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Astrogliosis in the Adult and Developing CNS: Is There a Role for Proinflammatory Cytokines?

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Abstract

Astrogliosis, characterized by the enhanced expression of GFAP, represents a remarkably homotypic response of astrocytes to all types of injuries of the CNS, including injuries of the developing CNS. As such, astrocytes serve as microsensors of the injured microenvironment regardless of their location in the CNS. The diversity of insults that engender astrogliosis and the brain-wide nature of the astrocytic response suggest that common injury factors serve as the trigger of this cellular reaction. One prominent theme that has emerged in recent years is that proinflammatory cytokines and chemokines serve as a stimulus for induction of astrogliosis. Here we present a brief critique of this hypothesis based on a review of literature and some of our own recent findings. Studies of astrocytes, in vitro, clearly indicate that these cell types are responsive to a variety of growth factors, including cytokines and chemokines. A somewhat different picture, however, can be seen from data obtained in vivo. It is true that trauma and diseases of the nervous system, as well as some exposures to neurotoxic chemicals, can be associated with the expression in brain of large varieties of cytokines and chemokines. That these same conditions result in astrogliosis has fostered the circumstantial link between cytokine/chemokine expression and the induction of astrogliosis. Several lines of evidence argue against this view, including (a) suppression of cytokine expression does not suppress gliosis, (b) gliosis can occur in the absence of enhanced expression of cytokines, (c) elevations in brain cytokines can occur in the absence of gliosis and (d) the patterns of cytokine expression in the adult and developing CNS are more consistent with a trophic role for these chemical messengers rather than a role in the induction of inflammation. Enhanced expression of cytokines and chemokines after brain injury appear to be signal transduction events unrelated to the induction of astrogliosis.

Keywords: Astrogliosis; Gliosis; GFAP; Cytokines; Chemokines; Inflammation; CNS

INTRODUCTION

Over the last 20 years, considerable evidence has accumulated to suggest that astrogliosis represents a homotypic response of astrocytes to all types of CNS injury, including damage resulting from exposure to chemicals (reviewed in Martin and O'Callaghan, 1996; Kimelberg and Norenberg, 1994; Norenberg, 1994; Eng and Ghirnikar, 1994; O'Callaghan, 1993; Norton et al., 1992; Eng et al., 1992; Malhotra et al., 1990; Eng, 1988; Eng and DeArmond, 1981). There has been some controversy regarding the astroglial response to injury of the developing CNS; at a minimum, astrocytes of the developing CNS have been thought to be less responsive to injury in comparison to astrocytes from the mature CNS (Barrett et al., 1984). With respect to chemically-induced damage of the developing CNS, however, we have not found this to be the case. Instead, we have observed that exposure to a variety of developmental neurotoxicants during the pre- or postnatal period results in large dose-,

Abbreviations: BBB, blood–brain barrier; CNS, central nervous system; CNTF, ciliary neurotrophic factor; COX, cyclooxygenase; bFGF, basic fibroblast growth factor; EAE, experimental autoimmune encephalomyelitis; GFAP, glial fibrillary acidic protein; GRO, growth related oncogene; IFN, interferon; IL-1, interleukin; IL-1ra, IL-1 receptor antagonist; LIF, leukemia inhibitory factor; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MIP-1, macrophage inhibitory protein; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TGF-β, transforming growth factor-β; TMT, trimethyl tin; TNF-α, tumor necrosis factor-α

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time- and region-dependent increases in the astrocyte protein, GFAP, findings consistent with an astroglial response in the target regions for these toxicants (O'Callaghan and Miller, 1985, 1986, 1988, 1989; Goldey et al., 1994). Numerous reports from other laboratories also document toxicant-induced astrogliosis early in development (Burtrum and Silverstein, 1993) as well as in early neonatal models of infection (Hornig et al., 1999), stroke/ischemia (Burtrum and Silverstein, 1994) or neural damage subsequent to genetic derangements in brain development [e.g. jimpy (Imamoto, 1985; Bignami and Dahl, 1974), twitcher (LeVine et al., 1994; Kobayashi et al., 1986; Chiu et al., 1988) and staggerer (Aono et al., 1985)]. Thus, it now appears that astrogliosis in the developing CNS exhibits the same features seen following trauma, disease and neurotoxicant exposure of the adult CNS (O'Callaghan, 1993; O'Callaghan et al., 1995). The fact that increases in GFAP appear to be a universal response to injury in both the adult and developing CNS suggests that a common set of factors may underlie this generic response of astrocytes to neural damage. What remains unknown are the origins and nature of the ''damage'' factors mediating astrogliosis. One dominant theme in contemporary neuroscience suggests that proinflammatory cytokines and chemokines constitute one such set of ''damage factors'' (Rabchevsky et al., 1998; Ridet et al., 1997; Ransohoff et al., 1996; Merrill and Jonakait, 1995; Owens et al., 1994; Perry and Andersson, 1992). Our purpose here is to provide a brief commentary on the role of cytokines in the brain injury response, in general, and the role of these pleiotropic messengers in neurotoxic responses, in particular. Specifically, we will discuss (1) the evidence supporting a role for cytokines as inducers of astrogliosis in the adult CNS, (2) the significance of data obtained with cytokine-related transgenics, knockouts, and with direct administration of cytokines into the brain and (3) the multiple roles for expression of cytokines in the developing CNS that likely are unrelated to inflammation.

What is the Evidence for Cytokines as Inducers of Astrogliosis in the Adult Rat?

Background

A dominant theme in the neurosciences is that inflammation, in general, and cytokines, in particular, are linked to glial activation after neuronal injury. Embodied in this view is the notion that reactive gliosis may be a component of an inflammatory process within the CNS (Scripter et al., 1997; Hong et al., 1995; Balasingam et al., 1994; da Cunha et al., 1993). In particular, the expression of the key proinflammatory cytokines, IL-1β and/or TNF-α, have been implicated as early signals that lead to gliosis. The literature on this subject is fairly extensive. Thus, the release or induction of endogenous cytokines/chemokines or effects of exogenously administered cytokines/chemokines has been associated with the onset and severity of many types of brain injury. Some of these conditions and the cytokines/chemokines associated with them are presented in Table 1.

Clearly, the large body of literature linking proinflammatory responses to different types of brain injuries is suggestive of an involvement of these mediators in astrogliosis, if for no other reason than astrogliosis is a dominant response to all types of brain injury. In reviewing this literature, however, we find that most evidence used to support a role for inflammation in gliosis is circumstantial at best and/or is based on results from in vitro studies using models that may not reflect the in vivo condition. Moreover, very little attention has been given to the possibility that inflammatory responses associated with CNS trauma or disease states may not be associated with the glial response to toxic insults of the adult or developing CNS. Indeed, recent data from our laboratory (reviewed below) suggest that the in vivo expression of proinflammatory mediators in the CNS is not required for toxicant-induced glial activation. Below, we will briefly review the results of these studies and other straightforward strategies designed to test the hypothesis that cytokines play a role in the induction of astrogliosis.

Suppressing Cytokine Expression does not Block Gliosis

Glucocorticoids suppress the expression of the proinflammatory mediators, IL-1β (Grosset et al., 1999; Nguyen et al., 1998; Goujon et al., 1995, 1996; Lee et al., 1988; Besedovsky et al., 1986), TNF-α (Goujon et al., 1996; Brenner et al., 1993), IL-6 (Miyazawa et al., 1998), IFN-γ (van der Velden et al., 1998), IL-8 (Krishnaswamy et al., 1998; van der Velden et al., 1998), RANTES (Meyer et al., 1998), LIF (Miyazawa et al., 1998), NOS (Brenner et al., 1994), COX-2 (Koistinaho et al., 1999; Newton et al., 1997; Lasa et al., 2001; Goppelt-Struebe et al., 2001; Zhang et al., 1999; Parsadaniantz et al., 2001; Kurumbail et al., 1996; Ristimaki et al., 1996; Liu et al., 1996; Masferrer and Seibert, 1994), and MCP-1 (Kawahara et al., 1991). Conversely, glucocorticoids up-regulate the expression of anti-inflammatory

Table 1
Expression of cytokines and chemokines after nervous system injury or disease

Injury/disease	Cytokines/chemokines expressed	References
LPS-induced brain inflammation	IL-1β	Dinarello (1988)
	MCP-1, MIP-1, KC, IP-10, RANTES	Hausmann et al. (1998)
	IL-1α, IL-1β, IL-6	Lemke et al. (1999)
Scrapie	IL-6	Kim et al. (1999), Williams et al. (1994)
	IL-1α, IL-1β, TNF-α	Campbell et al. (1994a)
Excitotoxicity	IL-1ra	Pawlinski and Janeczko (1997)
Multiple sclerosis/EAE	TNF-α	Martino et al. (1997)
	TNF-α, IFN-γ	Tanuma et al. (1999)
	IL-2	Renno et al. (1995)
	IP-10, MCP-1	Glabinski et al. (1999), Tani et al. (1996b), Ransohoff et al. (1993)
	MCP-1, MCP-2, MCP-3	McManus et al. (1998)
	TNF-α, IL-1β, IL-6	Hauser et al. (1990)
	RANTES, MIP-1α, MIP-1β, TCA-3, IP-10, MCP-1, KC, MCP-3	Godiska et al. (1995)
	RANTES, MIP-1α, GRO	Glabinski et al. (1998)
Alzheimer's disease	IL-1β	Griffin et al. (1998, 1989, 1995)
	TNF-α, TGF-β	Mattson et al. (1997)
	IL-6	Wood et al. (1993)
AIDS dementia	TNF-α, IL-6	Persidsky et al. (1997)
	IL-1β	Stanley et al. (1994)
Viral infection	TNF-α, IL-1α, IL-1β, IL-6	Sauder and de la Torre (1999), Campbell et al. (1994b)
	TNF-α, IL-1β, IL-6, IL-12, MCP-1, MIP-1β, MIP-2	Thomas et al. (1998), Hunter et al. (1992)
	TNF-α, IL-2, IFN-γ	Wege et al. (1998)
	IL-6	Marquette et al. (1996)
Trauma	IL-6	Arruda et al. (1998)
	IL-6, IL-10	Bell et al. (1997)
	TNF-α, IL-6	Shohami et al. (1994)
	TGF, M-CSF	Streit et al. (1998)
	RANTES, MIP-1β	Ghirnikar et al. (1996)
	LIX, MCP-1, MCP-5, GRO, IP-10, MIP-3α	McTigue et al. (1998)
	MCP-1	Ghirnikar et al. (1996, 1998a,b), Carroll and Frohnert (1998), Glabinski et al. (1995, 1996), Ransohoff and Tani (1998)
Irradiation	TNF-α, IL-1β	Hong et al. (1995)
Ischemia and stroke	MCP-1	Gourmala et al. (1997)
	IL-1ra	Loddick et al. (1997), Rothwell et al. (1997a), Feuerstein et al. (1997), Rothwell et al. (1997b), Hill et al. (1999)

cytokines such as IL-10 and IL-1ra (Barnes, 1998). Despite the anti-inflammatory action of glucocorticoids, their administration, even in very high immunosuppressive dosages, fails to attenuate astrogliosis resulting from hippocampal damage due to the organometal, trimethyl tin (TMT) (O'Callaghan et al., 1991) or striatal damage due to amphetamine (Miller and O'Callaghan, 1996). Nor do glucocorticoids decrease damage due to stroke/ischemia (Mulley et al., 1979; Sapolsky and Pulsinelli, 1985). In the facial nucleus injury model, where damage to the facial nerve results in gliosis within the facial nucleus, dexamethasone pretreatment also does not block gliosis (Kiefer and Kreutzberg, 1991). The use of an anti-sense construct to the chemokine MCP-1 reduced the number of infiltrating macrophages to a stab wound by 30%

but did not alter gliosis (Ghirnikar et al., 1998a,b). Together, these observations suggest that the astrocyte response to injury is not controlled by factors that are down-regulated by glucocorticoids, such as the proinflammatory cytokines (e.g. IL-1β, TNF-α) and chemokines (e.g. MIP, MCP-1).

Gliosis Occurs in the Absence of Cytokine Induction

Using the TMT model of hippocampal injury in the adult rat, we were unable to detect increases in proinflammatory cytokines in the hippocampus at 1, 2, 3, 5, 7, or 21 days post-dosing but a robust glial activation occurred in response to neuronal damage (Gordon and O'Callaghan, 1997; Balaban et al., 1988; Brock and O'Callaghan, 1987). The extensive loss of hippocampal pyramidal neurons caused by TMT results in several thousand-fold increases in GFAP commensurate with enhanced immunostaining of the protein in the target region (Brock and O'Callaghan, 1987). In our hands, induction of TNF-α, IL-1β and IL-6 does not accompany or precede gliosis in this injury model (Little and O'Callaghan, 1999a,c, 2001), although another report indicates a TMT-induced up-regulation of TNF-α, but without increases in IL-1β (Maier et al., 1995). Interestingly, the β-chemokine, MCP-1, is up-regulated by TMT, even though its expression usually is thought to require prior induction by proinflammatory cytokines (TNF-α or IL-1β). This suggests that not only are gliosis and inflammation functionally separate, but that MCP-1 may have a unique signaling role after injury, one distinct from the inflammatory context in which it is usually found.

Evidence obtained following exposure to other neurotoxicants indicates that gliosis can occur in the absence of up-regulation of IL-1β or TNF-α. For example, the cholinergic immunotoxin, 192IgG-saporin, destroys basal forebrain cholinergic neurons and results in an ensuing gliosis but it does not increase TNF-α, IL-1β, or IL-6 (Lemke et al., 1998, 1999). The dopaminergic neurotoxicant, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), destroys dopaminergic nerve terminals and causes a marked gliosis in the damaged region without an elevation of IL-1α or IL-1β (O'Callaghan et al., 1990). Together, the data obtained with a fairly diverse array of neurotoxic compounds indicate that expression of proinflammatory cytokines or chemokines is not required for the induction of astrogliosis.

Elevated Cytokine Levels in the CNS do not Result in Glial Activation

Not only can gliosis occur in the absence of cytokine expression, but cytokines also may be elevated without an accompanying gliosis. For example, peripheral administration of LPS causes increased IL-1β, IL-2, TNF-α, and IL-6 mRNA levels in the CNS in the absence of gliosis and neuronal damage (Little and O'Callaghan, 1999b; Rothwell et al., 1997b; Buttini et al., 1996, 1997; Goujon et al., 1996). Peripheral cytokines are known to be transported across the blood–brain barrier (McLay et al., 1997; Banks and Kastin, 1991, 1997; Pan et al., 1997a; Banks et al., 1989, 1991, 1993, 1994, 1995a,b; Gutierrez et al., 1993, 1994). Indeed, inflammation in the periphery induced by LPS up-regulates cytokines in the CNS (Goujon et al., 1996), however, this treatment does not result in gliosis (or neural damage) (Buttini et al., 1996). Finally, after peripheral injection of Freunds adjuvant, the BBB opens allowing peptides (including presumably cytokines) into the brain parenchyma without evidence for induction of gliosis (Rabchevsky et al., 1999).

The Patterns of Cytokine Expression Associated with Brain Injury are not Consistent with an Inflammatory Response

Astrogliosis is linked to the onset and duration of neural cell damage in the affected brain region. If proinflammatory mediators (and inflammation) serve as triggers of this response, their expression patterns should relate to the known sequence of events associated with inflammation, and their expression should follow a time-course consistent with the onset of gliosis in the target regions. With the exception of chronic neurological disease states with known inflammatory components (e.g. multiple sclerosis and Alzheimer's disease), very little data has been obtained, in vivo, where induction of the classic inflammatory cascade (Fig. 1) precedes the induction of astrogliosis.

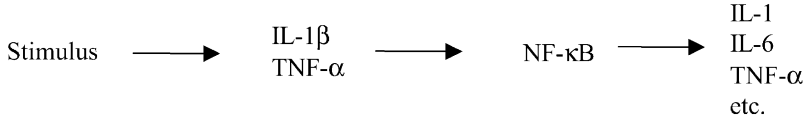

Fig. 1. Classic proinflammatory cytokine/chemokine response cascade associated with tissue injury. Stimulus can include physical or non-physical trauma as well as toxic exposures and disease states.

Acute inflammation in the periphery often involves the early and transient (1–6 h) expression of the proinflammatory cytokines, TNF-α and IL-1β, followed by other cytokines and chemokines such as IL-6, TGF-β and MCP-1, etc. (Fig. 1). Following trauma or chemical injury of the CNS, however, induction of cytokines and chemokines rarely conforms to this pattern. For example, we have observed that damage to hippocampal neurons due to TMT results in a large increase in MCP-1 prior to the onset of gliosis, yet this effect is not preceded nor followed by an increase in TNF-α or IL-1β or IL-6 (Little and O'Callaghan, 1999a). After facial nerve cut, IL-6 and TGF-β are induced in the facial nucleus, but IL-1β and TNF-α are not affected (Kiefer et al., 1993). Reports of cytokine expression in apparently undamaged tissue contralateral to the tissue damaged by ischemic injury (Davies et al., 1999; Zhai et al., 1997) also are inconsistent with an inflammatory response limited to the target region and the local activation of astrocytes. All of these examples raise the possibility that cytokine expression after many types of brain injury involves signal transduction events (neurotrophic/regenerative) unrelated to classical inflammation.

Experiments with Cytokine Transgenics, Cytokine Knockouts and Direct Administration of Cytokines into the Brain do not Support a Role for Cytokines in the Induction of Astrogliosis

Transgenic mice over-expressing cytokines and related signaling factors have been used to assess the role of inflammation in neural responses to injury, including astrogliosis. Most of these models have indeed been shown to be associated with an induction of gliosis. What often is overlooked, however, is that these same models result in neural degeneration as well as gliosis. For example, neuronal degeneration and gliosis both are part of the syndromes that occur in transgenic mice over-expressing TNF-α (Probert et al., 1995; Douni et al., 1995; Stalder et al., 1993), TGF-β (Rabchevsky et al., 1998; Wyss-Coray et al., 1995), IL-3 (Asensio et al., 1999; Campbell and Powell, 1996; Chiang et al., 1996; Powell et al., 1993), IFN-α (Akwa et al., 1998), and KC (Tani et al., 1996a; Ransohoff et al., 1996). IL-6 transgenic mice develop gliosis and increases in TNF-α, IL-1α and IL-1β throughout their life, but these effects also are associated with neurological deterioration (Hernandez et al., 1997; Castelnau et al., 1997; Di Santo et al., 1996; Tani et al., 1996b; Fattori et al., 1995; Chiang et al., 1994; Campbell et al., 1993, 1998; Raber et al., 1998; Campbell, 1998; Gruol and Nelson, 1997; Campbell and Powell, 1996; Gold et al., 1996). In aggregate, none of the results obtained with these models have resulted in an enhancement of our knowledge of the signaling pathways involved in the induction of gliosis. Rather, what appears to be the case is that a common feature of these transgenic models is neural damage, the most widely accepted ''stimulus'' for gliosis. The most likely explanation for this shared effect among diverse transgenics is that they all cause an inflammatory response that, in turn, results in neural damage. Thus, it seems quite likely that inflammation causes damage and damage triggers gliosis. In support of this conclusion, direct (i.c.v.) administration of IFN-γ (Balasingam et al., 1994), IL-2, IL-6 (Balasingam et al., 1994), CNTF and TNF-α (singly or together) (Kahn et al., 1995), bFGF (Eclancher et al., 1996), and TGF-1β (Laping et al., 1994) all result in gliosis. Again, it would seem unlikely that all of these chemical messengers serve as direct inducers of astrocyte activation. Nevertheless, we cannot exclude the possibility that diverse numbers of cytokines and growth factors act through equally diverse and perhaps overlapping pathways to elicit astrocytic activation. Clearly, a greater understanding of the signal transduction elements underlying gliosis would contribute to our understanding of this common feature of neural injury.

Recently, cytokine and cytokine receptor knockouts have been used to foster our understanding of the role of inflammatory processes in gliosis. As with the cytokine transgenics, the results of studies with cytokine and cytokine receptor knockout mice do not seem to have contributed substantially to our understanding of the molecular basis of astrogliosis. One can draw this conclusion just on the basis of the general lack of literature on this subject in the face of the widespread availability of cytokine and cytokine receptor knockouts. Only a few reports have shown a modulation of gliosis after traumatic or chemical-induced brain injury in a cytokine (IL-6) knockout (Klein et al., 1997; Ladenheim et al., 2001) and one report showed a failure of an IFN-γ knockout to alter the glial response to traumatic injury (Rostworowski et al., 1997). An antisense knock-down of MCP-1 reduced monocyte infiltration by 30% but failed to alter gliosis after stab injury (Ghirnikar et al., 1998a,b). Several studies using the TNF receptor (p55 and/or p75) KO reported an exacerbation of neuronal damage, findings suggestive of a neuroprotective role for the TNF-α pathway rather than a role in inflammation and induction of gliosis (Sullivan et al., 1999; Bruce et al., 1996; Gary et al., 1998). Indeed, TNF has been implicated in repair of

acute liver injury (Gallucci et al., 2000; Luster et al., 2000). Given the pleiotropic nature of cytokines/chemokines and related families of trophic factors, it may require more than a single entity (cytokine, chemokine, and receptor subtype) to be eliminated in order to reveal what is likely to be the complex signaling pathway(s) involved in the induction of gliosis. A definitive demonstration that a ''knock down'' of any of the putative glial activating factors results in blocked, delayed, or attenuated gliosis would provide the most convincing demonstration of the causative role of cytokines in gliosis.

Developmental Expression of Cytokines is Trophic, not Inflammatory: Precedent for Non-Inflammatory Signaling Roles in Response to Injury of the Adult CNS?

A complete review of cytokine action during development is beyond the scope of this commentary; the point to be made here is that the ontogeny of cytokines and chemokines in the CNS has not been linked to inflammatory processes. Instead, they have been implicated in diverse roles in brain development, roles suggestive of specific signaling functions related to key aspects of ontogeny.

New developmental roles for cytokines and chemokines and new members of cytokine families are increasingly being identified (Merrill and Jonakait, 1995; Merrill, 1992a; Pan et al., 1997b). Some cytokines are expressed early in development such as, IL-3, IL-4, IL-7, and IL-9, findings suggestive of roles in neurogenesis and gliogenesis (Michaelson et al., 1996; Chang et al., 1994; Mehler and Kessler, 1997). Bone morphogenetic proteins (BMPs), members of the TGF family, also are expressed early in the development of the murine brain (E13) (Merrill and Jonakait, 1995; Mehler and Kessler, 1997) and appear to affect CNS development via regulation of homeotic genes which, in turn, regulate neural tube formation and neurogenesis (Merrill and Jonakait, 1995; Schluesener and Meyermann, 1994). TGF-β itself is important in neural tube development in the mouse (Kester et al., 2000) and ontogeny of the basal ganglia (Jordan et al., 1997; Unsicker et al., 1996). The existence of a large family of TGF- and TNF-like proteins, and the recent report (Born et al., 2000) of an emerging family of IL-1 receptor-like proteins, suggests a number of roles for these factors in the developing CNS. Differences in binding affinity for IL-1 receptors in the CNS, compared with those on lymphocytes, suggests that these receptors may subserve different functions in the CNS and the immune system (Merrill, 1992a). Low levels of TNF-α appear to play a role early in neurodevelopment, perhaps in regulating apoptosis (Pan et al., 1997b; Munoz-Fernandez and Fresno, 1998; Wride and Sanders, 1993). Expression of TNF-α and IL-1β later in ontogeny corresponds to periods of intense synaptogenesis (Dziegielewska et al., 2000). IL-1β is increasingly expressed in brain along with TNF-α during the first trimester in humans suggesting a role for them in brain development (Mousa et al., 1999). Finally, LIF is important in neural stem cell differentiation and growth arrest (Kurzrock et al., 1991) and is a differentiation and survival factor for cholinergic neurons (Merrill and Jonakait, 1995). Thus, cytokines may be involved in key aspects of brain development as they seem to have multiple functional effects on morphogenesis and cellular maturation. These trophic actions of cytokines on specific phases of neuronal and glial ontogeny are quite distinct from their effects as initiators of inflammation.

Astrocytes are a source of trophic factors (Ridet et al., 1997) and their response to many types of injury may serve more of a trophic/support function instead of an impediment to neural survival or regeneration (e.g. glial ''scarring''). Given the potential trophic roles of cytokines in brain development, they too may serve a trophic function to support neural regeneration after injury. Such a function could explain their association with neural damage and gliosis and also may explain the unusual time-course for expression of cytokines after CNS injury (Maier et al., 1995; Bruccoleri et al., 1998), i.e. a temporal pattern of expression that is inconsistent with inflammation (see Section 'The Patterns of Cytokine Expression Associated with Brain Injury are not Consistent with an Inflammatory Response' above).

SUMMARY

We have presented a brief review of the evidence supporting a role for cytokines in injury-induced glial activation. While we acknowledge that a large body of data exists implicating such a role for these chemical messengers, especially data from in vitro studies, data from in vivo studies do not appear to support an obligatory role for inflammatory mediators in the initiation of astroglial responses to neural injury. This especially seems to be the case for damage resulting from exposure to chemical toxicants. We base our conclusions on the fact that the key proinflammatory cytokines, IL-1β, TNF-α (and/or other cytokines) do

not appear to induce gliosis in vivo; cytokines can be induced in the absence of gliosis and gliosis can be induced in the absence of cytokines. Moreover, experiments with transgenics, knockouts, as well as studies where cytokines are directly administered into the brain, have provided either strong evidence against cytokines as obligate signals for gliosis or have been equivocal. Damage to cellular and subcellular elements of the mature and developing CNS remains the dominant, albeit uncharacterized ''stimulus'' for reactive gliosis. The ''damage factors'' common to this stimulus may, in combination with cytokines, chemokines, and other growth factors, influence the course of gliosis without initiating its induction. Given the potential trophic role of cytokines during development and the potential trophic role of astrocytes after neural injury, it is likely that enhanced expression of cytokines and chemokines after brain injury represents a cell-signaling cascade that is unrelated to an inflammatory process.

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