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## Astrogliosis in CNS Pathologies: Is There A Role for Microglia?

**Dan Zhang,**

Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709, USA

**Xiaoming Hu,**

Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709, USA

Department of Neurology and Pittsburgh Institute of Neurodegenerative Diseases, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, USA

**Li Qian,**

Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709, USA

Comprehensive Center for Inflammatory Disorders, University of North Carolina, Chapel Hill, NC 27599, USA

**James P. O’Callaghan, and**

Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Morgantown, WV 26505, USA

**Jau-Shyong Hong**

Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709, USA

Dan Zhang: zhangd2@niehs.nih.gov

### Abstract

Astrogliosis, a cellular reaction with specific structural and functional characteristics, represents a remarkably homotypic response of astrocytes to all kinds of central nervous system (CNS) pathologies. Astrocytes play diverse functions in the brain, both harmful and beneficial. Mounting evidence indicates that astrogliosis is an underlying component of a diverse range of diseases and associated neuropathologies. The mechanisms that lead to astrogliosis are not fully understood, nevertheless, damaged neurons have long been reported to induce astrogliosis and astrogliosis has been used as an index for underlying neuronal damage. As the predominant source of proinflammatory factors in the CNS, microglia are readily activated under certain pathological conditions. An increasing body of evidence suggests that release of cytokines and other soluble products by activated microglia can significantly influence the subsequent development of astrogliosis and scar formation in CNS. It is well known that damaged neurons activate microglia very quickly, therefore, it is possible that activated microglia contribute factors/mediators through which damaged neuron induce astrogliosis. The hypothesis that activated microglia initiate and maintain astrogliosis suggests that suppression of microglial overactivation might effectively attenuate reactive astrogliosis. Development of targeted anti-microglial activation therapies might slow or halt the progression of astrogliosis and, therefore, help achieve a more beneficial environment in various CNS pathologies.

## Keywords

Astrocyte; GFAP; Astrogliosis; Microglia; Cytokine

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## Astrocyte and Astrogliosis

Astrocytes, also known as astroglia, are the most abundant cells in the central nervous system (CNS). Astrocytes are classically identified as cells expressing the intermediate filament glial fibrillary acidic protein (GFAP). Although originally defined as gap fillers for the neuronal network, astrocytes now have been found to play a number of active roles in the brain. Many reports show that astrocytes express ion channels, both ligand-gated and voltage-dependent [1], have the general functions of clearing neurotransmitters and ions away from the synapse [2, 3] and more direct and active roles in synapse function [4, 5]. There also are some reports showing that astrocytes play an important role in regulating the function of oligodendrocytes [6, 7] and neural stem cells [8, 9].

In various CNS pathologies, astrocytes are likely to react promptly to the injury, leading to activation of astroglia or astrogliosis [10]. Astrogliosis is characterized by the increase of intermediate filaments with accompanying cellular hypertrophy and an abnormal apparent increase in the number of astrocytes. Upregulation of intermediate filament proteins, in particular vimentin and GFAP by astrocytes, is regarded as the hallmark of astrogliosis. GFAP is the major intermediate filament protein in mature astrocytes and forms an important part of the intermediate filament cytoskeleton of the astrocyte. Increased protein content or immunostaining of GFAP has been found in numerous experimental models involving astrogliosis [10–14]. O’Callaghan has proposed that GFAP is a sensitive and early biomarker of astrogliosis after neurotoxic insults [15–18]. The levels of vimentin, another intermediate filaments, in astrocytes range from very low to intermediate, depending on the subpopulation of astrocytes. It is suggested that vimentin re-expression following injury in reactive astrocytes is indicative of these cells recapitulating developmental migratory processes [19, 20]. In the absence of an examination of intermediate filaments, astrocyte hypertrophy and the appearance astrocyte proliferation serve as features of astrogliosis [21, 22].

The functions of reactive astrocytes are not well understood, and both harmful and beneficial activities are reported. Reactive astrogliosis is highly conserved, an observation suggestive of its benefits, and given credence by astrocytic functions such as releasing neurotrophic factors, glutamate uptake, and free radical elimination [23]. Over time, however, astrogliosis may become detrimental by restricting axon regeneration, hindering functional recovery and secreting excessive neurotoxic substances.

## Multiple roles of Reactive Astrogliosis after CNS Insults

### Reactive Astrogliosis Protects Neurons and Neural Function

Under normal conditions, astrocytes maintain homeostasis in the CNS to support the survival and information processing functions of neurons. Upon activation, astrocytes up-modulate a large number of molecules and benefit the injured nervous system by regulating diverse biological processes. For at least a century, the neuropathology literature has documented that damage to the CNS results in conversion of astrocytes into their “reactive” or “activated” form. Trauma [24], ischemia [25], infectious [26] and neurological diseases [27] and, more recently, chemical exposures [28], all are known to have the capacity to induce astrogliosis. Moreover, despite the brain region and cell-type selective nature of nervous system diseases and neurotoxicity, damage to any cell, anywhere in the CNS,

appears to result in local activation of astroglia. Despite the recognition of astrogliosis as a universal response to nervous system damage, biochemical features of glial activation only recently have been documented. While the functional significance of astrogliosis remains to be more clearly defined, recognition that it is a rapid and universal response to all types of brain insults argue in favor of a role for astrogliosis in repair and recovery [18, 29, 30]. As examples of the trophic role of astrocytes, activated astrocyte upregulate the expression of neurotrophic factors including glial-cell-derived-neurotrophic factors (GDNF) and BDNF. The studies in the GFAP–GDNF transgenic mouse reported that increased expression of GDNF in astrocytes elevated the number of neighboring motoneurons of certain subpopulations by diminishing programmed cell death during development [31]. Additionally, astrocyte-derived GDNF was protective to facial motoneurons against injury-induced cell death [32]. Astrocytes are also known to play a crucial role in regulating extracellular glutamate and restrict glutamate excitotoxicity to neurons and other cell types [33]. Thus, an impairment of astroglial performance has the potential to exacerbate neuronal dysfunction. Transgenic ablation of reactive astrocytes after CNS injury markedly increase neuronal death and exacerbates tissue degeneration [34–36].

### **Reactive Astrogliosis Restores Blood Brain Barrier (BBB) Function and Remodel Neurovascular Unit after CNS Injury**

The BBB is a dynamic structure that can be remodeled by many factors including inflammatory cytokines, angiogenic factors, glutamatergic toxicity, and oxidative stress [37]. Astrocytes play fundamental roles in maintenance and repair of the BBB after CNS injury. The ablation of reactive astrocytes after CNS injury impairs BBB repair, which can be restored by grafting nontransgenic astrocytes [34]. The normal BBB consists of a series of structures collectively known as neurovascular units, which are composed of endothelial cells and astrocyte end feet separated by a basal lamina at their interface.

Astrocytes have been shown to contribute to development of the BBB presumably by their secretion of factors that differentiate capillaries to the BBB type, in terms of developing far less impermeable tight junctions. Recently, GDNF were reported to be one of those factors. Astrocytes also secrete several angiogenic factors such as angiopoietin-1 and neurotrophins that are thought to play a role in the development of the new brain capillary function [38]. On the molecular level, increased expression of barrier-relevant proteins (e.g., tight junction proteins) is documented in the presence of astrocyte-derived factors, and many studies demonstrate the improvement of physiological parameters, such as increased transendothelial resistance and decreased paracellular permeability, in different in vitro models of the BBB [39].

### **Reactive Astrogliosis Inhibits Axon Regeneration**

Astrocytes provide support and guidance for axonal growth and aid in improving functional recovery after CNS injury [40]. However, prolonged activation of astrocytes becomes detrimental to axon growth. Hypertrophic astrocytic processes enmesh the lesion site and deposit an inhibitory extracellular matrix consisting primarily of chondroitin sulfate proteoglycans. This tissue reaction results in the formation of a dense complicated structure that is inhibitory to regenerating axons [41]. The glial scar formed mainly by reactive astroglia represents an inhibitory physical and chemical barrier for axonal regeneration and functional connection reestablishment [42]. Increased axon regeneration has been reported in transgenic mice deficient in both GFAP and vimentin, thereby altering astrocyte reactivity after injury [43, 44]. Thus, limiting astrogliosis could be critical for the axon regeneration after neuronal injury.

## Reactive Astrogliosis has the Potential for Neural Toxicity

Reactive astrocytes can produce proinflammatory and cytotoxic cytokines that are harmful to neurons or oligodendrocytes in the lesioned brain, which in turn can lead to further damage via, e.g., nitric oxide radicals and TNF- $\alpha$  [45]. Expression of nitric oxide synthase is elevated in astrocytes in many neurological diseases. Nitric oxide produced by reactive astrocytes is able to damage local neural cells, oligodendrocytes and other cell types [46]. TNF- $\alpha$ , which is known to play an important role in the initiation of inflammation and pathologic consequences, has been found to be released from activated astrocyte after brain injuries and other neurological disorders [47]. It has been reported that when astrogliosis is pharmacologically inhibited *in vivo*, cytokine production is reduced and the neuronal damage is attenuated [48].

Astrogliosis is reported to be linked to the onset and duration of neural cell damage in the affected brain region and is believed to be an underlying component of a diverse range of diseases and associated neuropathology, including epilepsy [49, 50], multiple sclerosis [51], amyotrophic lateral sclerosis [52, 53], HIV infection [54, 55], stroke [56], cerebral ischemia [22], etc. Neuronal damage after acute traumatic brain injury also is closely linked to the formation of astrogliosis [57]. In summary, reactive astrogliosis is one of the key components of the cellular response to CNS injury and it has been suggested to be an attempt by the CNS to restore homeostasis through isolation of the damaged region [58], while at the same time astrogliosis is commonly regarded as a major impediment to axonal regeneration. Reactive astrogliosis and scar formation might delay or inhibit regenerative responses, therefore, this astrocytic reaction may play an important role in the pathogenesis and progression of diverse neuropathological conditions.

## Microglia in CNS

Microglia are derived from myeloid cells in the periphery and are the resident macrophage-like cells in the CNS, comprising approximately 12% of cells in the brain. In the mature brain, microglia typically exist in a resting state characterized by ramified morphology and the expression of certain cell surface antigens, such as CD14, major histocompatibility complex molecules, chemokine receptors, and several other markers [59]. By monitoring the brain environment, microglia perform homeostatic activity in the normal CNS, a function associated with high motility of their ramified processes and their constant phagocytic clearance of cell debris [60]. In response to certain pathological conditions of the brain such as viral [61] or bacterial infection [62] or CNS injury [63], microglia are readily activated and undergo a dramatic transformation from their resting ramified state into an amoeboid morphology. In their activated state, they can serve diverse beneficial functions essential to neuron survival, which include cellular maintenance and innate immunity. Activated microglia are also involved in regulating brain development and neurogenesis through the release of trophic and anti-inflammatory factors [64]. However, in certain circumstances, microglia will be over-activated and induce detrimental neurotoxic effects by releasing a diverse set of cytotoxic substances, including proinflammatory factors [TNF- $\alpha$ , prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), and interferon- $\gamma$ ] and oxidative stress factors [nitric oxide, hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), O<sub>2</sub><sup>-</sup>, and ONOO<sup>-</sup>/ONOOH], which are toxic to neurons [65].

## Microglia: The Immune Regulation of Astrogliosis

Although astrogliosis is associated with diverse neurological disorders, the cellular and molecular mechanisms leading to astrogliosis are still not completely understood. Damaged neurons have long been reported to induce astrogliosis and astrogliosis has been used as an index for neuronal damage [17]. Nevertheless, it is becoming more and more widely accepted that microglia might play an important role in astrogliosis. A recent *in vitro* studies

indicate the important impact of activated microglia on astrogliosis [66]. This assumption was further supported by the finding that the proinflammatory factors released by microglia play an important role as triggers and modulators of astrogliosis. Moreover, in animal models, reduced microglial activation is associated with reduced astrocyte cell number [67–69], which also indicates the important role of microglia on astrogliosis. There are a multitude of publications indicating that damaged neurons activate microglia [70, 71], suggesting that microglia are microsensors of, and respond to, neuronal pathology [72].

### **Microglial Activation Precedes Astrogliosis after CNS Injury**

The activation of microglia and astrocytes, and the accompanying elaboration of proinflammatory mediators, occurs in the CNS of patients with diverse diseases, such as AD, PD, ALS, etc. [70]. The level of glial cell reaction to a great extent reflects the severity of a brain injury. Innate immunity by antigen-presenting cells is the first line of defense against foreign materials. In the brain, this response is mainly orchestrated by microglial cells [73]. In the presence of pathogens, acute neuronal insults, and more chronic neurological diseases, neuronal loss activates microglial cells in the CNS. As the primary immune effector cells of the CNS, activated microglial cells phagocytose the proteins of dead neurons, present this neuronal fingerprint at their surface, and produce proinflammatory cytokines and toxic molecules that compromise neuron survival [70]. As the first line of defense in the CNS, microglia must respond immediately to the presence of danger signals [74], react quickly to increased inflammatory signals and destroy the infectious agents before they damage sensitive neural tissue. Since this process must be done quickly to prevent potentially fatal damage, microglia are extremely sensitive to even small pathological changes in the CNS [59, 75]. In contrast to the rapidly occurring microglial response, the astrocyte response is usually delayed. It is suggested that in conjunction with the secretion of cytokines, activated microglia disturb astrocyte functions [76] and may, as a consequence, contribute to the subsequent activation of astrocytes.

In human studies, microglial activation and astrogliosis were examined on spinal cord tissues of five patients who died after unilateral infarction of the middle cerebral artery territory, and five control cases. In patients who died shortly after a stroke, increased microglia-immunoreactivity could be observed in the intermediate gray matter, whereas a moderate increase of GFAP-positive astrocytes could only be observed in the gray matter of patients with longer survival times after stroke [77]. In another Creutzfeldt-Jakob disease human study, the presence of class II-positive microglia (activated microglia) correlated well with the presence of vacuolation in the brain in early stage, at later stages, however, diseased microglia could produce harmful factors which mediate both astrogliosis and neuronal injury [78]. The results support the point that astrogliosis is a later response compared to microglial activation. This phenomenon also has been confirmed in animals. In several lesion paradigms, a microglial response is reported to be followed by an astrocyte reaction [79]. Reaction of microglia and astrocytes in the cortex of the rat resulting from stereotaxic lesioning of the entorhinal cortex were studied and the data provide evidence that microglia react to the injury more rapidly and intensively than astrocytes [80]. Activated microglia have also been observed within and adjacent to the primary traumatic injury site within several hours after injury, whereas astrogliosis occurred several days later [81, 82]. In MPTP-induced neuropathological damage in mice, activation of microglia peaked at 2 days and activation of astrocyte peaked at 4 days after injection [83]. In a trimethyl tin-intoxication-induced rat brain injury model, activated microglia first appeared at 2 days after intoxication, characterized by microglial hypertrophy and the formation of phagocytic clusters. Significant increases in the expression of GFAP protein, which indicated the presence of astrogliosis, typically occurred after microglial activation was already underway [84]. To further study the process of microglial activation and astrocyte activation, primary

mesencephalic neuron-glia cultures were prepared. The neuronal damage in the cultures were induced by adding 0.5  $\mu\text{M}$  1-methyl-4-phenylpyridinium ( $\text{MPP}^+$ ), which is an active metabolite of dopaminergic neurotoxin MPTP. At different time points after  $\text{MPP}^+$  challenge, Iba-1 and GFAP protein expression were evaluated as markers of microglial and astrocyte activation, respectively. The results shown in Fig. 1 indicated neuronal damage induced by  $\text{MPP}^+$  first triggered microglial activation; while the presence of astrocyte activation emerged later than microglial activation. These results all suggested that microglial and astroglial reactions which occur in response to neuronal death are separated in time, with microglial activation preceding astrogliosis. This widely documented temporal relationship suggests that microglial activation might be involved in the onset and maintenance of astrogliosis.

### Proinflammatory Cytokines from Microglia Induce Astrogliosis

Recent studies focused on the cellular and molecular mechanisms underlying astrogliosis suggest that proinflammatory cytokines and chemokines might play an important role as triggers and modulators of astrogliosis. Cytokines can serve the function of cellular communication. Released for auto- and paracrine signaling, membrane-associated for cell-cell interaction, or occasionally carrying biological information through body fluids, cytokines are reported to regulate cell growth, survival, differentiation, and other activities [85]. Countless cellular interactions within and between brain tissues are based on the exchange of cytokines and chemokines. Activated microglia are a predominant source of cytokines within the CNS and are reported to release a series of proinflammatory cytokines and chemokines, such as interleukins, monocyte chemoattractant protein-1 (MCP-1), macrophage colony stimulating factor (M-CSF), macrophage inflammatory protein-1 $\alpha/\beta$  (MIP), TNF- $\alpha$ , etc. [86]. The levels of microglia-derived cytokines are known to be elevated following injury [87] and the receptors for most of these cytokines have been identified on astrocytes. Astrocytes express receptors for IL-1 [88], IL-6 [89], IL-8 [90], MIP [91], and M-CSF [92]. Additionally, TNF- $\alpha$  receptors are reported to be constitutively expressed on astrocytes and have effects on glutamate transmission directly and indirectly by inhibiting glial glutamate transporters on astrocytes [93, 94]. Microglia may initiate or modulate astrogliosis by acting on these cytokine receptors.

The effect of proinflammatory factors on the induction of astrogliosis has been examined in several studies. In vivo data obtained with cytokine-related transgenics, knockouts, and with direct administration of cytokines into brain indicate that different kinds of cytokines markedly facilitate astrogliosis. Prominent representatives of proinflammatory factors such as IL-1, IL-6, and TNF- $\alpha$  have been shown to induce, enhance, or accompany astrogliosis [95–99]. Balasingam et al. [100] utilized a neonatal stabwound mouse model where cytokines were microinjected into the wound site at the time of injury. All cytokines tested (IL-1, IL-2, IL-6, TNF- $\alpha$ , and M-CSF) resulted in a significantly increased astrogliosis, the minimal GFAP immunoreactivity observed following a stab injury to the neonatal brain can be converted to extensive GFAP immunoreactivity by these single microinjection of cytokines. It also has been reported that recombinant forms of IL-1 injected into the cerebral cortex of adult rats elicit astrogliosis and that IL-1 receptor antagonists prevent astroglial proliferation [101]. It has also been found that corticectomy injury induced more astrogliosis in IL-1 $\beta^{+/+}$  mice than in IL-1 $\beta^{-/-}$  mice [102]. Similarly, a standard MPTP regimen induced more astrogliosis in IL-6 $^{+/+}$  mice than in IL-6 $^{-/-}$  mice [96], although an acute regimen of MPTP did not show more astrogliosis in IL-6 $^{+/+}$  mice than in IL-6 $^{-/-}$  mice [103]. In aggregate, these in vivo studies support a role for cytokines in astrogliosis. There also are several publications indicating effects of cytokines on astrogliosis based on in vitro data. TNF- $\alpha$  is reported to directly induce astrocyte proliferation and an increase in GFAP expression in culture system [95, 99]. Addition of IL-1 $\beta$  to the culture medium significantly

increased the ratio of GFAP<sup>+</sup> glia cells and consequently increased intracellular GFAP content. Neutralizing antibody to IL-1 $\beta$  receptor antagonist completely abolished the stimulating effect of IL-1 $\beta$  on astrocyte activation [104]. In addition to cytokines, evidence linked to prostaglandin release by activated microglia implicates their involvement in astrogliosis as well. PGD<sub>2</sub> over-expressed mice showed more astrogliosis after brain damage and PGD<sub>2</sub> can induce significant activation of primary cultured astrocyte [98]. PGE<sub>2</sub> also has been reported to play a critical role in microglia-induced astrocyte proliferation [76].

Although microglia are major sources of cytokines, there also is evidence for induction of cytokines in astrocytes. Moreover, astrocytes produce cytokines that can act on microglia, thus creating a paracrine and autocrine feedback loop whereby microglia-derived factors and astroglial-derived factors regulate each other [105].

## Microglial Modulation: New Treatment Opportunities for Over-Activated Astrogliosis

The importance of microglia for astrogliosis also has been provided by experimental data where suppression of astrogliosis can be achieved by inhibiting the activation of microglia. Minocycline is a selective microglial activation inhibitor. It is reported that in animal models of neuropathic pain, minocycline-induced microglial activation inhibition was associated with astrogliosis suppression [106]. In a progressive brain injury rat model, astrogliosis induced by hypoxia-ischemia was also diminished after administration of minocycline, demonstrated by low level of GFAP immunoreactivity [107]. M-CSF is a cytokine that stimulates and activates microglia. Raivich et al. used 6-aminonicotinamide to induce degeneration of brainstem neuroglial cells in the gray matter and found that there was astrogliosis in the damaged brain areas. The numbers of reactive astrocytes in the damaged areas were significantly decreased in M-CSF<sup>-/-</sup> mice relative to controls, indicating an association between microglial activation and astroglial cell number [108]. Similarly, reduced astrogliosis was observed in SN pars compacta of IL-6<sup>-/-</sup> mice with compromised microgliosis [96].

The possible impact of microglial activation/proliferation on reactive astrogliosis after spinal cord injury was also determined in rats with hemi-section injury. After injury, astrogliosis were observed in the gray matter with intensive immunoreactivity to GFAP; thick, richly branched processes with GFAP-positive staining in both rostral and caudal areas to the hemi-section. In the group treated with the cell cycle inhibitor olomoucine, in which microglial proliferation was markedly suppressed, GFAP staining showed much weaker immunoreactivity than that in the vehicle-treated group. In addition, olomoucine also effectively attenuated the astroglial proliferation and subsequent glial scar formation and ameliorated behavior outcome of injured rats, which implied the direct impact of microglial inhibition on attenuated astroglial scar formation [109]. Another study reported that the tissue response to electrodes in the brain was characterized by the formation of glial scar and electrode encapsulation. In the electrode encapsulation, microglia are the frontline cells in direct contact with the electrode surface and astroglial scar around microglia will form several weeks later. It is found that neuroimmunomodulatory peptide-modified electrode reduced the microglial response post-implantation by making the electrode surface inherently anti-inflammatory. As a result of microglial inhibition, the astrocyte response, i.e., the formation of scar was attenuated [110].

## Conclusions and Future Directions

The role of astrogliosis in surrounding a lesion is complex, as it involves features promoting both neuronal survival and delayed neuronal injury. More recent evidence suggests that the

process of astroglial reactivity may actually be an attempt by these cells to promote CNS recovery. Nevertheless, the glial scar, comprised largely of activated astrocytes, can promote neurotoxic effects and be inhibitory to axon regeneration. We have presented a brief review of the evidence showing the involvement of astrogliosis in a variety of CNS pathologies. Modulation of astrogliosis after CNS injury with one or more interventions, at a minimum, would enhance our understanding of the role of astrocytes in CNS injury and repair. Ideally, astroglial “therapy” may promote a beneficial environment in the CNS. Although different combinations of mechanisms might be involved in the initiation and progression of astrogliosis, accumulating evidence indicates the involvement of activated microglia (Fig. 2). The references presented here shed light on the potentially important role of microglia in astrogliosis. Under CNS pathological circumstance, the occurrence of astrogliosis at least partially depends on the activation of microglia. Proinflammatory cytokines derived from activated microglia appear to function, at least in part, in the conversion of astrocytes into a reactive state. These findings that activated microglia initiate the onset and maintains astrogliosis suggest that suppression of microglial over-activation might effectively attenuate late reactive astrogliosis in response to the CNS trauma. Thus, pharmacological modulation of activated microglia may serve as a component of therapies designed to treat neurological diseases.

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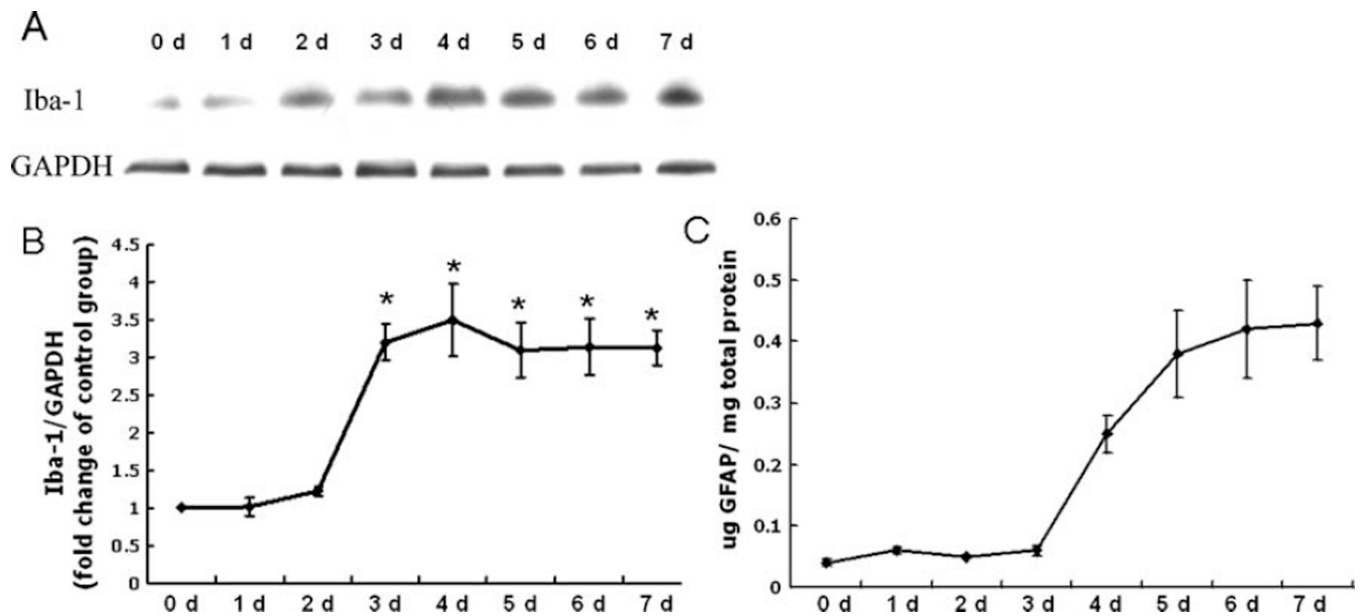
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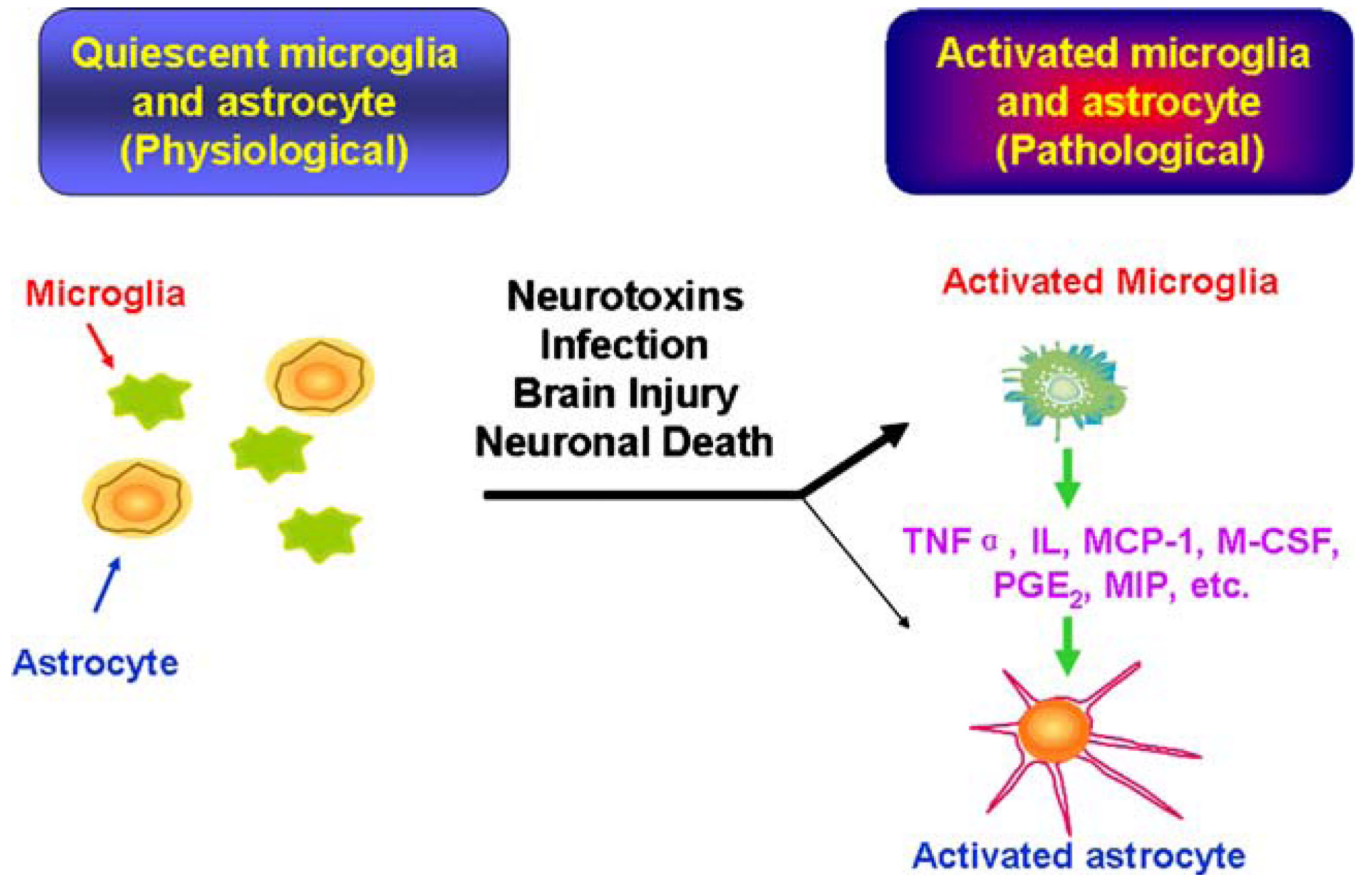
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**Fig. 1.** Microglial activation precedes astrogliosis after neuronal damage induced by MPP<sup>+</sup>. Primary mixed neuron-glia cultures from rats were treated with 0.5  $\mu$ M MPP<sup>+</sup>. At different time points after MPP<sup>+</sup> challenge, Iba-1 and GFAP protein expression were evaluated as markers of microglial and astrocyte activation, respectively. **a** At different time points after MPP<sup>+</sup> treatment, Iba-1 protein expression was assayed using Western blot. **b** Quantitative analysis of Iba-1 protein expression. Data have been normalized to GAPDH expression. **c** At different time points after MPP<sup>+</sup> treatment, GFAP protein expression was assayed using ELISA. Data are mean $\pm$ SEM of three experiments performed in triplicate. \* $p$ <0.05, compared with corresponding control cultures



**Fig. 2.**

Proinflammatory factors from activated microglia are triggers and modulators of astrogliosis. Insults such as neurotoxins, infections, and trauma to the CNS can directly trigger neuronal damage. Injured neurons can activate the surrounding microglia and astrocyte and induce further glial reaction. Compared with astrocyte, microglia are more sensitive, more readily activated and undergo a dramatic transformation from their resting ramified state into an amoeboid morphology. In their activated state, microglia can release a diverse set of proinflammatory factors, such as cytokines, eicosanoids, chemokines, reactive free radicals and proteases. These inflammatory mediators not only can further modulate microglial activity but also can have a very important influence on surrounding astrocytes. The proinflammatory mediators can induce astrogliosis through their receptors on astrocyte, thus serve the function of triggers and modulators of astrogliosis