Molecular Neurobiology

ISSN0893-7648/98/24(1–3): 169–181/$13.25

The Duality of the Inflammatory Response to Traumatic Brain Injury

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Abstract

One and a half to two million people sustain a traumatic brain injury (TBI) in the US each year, of which approx 70,000–90,000 will suffer from long-term disability with dramatic impacts on their own and their families' lives and enormous socio-economic costs. Brain damage following traumatic injury is a result of direct (immediate mechanical disruption of brain tissue, or primary injury) and indirect (secondary or delayed) mechanisms. These secondary mechanisms involve the initiation of an acute inflammatory response, including breakdown of the blood-brain barrier (BBB), edema formation and swelling, infiltration of peripheral blood cells and activation of resident immunocompetent cells, as well as the intrathecal release of numerous immune mediators such as interleukins and chemotactic factors. An overview over the inflammatory response to trauma as observed in clinical and in experimental TBI is presented in this review. The possibly harmful/beneficial sequelae of post-traumatic inflammation in the central nervous system (CNS) are discussed using three model mediators of inflammation in the brain, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and transforming growth factor-β (TGF-β). While the former two may act as important mediators for the initiation and the support of post-traumatic inflammation, thus causing additional cell death and neurologic dysfunction, they may also pave the way for reparative processes. TGF-β, on the other hand, is a potent anti-inflammatory agent, which may also have some deleterious long-term effects in the injured brain. The implications of this duality of the post-traumatic inflammatory response for the treatment of brain-injured patients using anti-inflammatory strategies are discussed.

Index Entries: Traumatic brain injury; inflammation; neurons; astrocytes; microglia; blood brain barrier; cytokines; interleukin-6; transforming growth factor-β; tumor necrosis factor-α.

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Inflammatory Events Following TBI

Traumatic brain injury (TBI) may lead to a profound but variable swelling of brain tissue, clinically apparent as elevation of intracranial pressure (ICP). This swelling of the brain results in elevated ICP and reduced cerebral perfusion pressure (CPP), and is generally believed to be one of the leading causes of unfavorable outcome following TBI *(1).* The post-traumatic edema formation is associated with complex cytotoxic events and vascular leakage following the breakdown of the blood-brain barrier (BBB) *(2,3).* A profound disruption of the BBB has been observed in a variety of experimental TBI models *(2–8),* as well as in human TBI *(9–11).*

Infiltration and accumulation of polymorphonuclear leukocytes (PMNs) into brain parenchyma have been documented to occur in the acute post-traumatic period, reaching a peak by 24 h postinjury *(12,13).* Zhuang et al. *(14)* have suggested a relationship between cortical PMN accumulation and secondary brain injury, including lowered cerebral blood flow (CBF), increased edema, and elevated ICP. The migration of leukocytes into damaged tissue typically requires the adhesion of these cells to the endothelium, which is mediated by the expression of the intercellular adhesion molecule (ICAM-1), a member of the immunoglobulin super gene family. An upregulation of ICAM-1 has, in fact, been described in a variety of experimental TBI models *(15–18),* suggesting a role for leukocyte adhesion in the pathobiology of post-traumatic cell infiltration in the brain. In humans, soluble ICAM-1 (sICAM-1) in the cerebrospinal fluid (CSF) has been associated with the breakdown of the BBB after severe isolated TBI *(11).*

Alterations in blood-borne immunocompetent cells have been described in head-injured patients *(19–23).* Although it has been shown that influx of leukocytes and lymphocytes into the brain can occur in those regions in which tight junctions are missing, e.g., the circumventricular organs, or in the absence of BBB disruption via transendothelial migration, it is believed that BBB dysfunction in the acute post-traumatic period facilitates the intracerebral accumulation of these cells and affects neuronal survival/death (for review, *see* Perry et al., ref. *[24]*).

Immunocytochemical studies have further demonstrated the presence of macrophages, natural killer (NK) cells, helper T-cells, and T-cytotoxic suppressor cells as early as 2 d postinjury *(25,26).* The entry of macrophages into brain parenchyma following brain injury has been shown to be maximal by 24–48 h following lateral fluid-percussion (FP) brain injury in rats and after human TBI *(12,26,25).* A recent study in patients suffering from severe TBI suggested that the activated cell population following CNS trauma appears to be predominantly of the macrophage/microglia lineage, as opposed to the T-cell lineage *(27).* Both macrophages and microglia have been proposed as key cellular elements in the progressive tissue necrosis following spinal cord as well as brain trauma, presumably associated with the release of cytotoxic molecules (among them oxygen free radicals and inflammatory cytokines) that may be involved in mediating the local inflammatory response to trauma and the phagocytosis of debris from dying cells *(28–34).*

The specific cytokines and growth factors that have been implicated in the post-traumatic inflammatory cascade include tumor necrosis factor (TNF) and the interleukin (IL) family of peptides, as well as nerve growth factor (NGF) and transforming growth factor-β (TNF-β) *(35–38).* Alterations in systemic and intrathecal concentrations of cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-10, IL-12, and TNF-α as well as TGF-β have been reported to occur in human patients following severe head injury *(9,35–37,39–46),* and regional mRNA and protein concentrations of several of these cytokines have been shown to increase markedly in the acute post-traumatic period following experimental brain trauma in the rat *(47–53).*

As described earlier, the traumatized brain shows the classic hallmarks of inflammation: edema formation and swelling, activation of resident immune cells as well as cerebral infil-

tration by blood-borne immunocompetent cells, and impaired function. CNS inflammation was long believed to be a catastrophic event leading to sustained functional impairment and even death, as observed in other neuropathologies such as bacterial meningitis. However, there is increasing evidence that in the setting of brain trauma, inflammatory pathways may be of vital importance for initiation of a regenerative response. In order to highlight this possible duality of post-traumatic inflammation, the role of three different inflammatory mediators is elucidated below.

Tumor Necrosis Factor-α

Tumor necrosis factor-α, a pro-inflammatory cytokine of 17 kD, can be synthesized by several immune and nervous cells and is rapidly released after many types of insults to the CNS *(54).* As an early mediator, this cytokine shares several functions displayed by IL-1 and has the ability to induce a large number of pro-and anti-inflammatory cytokines, chemokines, and adhesion molecules. There are two receptors for TNF: TNFR1 (or p55) and TNFR2 (or p75). In the nervous system, these receptors are primarily expressed on glial and neuronal cells. It has been recently recognized that p55 signaling pathway determines the pathological features of TNF, whereas p75 seems to have a more protective role. Ligation of p55 activates a FADD (Fas-associated death domain)-mediated and/or FLICE (FADD-like IL-1-converting enzyme)-mediated pathway involving activation of caspases ultimately leading to cell apoptosis, or may conversely lead to TRADD (TNF receptor-associated death domain)-mediated activation of the transcription factor NF-κB, which may trigger repair mechanisms after experimental TBI *(55,56).* Activation of the p75 TNF receptor also leads to NF-κB activation. Both receptors are also released in a soluble form.

TNF-α has been detected in the CSF and serum of patients with TBI *(9,42,57).* Csuka and coworkers (1999) described individual patterns of TNF concentrations among 28 TBI patients over a 3-wk study period, with CSF levels generally higher than those found in serum. These observations, together with the detection of TNF-α mRNA and protein in the injured rodent brain, suggest that this cytokine is markedly and acutely unregulated in brain tissue following TBI *(48–50,52,58).* Following severe lateral FP injury, increases in TNF expression were immunohistochemically localized primarily to neurons, and to a much lesser extent to astrocytes *(49),* while after penetrating brain injury the increase of TNF-α has been related to trauma-induced astrogliosis *(59).* The upregulation of TNF-α therefore appears to be an endogenous response of the brain parenchyma to trauma, as opposed to being the result of an unspecific invasion of the brain by peripheral blood leukocytes.

TNF-α may mediate secondary damage following TBI through several different mechanisms (for an extensive review, *see* ref. *60*). This cytokine is known to affect BBB integrity, leading to cerebral edema and infiltration of blood leukocytes, and it has been shown to induce the receptor for the potent secondary inflammatory mediator anaphylatoxin (or C5a) on neurons *(61).* Furthermore, TNF can induce both apoptosis and necrosis via intracellular signaling pathways *(62).* It is therefore not surprising that both direct and indirect inhibition of TNF-α activity have been shown to be beneficial in numerous experimental TBI studies. Administration of the immunosuppressive pentoxifylline as well as of TNF binding protein (TBP), a physiological inhibitor of TNF-α activity, have been shown to significantly diminish edema formation and enhance motor function recovery following experimental TBI *(63).* Intravenous administration of the anti-inflammatory cytokine IL-10 improved neurological recovery and significantly reduced TNF expression in the traumatized cortex after injury *(64).* These studies suggest a detrimental effect of TNF in the sequelae of TBI. However, more recent investigations in genetically modified animals point toward a dual role of this cytokine following TBI. Mice deficient in both

subtypes of TNF receptors have been shown to be more vulnerable to TBI than wild-type animals, suggesting a neuroprotective role for TNF-α in the pathological sequelae of head injury *(56).* Moreover, brain-injured TNF deficient (–/–) mice show an early benefit from the lack of TNF with neurologic motor scores initially better than brain-injured wild-type controls. However, this trend is reversed from 1–4 wk after injury as the injured wild-type animals recover while the TNF–/– mice do not *(65).* Taken together, these data suggest that a differential role of this cytokine may be dependent on the temporal profile of its release within the post-traumatic cytokine cascade. These data suggest that antagonism of TNF activity may be beneficial for the injured brain in the acute post-traumatic period, but may prove deleterious if extended into the chronic phase, when it may participate in a regenerative response.

The induction of NGF in astrocytes by TNF-α in conjunction with IL-1 may be one mechanism by which pro-inflammatory cytokines may exert a beneficial action *(64,66).* More recently, TNF-α has been shown to modulate neural progenitor cells in the subventricular zone of adult rat brains *(67),* pointing toward an additional pathway through which this cytokine may enhance regeneration following trauma. It has also been suggested that in the chronic phase following brain injury, TNF may activate "anti-death "pathways, thereby becoming neuroprotective *(8,60).* In fact, activation of NF-κB by TNF-α may be associated with its anti-apoptotic effect on neurons and astrocytes *(68),* since prolonged activation of this transcription factor has been demonstrated in neurons and glia following experimental TBI in rats *(69)* (Fig. 1). However, further studies are necessary to solve the apparent dichotomy of TNF action in the post-traumatic setting. The exact time course of the cytokine release as well as the interaction with other pro- and anti-inflammatory mediators may well prove crucial for determining whether TNF has indeed both a beneficial and/or detrimental effect in the pathobiology of TBI.

Interleukin-6

The pleiotropic cytokine IL-6 has been implicated in a variety of physiological as well as pathological processes (for a comprehensive review *see* ref. 70). TNF-α is a potent inducer of IL-6 most likely via activation of nuclear factor-κB (NF-κB) *(71)* (Fig. 1). IL-6 was the first cytokine to be associated with neurotrophic properties, either directly when added to neuronal cultures *(72)* or indirectly through the induction of neurotrophin and NGF production by astrocytes *(73,74).* The IL-6 receptor belongs to the large family of class I receptors, which includes most of interleukins, GM-/F-CSF, Epo, LIF, and CNTF. The IL-6 receptor can be released in a soluble form (sIL-6R), which binds to the cytokine IL-6 forming a complex (IL-6/IL-6R), which then associates to the transmembrane protein gp130, known to transduce the signal. This peculiar structure is of particular importance for cells like neurons, which produce IL-6, and do not express the IL-6R but only gp130, and are therefore still susceptible to the actions of IL-6. Activation of gp130 results in a signaling pathway that involves the transcription factor JAK/STAT and in particular STAT-3 *(75).* It seems that class I cytokine receptors, despite an intrinsic tyrosine kinase activity, activate tyrosine phosphorylation of various proteins, MAP kinases, and induction of c-fos. Interestingly, it seems that distinct receptor domains are responsible for the various activities triggered by IL-6 such as induction of acute phase proteins, cell proliferation, and differentiation. Moreover, a synergistic function has been demonstrated for sIL-6R when combined with IL-6. IL-6 has been shown to protect cholinergic neurons in the rat striatum from N-methyl-D-aspartate (NMDA)-excitotoxicity *(76),* while it appears to conversely enhance NMDA-receptor mediated neurotoxicity in cerebellar granule neurons *(77).*

Elevated levels of IL-6 have been detected in the CSF and the serum of patients with severe TBI over a period of up to 3 wk following trauma *(37,40,78).* The pattern of IL-6 expression in these patients (higher concentrations in CSF than in serum) suggests an intrathecal

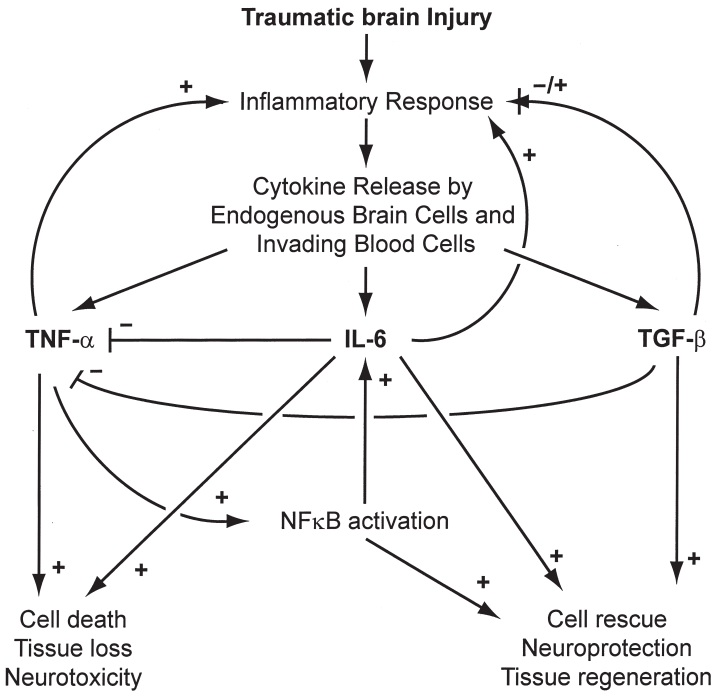

Fig. 1. Complex interrelationships between pro- and anti-inflammatory cytokines following traumatic brain injury. TBI leads to a profound inflammatory response with release of a myriad of inflammatory mediators. These mediators (e.g., tumor necrosis factor-α, interleukin-6, and transforming growth factor-β in turn have stimulatory (+) and/or inhibitory (–) effects on each other and the tissue response to trauma, leading to either cell death and tissue loss or neuroprotection and regeneration depending on the time point and location of action (*see* text for details).

production of this factor, which has been reported to occur in several models of experimental mechanical injury to the rodent brain *(51–52).* In a model of impact acceleration brain injury in rats, Hans and co-workers *(53)* demonstrated that IL-6 mRNA was upregulated in cortical and thalamic neurons as well as in infiltrating macrophages in the subarachnoid spaces as early as 1 h postinjury. IL-6 immunoreactivity on brain cryosections and IL-6 protein levels measured in rat CSF peaked within the first 24 h after the trauma *(53).* Thus, in this model, elevation of IL-6 in the CSF may be attributed to the production of IL-6 in brain parenchyma with consequent diffusion into the CSF of the ventricular system, as well as to production by macrophages in the subarachnoid spaces with direct secretion into the CSF.

There is little data elucidating the effect of this cytokine following TBI. In a study by Kossmann et al. *(78),* a relationship between high CSF concentrations of IL-6 and the detection of NGF in CSF was noted in brain-injured patients. In vitro experiments using CSF from these patients showed that IL-6 contained in these samples dose-dependently stimulated cultured primary mouse astrocytes to produce NGF, an effect that could be significantly attenuated by pre-incubation with anti-IL-6 antibodies *(78).* IL-6 released in the CNS has also been shown to be associated with the systemic acute-phase response following severe TBI in humans *(40),* indicating that centrally released immune mediators may evoke a substantial systemic response to trauma, with profound implications for the outcome of the patient.

Two studies employing mice genetically engineered to overexpress IL-6 reveal how the effect of IL-6 may vary greatly depending on the source and the target of this cytokine in the CNS. IL-6 overexpression in astrocytes under the control of a glial fibrillary acidic protein (GFAP) promoter leads to neuronal loss, BBB insufficiency, and vascular abnormalities with concurrent severe neurologic disease *(79).* However, if IL-6 expression is restricted to neurons using a neuron-specific enolase (NSE) promoter, animals still exhibit strong reactive gliosis similar to the GFAP-IL-6 mice, but they completely lack any overt neuronal pathology, vascular changes, or behavioral abnormalities *(80).* In a study subjecting IL-6 knockout mice and their wild-type littermates to a cortical freeze lesion, Penkowa and colleagues *(81)* found that the lack of IL-6 greatly reduced reactive astrogliosis and the appearance of brain macrophages around the lesion site. Interestingly, IL-6 deficiency also caused greater lesion-induced neuronal cell loss. These observations highlight the dual role that this pleiotropic cytokine may play in the post-traumatic cascade. Conversely, a recent study using IL-6 knockout mice subjected to experimental closed head injury showed that these animals were not significantly different from their wild-type littermates in their response to TBI in several outcome measures, such as neurologic motor function, BBB permeability, intracerebral neutrophil infiltration, and neuronal cell loss *(13).* Therefore, IL-6 appears to promote an inflammatory response to trauma but at the same time also seems to enhance neuronal survival through direct and indirect mechanisms. The exact nature, severity, and type of the CNS injury as well as the timing of IL-6 release may be decisive for either a detrimental or a beneficial effect of this factor following TBI. This may prove even more difficult to determine in the setting of clinical TBI, because of the heterogeneous pattern of brain injuries found in these patients, as compared to more defined lesions in standardized experimental TBI models *(82).*

Transforming Growth Factor-β

Transforming growth factor-β can be synthesized by nearly all cells of the CNS and is upregulated in many CNS disorders including clinical and experimental TBI *(10,83).* It is induced by a number of the classical pro-inflammatory cytokines and has been shown to inhibit the production of IL-1, TNF, interferon-γ (IFN-γ), oxygen radicals, MHC class II antigen expression, T-cell activation, adhesion of blood leukocytes, and proliferation of various cells including astrocytes *(54,84–87)* (Fig. 1). TGF-β signaling involves its type I (RI) and type II (RII) receptors while receptor type III, a proteoglycan, does not seem to have signaling properties but rather appears to increase receptor I and II binding affinity and to be involved in stroge functions of this cytokine. TGF-β binds first to TGF-βRII, a constitutive receptor serine/threonine kinase, that associates with RI. The RI is then phosphorylated in a glycine-serine-rich region known as the GS domain. Phosphorylation of the GS domain leads to the activation of the RI receptor kinase, which is essential for propagation of signals of the TGF-β receptor complex. It appears that RI determines the specificity of the intracellular signals and that the so-called Smad proteins mediate signaling from the cytoplasm to the nucleus. They associate forming a complex and function both as a coactivator of gene transcription as well as a transcription factor by directly binding to DNA *(75).*

TGF-β has been implicated in various neurological disease, including TBI. In head-injured patients, TGF-β reaches its maximal concentrations in CSF within the first days after injury *(9,10),* with levels being higher in serum than in CSF. These elevated intrathecal concentrations may therefore be the result of the passage of serum TGF-β to the CNS across the damaged BBB. However, in several patients the amount of TGF-β found in the CSF could not be explained by diffusion from the periphery only, suggesting that this mediator may also be released locally in the brain, possibly in an

attempt to attenuate cerebral inflammation. While microglia appear to be the primary CNS resident source of TGF-β, there is evidence that both neurons and astrocytes may produce this cytokine as well *(88–90).*

A beneficial role of anti-inflammatory cytokines has been suggested in various neurological diseases. In bacterial meningitis, administration TGF-β resulted in attenuated edema formation and reduced intracranial pressure, as well as a decreased white blood cell count in CSF *(91).* Several in vitro and in vivo studies of NMDA excitotoxicity and ischemia also demonstrated a neuroprotective effect of TGF-β and a marked reduction of lesion size *(92,93).* This effect is believed to be the result of a direct modulatory action on the NMDA receptor *(92).*

Despite these beneficial effects, other actions of TGF-β may potentially be harmful for the brain-injured tissue. The response to TGF differs distinctly between local and systemic administration *(87).* If administered locally TGF-β has chemotactic properties leading to leukocyte recruitment and activation, which paradoxically may help maintain an inflammatory response in the injured brain. It also enhances deposition of extracellular matrix (ECM) and formation of a glial scar, both of which may impair regenerative processes *(94,95).* Moreover, systemic administration of TGF has a profound immune inhibitory effect *(87),* potentially rendering the brain-injured patient more susceptible to infections. There may also be a long-term detrimental effect of TGF-β release in the brain, since evidence suggests that TGF-β increases expression of amyloid precursor protein (APP) and deposition of beta amyloid (Aβ), thereby playing a potential role in the pathogenesis of Alzheimer's disease (AD) *(96,97).* Epidemiological studies have suggested that head injury may be a risk factor for AD. *(98,99).* Cognitive dysfunction, evident as deficits in both memory and learning, is a well-established consequence of TBI. Histopathological examination of brains from patients who died as a consequence of head trauma has revealed Aβ deposition *(100),* and upregulation or accumulation of β-amyloid precursor protein (β-APP) similar to that noted after human TBI *(101)* has been observed in a variety of experimental TBI models *(102–104).* Additionally, Aβ 1–42 (an amyloid β-peptide species terminating at amino acid residue 42) has been found to be elevated in the CSF of severely head-injured patients *(105)* and to correlate with CSF levels of TGF-β *(106).* This truncated form of the Alzheimer protein may exacerbate or contribute to cell death in selectively vulnerable brain regions following experimental FP brain injury *(107).* While the role of IL-1 in the neuronal expression of β-APP in the acute period following human head injury has been examined *(108),* to our knowledge, no such study has been performed in the context of TGF, β-APP/Aβ, and TBI. Since it is possible that the predominantly positive anti-inflammatory effects of TGF-β in the acute phase following TBI may be offset by a long-term increase of risk for the development of AD, further investigations along these lines are certainly warranted.

Conclusion

There is overwhelming evidence of a profound inflammatory response to head trauma, and as such, TBI appears to be, in part, an inflammatory disease. Although previously defined as immunologically privileged, the brain exhibits many features of inflammation found also in other tissues following trauma. This initial post-traumatic inflammation is sustained by infiltrating inflammatory cells and the release of a myriad of soluble inflammatory mediators.

The role of this inflammatory process in the setting of CNS injury is unclear and the question of whether inflammation is good or bad for the injured brain remains unanswered. The acute response to trauma with its early edema formation is likely to be associated with inflammatory events which, together with the

cytotoxic effects of immune mediators, is believed to be deleterious for the injured brain by causing further secondary damage and neurological dysfunction. But as we begin to better understand the interactions between inflammatory mediators, growth factors, and the resident cells of the CNS, it has become increasingly apparent that this response, however detrimental it may be in the acute period following TBI, sets the stage for regenerative and reparative processes in the chronic phase of this disease. Understanding these differences with regard to timing and extent of the release of the different immune mediators as well as differential effects on different target cells may prove to be the key to developing new modalities for anti-inflammatory therapy following TBI. Future work on possible therapeutic strategies will have to focus on how to modify carefully these pathways in order to abolish the deleterious effects of acute CNS inflammation without sacrificing its beneficial actions on recovery of function and plasticity. Only when we better understand the duality of post-traumatic inflammation in the CNS can we hope to find an effective intervention to modify this response for the good of the patient suffering from TBI.

Acknowledgments

Supported, in part, by grants from the NIH (NINDS P50-NS08803, RO1-NS40978, NIGMS RO1-GM34690), a Merit Review grant and a VA-DOD consortium grant from the United States Veteran's Administration. P.M. Lenzlinger was supported, in part, by a research fellowship from the Swiss National Science Foundation (SNF) and an NTRSA Neurodevelopmental Disabilities Training Grant (T32 NS07413–04).

References

1. Marmarou A., Anderson R. L., Ward J. D., Choi S. C., Young H. F., Eisenberg H. M., et al. (1991) Impact of ICP instability and hypotension on outcome in patients with severe head trauma. *J. Neurosurg.* **75,** S59–S66.
2. Unterberg A. W., Stroop R., Thomale U. W., Kiening K. L., Pauser S., and Vollmann W. (1997) Characterisation of brain edema following "controlled cortical impact injury" in rats. *Acta Neurochir. (Supp.)* **70,** 106–108.
3. Baskaya M. K., Rao A. M., Dogan A., Donaldson D., and Dempsey R. J. (1997) The biphasic opening of the blood-brain barrier in the cortex and hippocampus after traumatic brain injury in rats. *Neurosci. Lett.* **226,** 33–36.
4. Hicks R. R., Baldwin S. A., and Scheff S. W. (1997) Serum extravasation and cytoskeletal alterations following traumatic brain injury in rats. Comparison of lateral fluid percussion and cortical impact models. *Mol. Chem. Neuropathol.* **32,** 1–16.
5. Barzo P., Marmarou A., Fatouros P., Corwin F., and Dunbar J. (1996) Magnetic resonance imaging-monitored acute blood-brain barrier changes in experimental traumatic brain injury. *J. Neurosurg.* **85,** 1113–1121.
6. Fukuda K., Tanno H., Okimura Y., Nakamura M., and Yamaura A. (1995) The blood-brain barrier disruption to circulating proteins in the early period after fluid percussion brain injury in rats. *J. Neurotrauma* **12,** 315–324.
7. Soares H. D., Thomas M., Cloherty K., and McIntosh T. K. (1992) Development of prolonged focal cerebral edema and regional cation changes following experimental brain injury in the rat. *J. Neurochem.* **58,** 1845–1852.
8. Cortez S. C., McIntosh T. K., and Noble L. J. (1989) Experimental fluid percussion brain injury: vascular disruption and neuronal and glial alterations. *Brain Res.* **482,** 271–282.
9. Csuka E., Morganti-Kossmann M. C., Lenzlinger P. M., Joller H., Trentz O., and Kossmann T. (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,** 211–221.
10. Morganti-Kossmann M. C., Hans V. H., Lenzlinger P. M., Dubs R., Ludwig E., Trentz O., and Kossmann T. (1999) TGF-beta is elevated in the CSF of patients with severe traumatic brain injuries and parallels blood-brain barrier function. *J. Neurotrauma* **16,** 617–628.
11. Pleines U. E., Stover J. F., Kossmann T., Trentz O., and Morganti-Kossmann M. C. (1998) Soluble ICAM-1 in CSF coincides with the extent of

cerebral damage in patients with severe traumatic brain injury. *J. Neurotrauma* **15,** 399–409.
12. Soares H. D., Hicks R. R., Smith D., and McIntosh T. K. (1995) Inflammatory leukocytic recruitment and diffuse neuronal degeneration are separate pathological processes resulting from traumatic brain injury. *J. Neurosci.* **15,** 8223–8233.
13. Stahel P. F., Shohami E., Younis F. M., Kariya K., Otto V. I., Lenzlinger P. M., et al. (2000) Experimental closed head injury: analysis of neurological outcome, blood-brain barrier dysfunction, intracranial neutrophil infiltration, and neuronal cell death in mice deficient in genes for pro-inflammatory cytokines. *J. Cereb. Blood Flow Metab.* **20,** 369–380.
14. Zhuang J., Shackford S. R., Schmoker J. D., and Anderson M. L. (1993) The association of leukocytes with secondary brain injury. *J. Trauma* **35,** 415–422.
15. Carlos T. M., Clark R. S., Franicola-Higgins D., Schiding J. K., and Kochanek P. M. (1997) Expression of endothelial adhesion molecules and recruitment of neutrophils after traumatic brain injury in rats. *J. Leukocyte Biol.* **61,** 279–285.
16. Isaksson J., Lewen A., Hillered L., and Olsson Y. (1997) Up-regulation of intercellular adhesion molecule 1 in cerebral microvessels after cortical contusion trauma in a rat model. *Acta Neuropathol.* **94,** 16–20.
17. Shibayama M., Kuchiwaki H., Inao S., Yoshida K., and Ito M. (1996) Intercellular adhesion molecule-1 expression on glia following brain injury: participation of interleukin-1 beta. *J. Neurotrauma* **13,** 801–808.
18. Rancan M., Otto V. I., Hans V. H., Gerlach I., Jork R., Trentz O., et al. (2001) Upregulation of ICAM-1 and MCP-1 but not of MIP-2 and sensorimotor deficit in response to traumatic axonal injury in rats. *J. Neurosci. Res.* **63,** 438–446.
19. Quattrocchi K. B., Miller C. H., Wagner F. C., Jr., DeNardo S. J., DeNardo G. L., Ovodov K., and Frank E. H. (1992) Cell-mediated immunity in severely head-injured patients: the role of suppressor lymphocytes and serum factors. *J. Neurosurg.* **77,** 694–699.
20. Quattrocchi K. B., Issel B. W., Miller C. H., Frank E. H., and Wagner F. C., Jr. (1992) Impairment of helper T-cell function following severe head injury. *J. Neurotrauma* **9,** 1–9.
21. Quattrocchi K. B., Frank E. H., Miller C. H., MacDermott J. P., Hein L., Frey L., and Wagner F. C., Jr. (1990) Suppression of cellular immune activity following severe head injury. *J. Neurotrauma* **7,** 77–87.
22. Hoyt D. B., Ozkan A. N., Hansbrough J. F., Marshall L., and vanBerkum-Clark M. (1990) Head injury: an immunologic deficit in T-cell activation. *J. Trauma* **30,** 759–766.
23. Piek J., Chesnut R. M., Marshall L. F., Berkum-Clark M., Klauber M. R., Blunt B. A., et al. (1992) Extracranial complications of severe head injury. *J. Neurosurg.* **77,** 901–907.
24. Perry V. H., Anthony D. C., Bolton S. J., and Brown H. C. (1997) The blood-brain barrier and the inflammatory response. *Mol. Med. Today* **3,** 335–341.
25. Holmin S., Soderlund J., Biberfeld P., and Mathiesen T. (1998) Intracerebral inflammation after human brain contusion. *Neurosurgery* **42,** 291–298.
26. Holmin S., Mathiesen T., Shetye J., and Biberfeld P. (1995) Intracerebral inflammatory response to experimental brain contusion. *Acta. Neurochir.* **132,** 110–119.
27. Lenzlinger P. M., Hans V. H. J., Morganti-Kossmann M. C., Joller H., Trentz O., and Kossmann T. (2001) Markers for cell-mediated immune response are elevated in cerebrospinal fluid and serum after severe traumatic brain injury in humans. *J. Neurotrauma* **18,** 479–489.
28. Aihara N., Hall J. J., Pitts L. H., Fukuda K., and Noble L. J. (1995) Altered immunoexpression of microglia and macrophages after mild head injury. *J. Neurotrauma* **12,** 53–63.
29. Korematsu K., Goto S., Nagahiro S., and Ushio Y. (1994) Microglial response to transient focal cerebral ischemia: an immunocytochemical study on the rat cerebral cortex using anti-phosphotyrosine antibody. *J. Cereb. Blood Flow Metab.* **14,** 825–830.
30. Kreutzberg G. W. (1996) Microglia: a sensor for pathological events in the CNS. *TINS* **19,** 312–318.
31. Popovich P. G., Wei P., and Stokes B. T. (1997) Cellular inflammatory response after spinal cord injury in Sprague- Dawley and Lewis rats. *J. Comp. Neurol.* **377,** 443–464.
32. Spranger M. and Fontana A. (1996) Activation of microglia: a dangerous interlude in immune function in the brain. *Neuroscientist* **2,** 293–299.
33. Thomas W. E. (1992) Brain macrophages: evaluation of microglia and their functions. *Brain Res. Rev.* **17,** 61–74.

34. Yamashita K., Niwa M., Kataoka Y., Shigematsu K., Himeno A., Tsutsumi K., et al. (1994) Microglia with an endothelin ETB receptor aggregate in rat hippocampus CA1 subfields following transient forebrain ischemia. *J. Neurochem.* **63,** 1042–1051.
35. Morganti-Kossmann M. C., Lenzlinger P. M., Hans V., Stahel P., Csuka E., Ammann E., et al. (1997) Production of cytokines following brain injury: beneficial and deleterious for the damaged tissue. *Mol. Psychiatry* **2,** 133–136.
36. Ott L., McClain C. J., Gillespie M., and Young B. (1994) Cytokines and metabolic dysfunction after severe head injury. *J. Neurotrauma* **11,** 447–472.
37. Hans V. H., Kossmann T., Joller H., Otto V., and Morganti-Kossmann M. C. (1999) Interleukin-6 and its soluble receptor in serum and cerebrospinal fluid after cerebral trauma. *Neuroreport* **10,** 409–412.
38. Rothwell N. J. and Hopkins S. J. (1995) Cytokines and the nervous system II: Actions and mechanisms of action. *TINS* **18,** 130–136.
39. Bell M. J., Kochanek P. M., Doughty L. A., Carcillo J. A., Adelson P. D., Clark R. S., et al. (1997) Interleukin-6 and interleukin-10 in cerebrospinal fluid after severe traumatic brain injury in children. *J. Neurotrauma* **14,** 451–457.
40. Kossmann T., Hans V. H., Imhof H. G., Stocker R., Grob P., Trentz O., and Morganti-Kossmann C. (1995) Intrathecal and serum interleukin-6 and the acute-phase response in patients with severe traumatic brain injuries. *Shock* **4,** 311–317.
41. Kossmann T., Stahel P. F., Lenzlinger P. M., Redl H., Dubs R. W., Trentz O., Schlalg G., and Morganti-Kossmann M. C. (1997) Interleukin-8 released into the cerebrospinal fluid after brain injury is associated with blood-brain barier dysfunction and nerve growth factor production. *J. Cereb. Blood Flow Metab.* **17,** 280–289.
42. Goodman J. C., Robertson C. S., Grossman R. G., and Narayan R. K. (1990) Elevation of tumor necrosis factor in head injury. *J. Neuroimmunol.* **30,** 213–217.
43. Young A. B., Ott L. G., Beard D., Dempsey R. J., Tibbs P. A., and McClain C. J. (1988) The acute-phase response of the brain-injured patient. *J. Neurosurg.* **69,** 375–380.
44. Cohen D., Phillips R., Ott L., and Young B. (1991) Increased plasma and ventricular fluid interleukin-6 levels in patients with head injury. *J. Lab. Clin. Med.* **118,** 225–231.
45. McClain C. J., Cohen D., Ott L., Dinarello C. A., and Young B. (1987) Ventricular fluid interleukin-1 activity in patients with head injury. *J. Lab. Clin. Med.* **110,** 48–54.
46. Whalen M. J., Carlos T. M., Kochanek P. M., Wisniewski S. R., Bell M. J., Clark R. S., et al. (2000) Interleukin-8 is increased in cerebrospinal fluid of children with severe head injury. *Crit. Care Med.* **28,** 929–934.
47. Fan L., Young P. R., Barone F. C., Feuerstein G. Z., Smith D. H., and McIntosh T. K. (1995) Experimental brain injury induces expression of interleukin-1 beta mRNA in the rat brain. *Mol. Brain Res.* **30,** 125–130.
48. Fan L., Young P. R., Barone F. C., Feuerstein G. Z., Smith D. H., and McIntosh T. K. (1996) Experimental brain injury induces differential expression of tumor necrosis factor-alpha mRNA in the CNS. *Mol. Brain Res.* **36,** 287–291.
49. Knoblach S. M., Fan L., and Faden A. I. (1999) Early neuronal expression of tumor necrosis factor-alpha after experimental brain injury contributes to neurological impairment. *J. Neuroimmunol.* **95,** 115–125.
50. Shohami E., Novikov M., Bass R., Yamin A., and Gallily R. (1994) Closed head injury triggers early production of TNF alpha and IL-6 by brain tissue. *J. Cereb. Blood Flow Metab.* **14,** 615–619.
51. Woodroofe M. N., Sarna G. S., Wadhwa M., Hayes G. M., Loughlin A. J., Tinker A., and Cuzner M. L. (1991) Detection of interleukin-1 and interleukin-6 in adult rat brain, following mechanical injury, by in vivo microdialysis: evidence of a role for microglia in cytokine production. *J. Neuroimmunol.* **33,** 227–236.
52. Taupin V., Toulmond S., Serrano A., Benavides J., and Zavala F. (1993) Increase in IL-6, IL-1 and TNF levels in rat brain following traumatic lesion. Influence of pre- and post-traumatic treatment with Ro5 4864, a peripheral-type (p site) benzodiazepine ligand. *J. Neuroimmunol.* **42,** 177–185.
53. Hans V. H., Kossmann T., Lenzlinger P. M., Probstmeier R., Imhof H. G., Trentz O., and Morganti-Kossmann M. C. (1999) Experimental axonal injury triggers interleukin-6 mRNA, protein synthesis and release into cerebrospinal fluid. *J. Cereb. Blood Flow Metab.* **19,** 184–194.
54. Benveniste E. N., Tang L. P., and Law R. M. (1995) Differential regulation of astrocyte TNF-alpha expression by the cytokines TGF-

beta, IL-6 and IL-10. *Int. J. Dev. Neurosci.* **13,** 341–349.
55. Kolesnick R. and Golde D. W. (1994) The sphingomyelin pathway in tumor necrosis factor and interleukin-1 signaling. *Cell* **77,** 325–328.
56. Sullivan P. G., Bruce-Keller A. J., Rabchevsky A. G., Christakos S., Clair D. K., Mattson M. P., and Scheff S. W. (1999) Exacerbation of damage and altered NF-kappaB activation in mice lacking tumor necrosis factor receptors after traumatic brain injury. *J. Neurosci.* **19,** 6248–6256.
57. Ross S. A., Halliday M. I., Campbell G. C., Byrnes D. P., and Rowlands B. J. (1994) The presence of tumor necrosis factor in CSF and plasma after severe head injury. *Br. J. Neurosurg.* **8,** 419–425.
58. Stover J. F., Schoning B., Beyer T. F., Woiciechowsky C., and Unterberg A. W. (2000) Temporal profile of cerebrospinal fluid glutamate, interleukin-6, and tumor necrosis factor-alpha in relation to brain edema and contusion following controlled cortical impact injury in rats. *Neurosci. Lett.* **288,** 25–28.
59. Rostworowski M., Balasingam V., Chabot S., Owens T., and Yong V. W. (1997) Astrogliosis in the neonatal and adult murine brain post-trauma: elevation of inflammatory cytokines and the lack of requirement for endogenous interferon-gamma. *J. Neurosci.* **17,** 3664–3674.
60. Shohami E., Ginis I., and Hallenbeck J. M. (1999) Dual role of tumor necrosis factor alpha in brain injury. *Cytokine Growth Factor Rev.* **10,** 119–130.
61. Stahel P. F., Kariya K., Shohami E., Barnum S. R., Eugster H., Trentz O., et al. (2000) Intracerebral complement C5a receptor (CD88) expression is regulated by TNF and lymphotoxin-alpha following closed head injury in mice. *J. Neuroimmunol.* **109,** 164–172.
62. Reid T. R., Torti F. M., and Ringold G. M. (1989) Evidence for two mechanisms by which tumor necrosis factor kills cells. *J. Biol. Chem.* **264,** 4583–4589.
63. Shohami E., Bass R., Wallach D., Yamin A., and Gallily R. (1996) Inhibition of tumor necrosis factor alpha (TNFalpha) activity in rat brain is associated with cerebroprotection after closed head injury. *J. Cereb. Blood Flow Metab.* **16,** 378–384.
64. Knoblach S. M. and Faden A. I. (1998) Interleukin-10 improves outcome and alters proinflammatory cytokine expression after experimental traumatic brain injury. *Exp. Neurol.* **153,** 143–151.
65. Scherbel U., Raghupathi R., Nakamura M., Saatman K. E., Trojanowski J. Q., Neugebauer E., et al. (1999) Differential acute and chronic responses of tumor necrosis factor-deficient mice to experimental brain injury. *Proc. Natl. Acad. Sci. USA* **96,** 8721–8726.
66. Gadient R. A., Cron K. C., and Oten U. (1990) Interleukin-1 beta and tumor necrosis factor-alpha synergistically stimulate nerve growth factor (NGF) release from cultured rat astrocytes. *Neurosci. Lett.* **117,** 335–340.
67. Wu J., Kuo J., Liu Y., and Tzeng S. (2000) Tumor necrosis factor-alpha modulates the proliferation of neural progenitors in the subventricular/ventricular zone of adult rat brain. *Neurosci. Lett.* **292,** 203–206.
68. Mattson M. P. and Camandola S. (2001) NF-kappaB in neuronal plasticity and neurodegenerative disorders. *J. Clin. Invest* **107,** 247–254.
69. Nonaka M., Chen X. H., Pierce J. E., Leoni M. J., McIntosh T. K., Wolf J. A., and Smith D. H. (1999) Prolonged activation of NF-kappaB following traumatic brain injury in rats. *J. Neurotrauma* **16,** 1023–1034.
70. Gruol D. L. and Nelson T. E. (1997) Physiological and pathological roles of interleukin-6 in the central nervous system. *Mol. Neurobiol.* **15,** 307–339.
71. Vanden Berghe W., Vermeulen L., De Wilde G., De Bosscher K., Boone E., and Haegegeman G. (2000) Signal transduction by tumor necrosis factor and gene regulation of the inflammatory cytokine interleukin-6. *Biochem. Pharmacol.* **60,** 1185–1195.
72. Kushima Y., Hama T., and Hatanaka H. (1992) Interleukin-6 as a neurotrophic factor for promoting the survival of cultured catecholaminergic neurons in a chemically defined medium from fetal and postnatal rat midbrains. *Neurosci. Res.* **13,** 267–280.
73. Marz P., Heese K., Dimitriades-Schmutz B., Rose-John S., and Otten U. (1999) Role of interleukin-6 and soluble IL-6 receptor in region-specific induction of astrocytic differentiation and neurotrophin expression. *GLIA* **26,** 191–200.
74. Frei K., Malipiero U. V., Leist T. P., Zinkernagel R. M., Schwab M. E., and Fontana A. (1989) On the cellular source and function of interleukin 6 produced in the central nervous system in viral diseases. *Eur. J. Immunol.* **19,** 689–694.

75. Benveniste E. N. (1998) Cytokine actions in the central nervous system. *Cytokine Growth Factor Rev.* **9,** 259–275.
76. Toulmond S., Vige X., Fage D., and Benavides J. (1992) Local infusion of interleukin-6 attenuates the neurotoxic effects of NMDA on rat striatal cholinergic neurons. *Neurosci. Lett.* **144,** 49–52.
77. Qiu Z., Sweeney D. D., Netzeband J. G., and Gruol D. L. (1998) Chronic interleukin-6 alters NMDA receptor-mediated membrane responses and enhances neurotoxicity in developing CNS neurons. *J. Neurosci.* **18,** 10,445–10,456.
78. Kossmann T., Hans V., Imhof H. G., Trentz O., and Morganti-Kossmann M. C. (1996) Interleukin-6 released in human cerebrospinal fluid following traumatic brain injury may trigger nerve growth factor production in astrocytes. *Brain Res.* **713,** 143–152.
79. Campbell I. L., Abraham C. R., Masliah E., Kemper P., Inglis J. D., Oldstone M. B., and Mucke L. (1993) Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6. *Proc. Natl. Acad. Sci. USA* **90,** 10061–10065.
80. Fattori E., Lazzaro D., Musiani P., Modesti A., Alonzi T., and Ciliberto G. (1995) IL-6 expression in neurons of transgenic mice causes reactive astrocytosis and increase in ramified microglial cells but no neuronal damage. *Eur. J. Neurosci.* **7,** 2441–2449.
81. Penkowa M., Moos T., Carrasco J., Hadberg H., Molinero A., Bluethmann H., and Hidalgo J. (1999) Strongly compromised inflammatory response to brain injury in interleukin-6-deficient mice. *GLIA* **25,** 343–357.
82. Laurer H. L., Lenzlinger P. M., and McIntosh T. K. (2000) Models of traumatic brain injury. *Euro. J. Trauma* **26,** 95–100.
83. Rimaniol A. C., Lekieffre D., Serrano A., Masson A., Benavides J., and Zavala F. (1995) Biphasic transforming growth factor-beta production flanking the pro-inflammatory cytokine response in cerebral trauma. *Neuroreport* **7,** 133–136.
84. Chao C. C., Hu S., Sheng W. S., Tsang M., and Peterson P. K. (1995) Tumor necrosis factor-alpha mediates the release of bioactive transforming growth factor-beta in murine microglial cell cultures. *Clin. Immunol. Immunopathol.* **77,** 358–365.
85. da Cunha A. and Vitkovic L. (1992) Transforming growth factor-beta 1 (TGF-beta 1) expression and regulation in rat cortical astrocytes. *J. Neuroimmunol.* **36,** 157–169.
86. Zhou D., Munster A., and Winchurch R. A. (1991) Pathologic concentrations of interleukin 6 inhibit T cell responses via induction of activation of TGF-beta. *FASEB J.* **5,** 2582–2585.
87. Wahl S. M. (1994) Transforming growth factor beta: the good, the bad, and the ugly. *J. Exp. Med.* **180,** 1587–1590.
88. Finch C. E., Laping N. J., Morgan T. E., Nichols N. R., and Pasinetti G. M. (1993) TGF-beta 1 is an organizer of responses to neurodegeneration. *J. Cell. Biochem.* **53,** 314–322.
89. Zhu Y., Roth-Eichhorn S., Braun N., Culmsee C., Rami A., and Krieglstein J. (2000) The expression of transforming growth factor-beta1 (TGF-beta1) in hippocampal neurons: a temporary upregulated protein level after transient forebrain ischemia in the rat. *Brain Res.* **866,** 286–298.
90. Lehrmann E., Kiefer R., Christensen T., Toyka K. V., Zimmer J., Diemer N. H., et al. (1998) Microglia and macrophages are major sources of locally produced transforming growth factor-beta1 after transient middle cerebral artery occlusion in rats. *GLIA* **24,** 437–448.
91. Frei K., Piani D., Pfister H. W., and Fontana A. (1993) Immune-mediated injury in bacterial meningitis. *Int. Rev. Exp. Pathol.* **34 Pt B,** 183–192.
92. Ruocco A., Nicole O., Docagne F., Ali C., Chazalviel L., Komesli S., et al. (1999) A transforming growth factor-beta antagonist unmasks the neuroprotective role of this endogenous cytokine in excitotoxic and ischemic brain injury. *J. Cereb. Blood Flow Metab.* **19,** 1345–1353.
93. Henrich-Noack P., Prehn J. H., and Krieglstein J. (1994) Neuroprotective effects of TGF-beta 1. *J. Neural Transm. Suppl* **43,** 33–45.
94. Logan A. and Berry M. (1993) Transforming growth factor-beta 1 and basic fibroblast growth factor in the injured CNS. *Trends Pharmacol. Sci.* **14,** 337–342.
95. Logan A., Berry M., Gonzalez A. M., Frautschy S. A., Sporn M. B., and Baird A. (1994) Effects of transforming growth factor beta 1 on scar production in the injured central nervous system of the rat. *Eur. J. Neurosci.* **6,** 355–363.
96. Gray C. W. and Patel A. J. (1993) Regulation of beta-amyloid precursor protein isoform mRNAs by transforming growth factor-beta 1 and interleukin-1 beta in astrocytes. *Brain Res. Mol. Brain. Res.* **19,** 251–256.

97. Frautschy S. A., Yang F., Calderon L., and Cole G. M. (1996) Rodent models of Alzheimer's disease: rat A beta infusion approaches to amyloid deposits. *Neurobiol. Aging* **17,** 311–321.
98. Mayeux R., Ottman R., Tang M. X., Noboa-Bauza L., Marder K., Gurland B., and Stern Y. (1993) Genetic susceptibility and head injury as risk factors for Alzheimer's disease among community-dwelling elderly persons and their first-degree relatives. *Ann. Neurol.* **33,** 494–501.
99. Mortimer J. A., Van Duijn C. M., Chandra V., Fratiglioni L., Graves A. B., Heyman A., et al. (1991) Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int. J. Epidemiol.* **20(Suppl. 2),** S28–S35.
100. Roberts G. W., Gentleman S. M., Lynch A., Murray L., Landon M., and Graham D. I. (1994) Beta amyloid protein deposition in the brain after severe head injury: implications for the pathogenesis of Alzheimer's disease. *J. Neurol. Neurosur. Psychiatry* **57,** 419–425.
101. Graham D. I., Gentleman S. M., Nicoll J. A., Royston M. C., McKenzie J. E., Roberts G. W., and Griffin W. S. (1996) Altered beta-APP metabolism after head injury and its relationship to the aetiology of Alzheimer's disease. *Acta. Neurochir. (Suppl.)* **66,** 96–102.
102. Lewen A., Li G. L., Nilsson P., Olsson Y., and Hillered L. (1995) Traumatic brain injury in rat produces changes of beta-amyloid precursor protein immunoreactivity. *Neuroreport* **6,** 357–360.
103. Pierce J. E., Trojanowski J. Q., Graham D. I., Smith D. H., and McIntosh T. K. (1996) Immunohistochemical characterization of alterations in the distribution of amyloid precursor proteins and beta-amyloid peptide after experimental brain injury in the rat. *J. Neurosci.* **16,** 1083–1090.
104. Van den Heuvel C., Blumbergs P. C., Finnie J. W., Manavis J., Jones N. R., Reilly P. L., and Pereira R. A. (1999) Upregulation of amyloid precursor protein messenger RNA in response to traumatic brain injury: an ovine head impact model. *Exp. Neurol.* **159,** 441–450.
105. Raby C. A., Morganti-Kossmann M. C., Kossmann T., Stahel P. F., Watson M. D., Evans L. M., et al. (1998) Traumatic brain injury increases beta-amyloid peptide 1–42 in cerebrospinal fluid. *J. Neurochem.* **71,** 2505–2509.
106. Emmerling M. R., Morganti-Kossmann M. C., Kossmann T., Stahel P. F., Watson M. D., Mehta P. D., et al. (2000) Traumatic brain injury elevates the Alzheimer's amyloid peptide A beta 42 in human CSF. A possible role for nerve cell injury. *Ann. NY Acad. Sci.* **903,** 118–122.
107. Smith D. H., Nakamura M., McIntosh T. K., Wang J., Rodriguez A., Chen X. H., et al. (1998) Brain trauma induces massive hippocampal neuron death linked to a surge in beta-amyloid levels in mice overexpressing mutant amyloid precursor protein. *Am. J. Pathol.* **153,** 1005–1010.
108. Griffin W. S., Sheng J. G., Gentleman S. M., Graham D. I., Mrak R. E., and Roberts G. W. (1994) Microglial interleukin-1 alpha expression in human head injury: correlations with neuronal and neuritic beta-amyloid precursor protein expression. *Neurosci. Lett.* **176,** 133–136.