of microglia. *Glia*, 36, 2, pp. 165-79.

Ankeny, D. P., et al. (2006). Spinal cord injury triggers systemic autoimmunity: evidence for chronic B lymphocyte activation and lupus-like autoantibody synthesis. *J Neurochem*, 99, 4, pp. 1073-87.

Appel, E., et al. (1997). Regulation of GDNF expression in cultured astrocytes by inflammatory stimuli. *Neuroreport*, 8, 15, pp. 3309-12.

Arand, M., et al. (2001). Early inflammatory mediator response following isolated traumatic brain injury and other major trauma in humans. *Langenbecks Arch Surg*, 386, 4, pp. 241-8.

Arend, W. P. (1991). Interleukin 1 receptor antagonist. A new member of the interleukin 1 family. *J Clin Invest*, 88, 5, pp. 1445-51.

Baskaya, M. K., et al. (1997). The biphasic opening of the blood-brain barrier in the cortex and hippocampus after traumatic brain injury in rats. *Neurosci Lett*, 226, 1, pp. 33-6.

Becher, B., et al. (2000). Brain-immune connection: immuno-regulatory properties of CNS-resident cells. *Glia*, 29, 4, pp. 293-304.

Beck, K. D., et al. (2010). Quantitative analysis of cellular inflammation after traumatic spinal cord injury: evidence for a multiphasic inflammatory response in the acute to chronic environment. *Brain*, 133, Pt 2, pp. 433-47.

Bell, M. D., et al. (1996). Overriding the brain's intrinsic resistance to leukocyte recruitment with intraparenchymal injections of recombinant chemokines. *Neuroscience*, 74, 1, pp. 283-92.

Bellinger, F. P., et al. (1993). Interleukin 1 beta inhibits synaptic strength and long-term potentiation in the rat CA1 hippocampus. *Brain Res*, 628, 1-2, pp. 227-34.

Beschorner, R., et al. (2000). Differential regulation of the monocytic calcium-binding peptides macrophage-inhibiting factor related protein-8 (MRP8/S100A8) and allograft inflammatory factor-1 (AIF-1) following human traumatic brain injury. *Acta Neuropathol*, 100, 6, pp. 627-34.

Block, M. L., et al. (2007). Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat Rev Neurosci*, 8, 1, pp. 57-69.

Carlos, T. M., et al. (1997). Expression of endothelial adhesion molecules and recruitment of neutrophils after traumatic brain injury in rats. *J Leukoc Biol*, 61, 3, pp. 279-85.

Chan, W. Y., et al. (2007). The origin and cell lineage of microglia: new concepts. *Brain Res Rev*, 53, 2, pp. 344-54.

Chiaretti, A., et al. (2008). Interleukin-6 and nerve growth factor upregulation correlates with improved outcome in children with severe traumatic brain injury. *J Neurotrauma*, 25, 3, pp. 225-34.

Chiaretti, A., et al. (2005). Interleukin 1beta and interleukin 6 relationship with paediatric head trauma severity and outcome. *Childs Nerv Syst*, 21, 3, pp. 185-93; discussion 194.

Cho, B. P., et al. (2006). Pathological dynamics of activated microglia following medial forebrain bundle transection. *Glia*, 53, 1, pp. 92-102.

Csuka, E., et al. (1999). IL-10 levels in cerebrospinal fluid and serum of patients with severe traumatic brain injury: relationship to IL-6, TNF-alpha, TGF-beta1 and blood-brain barrier function. *J Neuroimmunol*, 101, 2, pp. 211-21.

Czigner, A., et al. (2007). Kinetics of the cellular immune response following closed head injury. *Acta Neurochir (Wien)*, 149, 3, pp. 281-9.

Davalos, D., et al. (2005). ATP mediates rapid microglial response to local brain injury in vivo. *Nat Neurosci*, 8, 6, pp. 752-8.

DeKosky, S. T., et al. (1994). Upregulation of nerve growth factor following cortical trauma. *Exp Neurol*, 130, 2, pp. 173-7.

Dinarello, C. A. (1991). Interleukin-1 and interleukin-1 antagonism. *Blood*, 77, 8, pp. 1627-52.

Dinkel, K., et al. (2004). Neurotoxic effects of polymorphonuclear granulocytes on hippocampal primary cultures. *Proc Natl Acad Sci U S A*, 101, 1, pp. 331-6.

Engel, S., et al. (2000). Dynamics of microglial activation after human traumatic brain injury are revealed by delayed expression of macrophage-related proteins MRP8 and MRP14. *Acta Neuropathol*, 100, 3, pp. 313-22.

Fagan, A. M. and Gage, F. H. (1990). Cholinergic sprouting in the hippocampus: a proposed role for IL-1. *Exp Neurol*, 110, 1, pp. 105-20.

Fan, L., et al. (1995). Experimental brain injury induces expression of interleukin-1 beta mRNA in the rat brain. *Brain Res Mol Brain Res*, 30, 1, pp. 125-30.

Farber, K. and Kettenmann, H. (2005). Physiology of microglial cells. *Brain Res Brain Res Rev*, 48, 2, pp. 133-43.

Fee, D., et al. (2003). Activated/effector CD4+ T cells exacerbate acute damage in the central nervous system following traumatic injury. *J Neuroimmunol*, 136, 1-2, pp. 54-66.

Fleming, J. C., et al. (2006). The cellular inflammatory response in human spinal cords after injury. *Brain*, 129, Pt 12, pp. 3249-69.

Ford, A. L., et al. (1996). Microglia induce CD4 T lymphocyte final effector function and death. *J Exp Med*, 184, 5, pp. 1737-45.

Gabellec, M. M., et al. (1999). Expression of interleukin-1 genes and interleukin-1 receptors in the mouse brain after hippocampal injury. *Neurosci Res*, 33, 4, pp. 251-60.

Gao, H. M. and Hong, J. S. (2008). Why neurodegenerative diseases are progressive: uncontrolled inflammation drives disease progression. *Trends Immunol*, 29, 8, pp. 357-65.

Gebicke-Haerter, P. J., et al. (1996). Molecular mechanisms of microglial activation. A. Implications for regeneration and neurodegenerative diseases. *Neurochem Int*, 29, 1, pp. 1-12.

Gentleman, S. M., et al. (2004). Long-term intracerebral inflammatory response after traumatic brain injury. *Forensic Sci Int*, 146, 2-3, pp. 97-104.

Goodman, J. C., et al. (1990). Elevation of tumor necrosis factor in head injury. *J Neuroimmunol*, 30, 2-3, pp. 213-7.

Graham, D. I., et al. (2000). Recent advances in neurotrauma. *J Neuropathol Exp Neurol*, 59, 8, pp. 641-51.

Greve, M. W. and Zink, B. J. (2009). Pathophysiology of traumatic brain injury. *Mt Sinai J Med*, 76, 2, pp. 97-104.

Hanisch, U. K. and Kettenmann, H. (2007). Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nat Neurosci*, 10, 11, pp. 1387-94.

Hauben, E., et al. (2000). Passive or active immunization with myelin basic protein promotes recovery from spinal cord contusion. *J Neurosci*, 20, 17, pp. 6421-30.

Herx, L. M., et al. (2000). Central nervous system-initiated inflammation and neurotrophism in trauma: IL-1 beta is required for the production of ciliary neurotrophic factor. *J Immunol*, 165, 4, pp. 2232-9.

Hickey, W. F. (1999). Leukocyte traffic in the central nervous system: the participants and their roles. *Semin Immunol*, 11, 2, pp. 125-37.

Holmin, S. and Mathiesen, T. (1999). Long-term intracerebral inflammatory response after experimental focal brain injury in rat. *Neuroreport*, 10, 9, pp. 1889-91.

Holmin, S., et al. (1997). Delayed cytokine expression in rat brain following experimental contusion. *J Neurosurg*, 86, 3, pp. 493-504.

Hopkins, S. J. and Rothwell, N. J. (1995). Cytokines and the nervous system. I: Expression and recognition. *Trends Neurosci*, 18, 2, pp. 83-8.

Hoshino, S., et al. (1998). Emergence of immunoreactivities for phosphorylated tau and amyloid-beta protein in chronic stage of fluid percussion injury in rat brain. *Neuroreport*, 9, 8, pp. 1879-83.

Ide, C. F., et al. (1996). Cellular and molecular correlates to plasticity during recovery from injury in the developing mammalian brain. *Prog Brain Res*, 108, pp. 365-77.

Jain, K. K. (2008). Neuroprotection in traumatic brain injury. *Drug Discov Today*, 13, 23-24, pp. 1082-9.

Karman, J., et al. (2004). Initiation of immune responses in brain is promoted by local dendritic cells. *J Immunol*, 173, 4, pp. 2353-61.

Katayama, Y., et al. (1995). Role of excitatory amino acid-mediated ionic fluxes in traumatic brain injury. *Brain Pathol*, 5, 4, pp. 427-35.

Kempermann, G. and Neumann, H. (2003). Neuroscience. Microglia: the enemy within? *Science*, 302, 5651, pp. 1689-90.

Kettenmann, H., et al. (2011). Physiology of microglia. *Physiol Rev*, 91, 2, pp. 461-553.

Kigerl, K. A., et al. (2006). Comparative analysis of lesion development and intraspinal inflammation in four strains of mice following spinal contusion injury. *J Comp Neurol*, 494, 4, pp. 578-94.

Kil, K., et al. (1999). T cell responses to myelin basic protein in patients with spinal cord injury and multiple sclerosis. *J Neuroimmunol*, 98, 2, pp. 201-7.

Knoblach, S. M. and Faden, A. I. (2002). Administration of either anti-intercellular adhesion molecule-1 or a nonspecific control antibody improves recovery after traumatic brain injury in the rat. *J Neurotrauma*, 19, 9, pp. 1039-50.

Knoblach, S. M., et al. (1999). Early neuronal expression of tumor necrosis factor-alpha after experimental brain injury contributes to neurological impairment. *J Neuroimmunol*, 95, 1-2, pp. 115-25.

Kossmann, T., et al. (1997). Interleukin-8 released into the cerebrospinal fluid after brain injury is associated with blood-brain barrier dysfunction and nerve growth factor production. *J Cereb Blood Flow Metab*, 17, 3, pp. 280-9.

Lei, P., et al. (2009). Microarray based analysis of microRNA expression in rat cerebral cortex after traumatic brain injury. *Brain Res*, 1284, pp. 191-201.

Lenzlinger, P. M., et al. (2001). Markers for cell-mediated immune response are elevated in cerebrospinal fluid and serum after severe traumatic brain injury in humans. *J Neurotrauma*, 18, 5, pp. 479-89.

Ling, C., et al. (2003). In situ processing and distribution of intracerebrally injected OVA in the CNS. *J Neuroimmunol*, 141, 1-2, pp. 90-8.

Liu, G. J., et al. (2009). Glutamate induces directed chemotaxis of microglia. *Eur J Neurosci*, 29, 6, pp. 1108-18.

Loane, D. J. and Byrnes, K. R. (2010). Role of microglia in neurotrauma. *Neurotherapeutics*, 7, 4, pp. 366-77.

Maas, A. I., et al. (2006). Efficacy and safety of dexanabinol in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial. *Lancet Neurol*, 5, 1, pp. 38-45.

Maas, A. I., et al. (2008). Moderate and severe traumatic brain injury in adults. *Lancet Neurol*, 7, 8, pp. 728-41.

Mantovani, A., et al. (2004). The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol*, 25, 12, pp. 677-86.

McCluskey, L. P. and Lampson, L. A. (2000). Local neurochemicals and site-specific immune regulation in the CNS. *J Neuropathol Exp Neurol*, 59, 3, pp. 177-87.

McKeating, E. G., et al. (1998). Leukocyte adhesion molecule profiles and outcome after traumatic brain injury. *Acta Neurochir Suppl*, 71, pp. 200-2.

Minambres, E., et al. (2003). Correlation between transcranial interleukin-6 gradient and outcome in patients with acute brain injury. *Crit Care Med*, 31, 3, pp. 933-8.

Moalem, G., et al. (1999). Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. *Nat Med*, 5, 1, pp. 49-55.

Morganti-Kossmann, M. C., et al. (2001). Role of cerebral inflammation after traumatic brain injury: a revisited concept. *Shock*, 16, 3, pp. 165-77.

Morganti-Kossmann, M. C., et al. (2002). Inflammatory response in acute traumatic brain injury: a double-edged sword. *Curr Opin Crit Care*, 8, 2, pp. 101-5.

Nagamoto-Combs, K., et al. (2007). Prolonged microgliosis in the rhesus monkey central nervous system after traumatic brain injury. *J Neurotrauma*, 24, 11, pp. 1719-42.

Nakamura, Y. (2002). Regulating factors for microglial activation. *Biol Pharm Bull*, 25, 8, pp. 945-53.

Neumann, H., et al. (1996). Neuronal control of MHC class II inducibility in rat astrocytes and microglia. *Eur J Neurosci*, 8, 12, pp. 2582-90.

Nguyen, H. X., et al. (2007). Polymorphonuclear leukocytes promote neurotoxicity through release of matrix metalloproteinases, reactive oxygen species, and TNF-alpha. *J Neurochem*, 102, 3, pp. 900-12.

Nimmerjahn, A., et al. (2005). Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science*, 308, 5726, pp. 1314-8.

Patel, H. C., et al. (2003). Interleukin-1 in the brain: mechanisms of action in acute neurodegeneration. *Ann N Y Acad Sci*, 992, pp. 39-47.

Penkowa, M., et al. (2003). Astrocyte-targeted expression of interleukin-6 protects the central nervous system during neuroglial degeneration induced by 6-aminonicotinamide. *J Neurosci Res*, 73, 4, pp. 481-96.

Penkowa, M., et al. (2000). Impaired inflammatory response and increased oxidative stress and neurodegeneration after brain injury in interleukin-6-deficient mice. *Glia*, 32, 3, pp. 271-85.

Pleines, U. E., et al. (1998). Soluble ICAM-1 in CSF coincides with the extent of cerebral damage in patients with severe traumatic brain injury. *J Neurotrauma*, 15, 6, pp. 399-409.

Popovich, P. G. and Longbrake, E. E. (2008). Can the immune system be harnessed to repair the CNS? *Nat Rev Neurosci*, 9, 6, pp. 481-93.

Popovich, P. G., et al. (1996). Concept of autoimmunity following spinal cord injury: possible roles for T lymphocytes in the traumatized central nervous system. *J Neurosci Res*, 45, 4, pp. 349-63.

Postler, E., et al. (1997). Expression of the S-100 proteins MRP-8 and -14 in ischemic brain lesions. *Glia*, 19, 1, pp. 27-34.

Raivich, G. (2005). Like cops on the beat: the active role of resting microglia. *Trends Neurosci*, 28, 11, pp. 571-3.

Ramlackhansingh, A. F., et al. (2011). Inflammation after trauma: Microglial activation and traumatic brain injury. *Ann Neurol*.

Ransohoff, R. M. (2002). The chemokine system in neuroinflammation: an update. *J Infect Dis*, 186 Suppl 2, pp. S152-6.

Rhodes, J. (2011). Peripheral immune cells in the pathology of traumatic brain injury? *Curr Opin Crit Care*, 17, 2, pp. 122-30.

Riva-Depaty, I., et al. (1994). Contribution of peripheral macrophages and microglia to the cellular reaction after mechanical or neurotoxin-induced lesions of the rat brain. *Exp Neurol*, 128, 1, pp. 77-87.

Rivest, S. (2009). Regulation of innate immune responses in the brain. *Nat Rev Immunol*, 9, 6, pp. 429-39.

Romano, M., et al. (1997). Role of IL-6 and its soluble receptor in induction of chemokines and leukocyte recruitment. *Immunity*, 6, 3, pp. 315-25.

Rothwell, N. J. and Hopkins, S. J. (1995). Cytokines and the nervous system II: Actions and mechanisms of action. *Trends Neurosci*, 18, 3, pp. 130-6.

Rothwell, N. J. and Luheshi, G. N. (2000). Interleukin 1 in the brain: biology, pathology and therapeutic target. *Trends Neurosci*, 23, 12, pp. 618-25.

Sanderson, K. L., et al. (1999). Interleukin-1 receptor antagonist attenuates regional neuronal cell death and cognitive dysfunction after experimental brain injury. *J Cereb Blood Flow Metab*, 19, 10, pp. 1118-25.

Scherbel, U., et al. (1999). Differential acute and chronic responses of tumor necrosis factor-deficient mice to experimental brain injury. *Proc Natl Acad Sci U S A*, 96, 15, pp. 8721-6.

Schwartz, M., et al. (2009). Boosting T-cell immunity as a therapeutic approach for neurodegenerative conditions: the role of innate immunity. *Neuroscience*, 158, 3, pp. 1133-42.

Schwartz, M., et al. (2003). Protective autoimmunity against the enemy within: fighting glutamate toxicity. *Trends Neurosci*, 26, 6, pp. 297-302.

Schwartz, M. and Shechter, R. (2010). Systemic inflammatory cells fight off neurodegenerative disease. *Nat Rev Neurol*, 6, 7, pp. 405-10.

Semple, B. D., et al. (2010b). Role of CCL2 (MCP-1) in traumatic brain injury (TBI): evidence from severe TBI patients and CCL2-/- mice. *J Cereb Blood Flow Metab*, 30, 4, pp. 769-82.

Semple, B. D., et al. (2010a). Deficiency of the chemokine receptor CXCR2 attenuates neutrophil infiltration and cortical damage following closed head injury. *Neurobiol Dis*, 40, 2, pp. 394-403.

Serpe, C. J., et al. (2003). CD4+ T, but not CD8+ or B, lymphocytes mediate facial motoneuron survival after facial nerve transection. *Brain Behav Immun*, 17, 5, pp. 393-402.

Shiozaki, T., et al. (2005). Cerebrospinal fluid concentrations of anti-inflammatory mediators in early-phase severe traumatic brain injury. *Shock*, 23, 5, pp. 406-10.

Shlosberg, D., et al. (2010). Blood-brain barrier breakdown as a therapeutic target in traumatic brain injury. *Nat Rev Neurol*, 6, 7, pp. 393-403.

Shohami, E., et al. (1997). Cytokine production in the brain following closed head injury: dexanabinol (HU-211) is a novel TNF-alpha inhibitor and an effective neuroprotectant. *J Neuroimmunol*, 72, 2, pp. 169-77.

Shohami, E., et al. (1994). Closed head injury triggers early production of TNF alpha and IL-6 by brain tissue. *J Cereb Blood Flow Metab*, 14, 4, pp. 615-9.

Singhal, A., et al. (2002). Association between cerebrospinal fluid interleukin-6 concentrations and outcome after severe human traumatic brain injury. *J Neurotrauma*, 19, 8, pp. 929-37.

Smith, D. H., et al. (1997). Progressive atrophy and neuron death for one year following brain trauma in the rat. *J Neurotrauma*, 14, 10, pp. 715-27.

Spranger, M., et al. (1990). Regulation of Nerve Growth Factor (NGF) Synthesis in the Rat Central Nervous System: Comparison between the Effects of Interleukin-1 and Various Growth Factors in Astrocyte Cultures and in vivo. *Eur J Neurosci*, 2, 1, pp. 69-76.

Streit, W. J., et al. (1999). Reactive microgliosis. *Prog Neurobiol*, 57, 6, pp. 563-81.

Tehranian, R., et al. (2002). Improved recovery and delayed cytokine induction after closed head injury in mice with central overexpression of the secreted isoform of the interleukin-1 receptor antagonist. *J Neurotrauma*, 19, 8, pp. 939-51.

Toulmond, S. and Rothwell, N. J. (1995). Interleukin-1 receptor antagonist inhibits neuronal damage caused by fluid percussion injury in the rat. *Brain Res*, 671, 2, pp. 261-6.

Tyurin, V. A., et al. (2000). Oxidative stress following traumatic brain injury in rats: quantitation of biomarkers and detection of free radical intermediates. *J Neurochem*, 75, 5, pp. 2178-89.

Wang, C. X. and Shuaib, A. (2002). Involvement of inflammatory cytokines in central nervous system injury. *Prog Neurobiol*, 67, 2, pp. 161-72.

Weaver, K. D., et al. (2000). Effect of leukocyte-endothelial adhesion antagonism on neutrophil migration and neurologic outcome after cortical trauma. *J Trauma*, 48, 6, pp. 1081-90.

Whalen, M. J., et al. (1999). Effect of traumatic brain injury in mice deficient in intercellular adhesion molecule-1: assessment of histopathologic and functional outcome. *J Neurotrauma*, 16, 4, pp. 299-309.

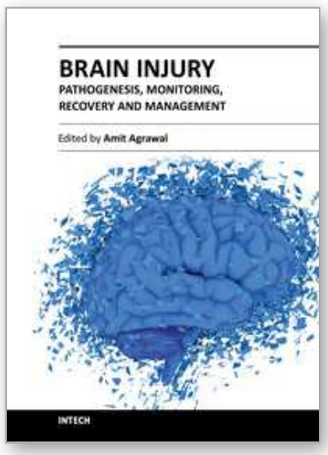
Whalen, M. J., et al. (1999). Neutrophils do not mediate blood-brain barrier permeability early after controlled cortical impact in rats. *J Neurotrauma*, 16, 7, pp. 583-94.

Whalen, M. J., et al. (2000). Interleukin-8 is increased in cerebrospinal fluid of children with severe head injury. *Crit Care Med*, 28, 4, pp. 929-34.

Winter, C. D., et al. (2002). A microdialysis method for the recovery of IL-1beta, IL-6 and nerve growth factor from human brain in vivo. *J Neurosci Methods*, 119, 1, pp. 45-50.

Wolf, S. A., et al. (2002). Neuroprotection by T-cells depends on their subtype and activation state. *J Neuroimmunol*, 133, 1-2, pp. 72-80.

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The present two volume book "Brain Injury" is distinctive in its presentation and includes a wealth of updated information on many aspects in the field of brain injury. The Book is devoted to the pathogenesis of brain injury, concepts in cerebral blood flow and metabolism, investigative approaches and monitoring of brain injured, different protective mechanisms and recovery and management approach to these individuals, functional and endocrine aspects of brain injuries, approaches to rehabilitation of brain injured and preventive aspects of traumatic brain injuries. The collective contribution from experts in brain injury research area would be successfully conveyed to the readers and readers will find this book to be a valuable guide to further develop their understanding about brain injury.

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