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TGF-β1 Is an Organizer of Responses to Neurodegeneration

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Abstract TGF-β1 mRNA and protein were recently found to increase in animal brains after experimental lesions that cause local deafferentation or neuron death. Elevations of TGF-β1 mRNA after lesions are prominent in microglia but are also observed in neurons and astrocytes. Moreover, TGF-β1 mRNA autoinduces its own mRNA in the brain. These responses provide models for studying the increases of TGF-β1 protein observed in βA/amyloid-containing extracellular plaques of Alzheimer's disease (AD) and Down's syndrome (DS) and in brain cells of AIDS victims. Involvement of TGF-β1 in these human brain disorders is discussed in relation to the potent effects of TGF-β1 on wound healing and inflammatory responses in peripheral tissues.

We hypothesize that TGF-β1 and possibly other TGF-β peptides have organizing roles in responses to neurodegeneration and brain injury that are similar to those observed in non-neural tissues. Work from many laboratories has shown that activities of TGF-β peptides on brain cells include chemotaxis, modification of extracellular matrix, and regulation of cytoskeletal gene expression and of neurotrophins. Similar activities of the TGF-β's are well established in other tissues.

Key words: neurodegeneration, TGF-β, Alzheimer's disease

INTRODUCTION

The TGF-β's (β1–3) are from a family of homodimeric polypeptides with 70–80% sequence identity that is gaining the attention of neurobiologists. Recent data show increases of TGF-β1 mRNA and protein in different types of brain cells during responses to Alzheimer's disease (AD), AIDS, and experimental lesions. The meaning of these changes in TGF-β1 is unclear, because the roles of the TGF-β's in the mammalian brain are less well described than in non-neural tissues.

TGF-β1 in particular is recognized for effects on inflammatory mechanisms after different types of injury. For example, exogenous TGF-β1 can accelerate the healing of skin wounds [Pierce et al., 1991] and can reduce the amount of superoxide anions after myocardial ischemia [Lefer et al., 1990]. The TGF-βs also are implicated in many types of cell-cell interactions in the vertebrate embryo [Mummer and Van Den Eijnden-Van Raaij, 1993; Mahmood et al., 1992]. Other activities of the TGF-βs pertinent to brain responses to injury include influences on angiogenesis, B- and T-cell functions, chemotaxis, cell proliferation, production of extracellular matrix, secretion of other growth factors, and expression of cytoskeletal protein genes. In general, the TGF-βs' actions are thought of as paracrine and autocrine participants in pleiotropic networks with considerable complexity and redundancy, in which the extent of a response may depend on interactions with other cytokines and growth factors. This review emphasizes TGF-β1, because its activities during responses to brain injury are better understood than those of TGF-β2 and -β3. For most information cited without references, see general reviews and recent papers [Wahl, 1992; Roberts and Sporn, 1990; da Cunha et al., 1993; Morgan et al., 1993; Pasinetti et al., 1993].

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LOCATIONS OF TGF-β1 mRNA AND PROTEIN

Normal Adult Brains

The mRNAs for TGF-β1-3 are easily detected in normal adult brain tissues by RNA blot hy-

bridization [da Cunha et al., 1993; Nichols and Finch, 1991; Unsicker et al., 1991]. At a cellular level, the meninges and choroid plexus of normal rodent and human brains clearly contain both TGF-β1 mRNA and protein. However, more work is needed to resolve all the cell types that contain TGF-β1-3 mRNAs in the normal brain. By in situ hybridization, da Cunha et al. [1993] detected β1-mRNA in glia. TGF-β1 mRNA could also be present in neurons, but at lower prevalence. There is also considerable TGF-β1 mRNA in primary cultures of microglia, astrocytes, and oligodendroglia [e.g., Lindholm et al., 1990; da Cunha et al., 1993; Morganti-Kossmann et al., 1992]. This broad range of brain cell types is consistent with the widespread expression of the TGF-β genes in non-neural tissues, depending on the circumstances.

Da Cunha et al. [1993] argued convincingly that TGF-β1 protein is not present in normal brain neurons or glia, whereas it does appear in certain diseases (see later). In contrast to TGF-β1, immunocytochemical evidence shows that TGF-β2 and -β3 are abundant in select neurons of normal brain. In hippocampal pyramidal neurons, β2 and β3 are much more prevalent than in cerebellar Purkinje neurons; the choroid plexus also shows this same relative prevalence [Unsicker et al., 1991]. Outside of the brain, TGF-β1 protein is common, e.g., anterior pituitary [Sarkar et al., 1992] and adrenal cortex [Keramidas et al., 1991]. TGF-β protein is also found in macrophages, neutrophils, platelets, and vascular endothelia.

In general, it is thought from studies of non-neural tissues that the TGF-βs are made by local cells and are secreted for paracrine or autocrine functions. Nonetheless, as neurobiologists evaluate whether TGF-β proteins are made by local brain cells, it may be important that TGF-β1 can bind to at least 10 different proteins [Lin and Lodish, 1993]. For example, TGF-β1 binds to α2-macroglobulin [O'Conner-McCourt and Wakefield, 1990], a plasma protein also detected in AD brains by immunocytochemistry in neuritic plaques, microglia, and some neurons [Van Gool et al., 1993]. Moreover, the β-amyloid precursor protein, which is found in AD plaques, can also bind TGF-β1 and β2 [Bodmer et al., 1990]. Thus, immunocytochemically detected TGF-βs could be of hematogenous origin and accumulated locally upon disturbance of the blood-brain barrier.

Human Neurodegenerative Diseases

In AD and in adult DS, a subset of neuritic (senile) plaques are immunoreactive for TGF-β1 [van der Wal et al., 1993]. The βA4-amyloid rich plaques and associated microglia and astrocytes contain numerous other inflammatory proteins, including early and later complement components, IL-1, and IL-6, among other acute phase proteins [reviewed in Baler et al., 1992; Berkenbosch et al., 1992; McGeer et al., 1993; Lampert-Etchells et al., 1993]. While complement and cytokines are widely recognized as inflammatory indices, there is no association of AD plaques with B or T cells or immunoglobulins, which differentiates the "plaques of AD" from the "plaques of MS" in which reactive T cells have a well-recognized role.

In AIDS brains, infiltrating macrophages and monocytes are immunopositive for TGF-β1, as are local astrocytes [Wahl et al., 1991; da Cunha et al., 1993]. Of great interest is the strong correlation between the amounts of TGF-β1 and IL-1 protein. In the inflammatory lesions of MS, local capillary endothelial cells become immunopositive for TGF-β1 [Sriram et al., 1991]. The implication that AD involves inflammatory mechanisms has led to exploratory studies on anti-inflammatory drugs that may slow cognitive decline [Rogers et al., 1993; Schnabel, 1993].

Experimental Brain Lesions

Brain microglia/macrophages[1] are a potential source of local TGF-β1 in response to experimental lesions. By in situ hybridization in combination with immunocytochemistry for OX-42, TGF-β1 mRNA was elevated in microglia/macrophages, particularly in the zones of degenerating terminals after deafferenting lesions of the hippocampus [Morgan et al., 1993] and striatum [Pasinetti et al., 1993]. OX-42 is a general microglial/macrophage epitope associated with CR3, a complement receptor. TGF-β1 mRNA was not detected in a resting ("nonactivated") microglial/macrophage morphotype, but was found in activated microglia/macrophages with

[1]It is generally uncertain whether a given microglial cell arrived only recently as a bone marrow-derived macrophage or whether it had resided there since development. Macrophages appear to traffic continuously through the adult brain and probably change their morphology and epitopes within hours [Perry and Lawson, 1992]. Moreover, brain lesions stimulate the immigration of hematogenous macrophages.

short stubby processes and in ameboid cells near the wound edge that are probably infiltrating macrophages [Morgan et al., 1993] (Fig. 1). Besides the increases of TGF-β1 mRNA, we observed increased fibronectin mRNA (Fig. 2); this association was tested by the infusion of TGF-β1 (next section). Excitotoxins induce similar increases of TGF-β1 mRNA in hippocampus [Morgan et al., 1993]. Surgical wounds also cause local induction of TGF-β1 mRNA in putative microglia/macrophages in cortex [Lindholm et al., 1992; Logan et al., 1992] and major increases of TGF-β1 mRNA and protein in the choroid plexus and meninges [Logan et al., 1992]. There are no data on how brain cells control the translation of TGF-β mRNA, its secretion, and activation.

The coexistence of several morphotypes of microglia/macrophages in brains that differ in TGF-β1 mRNA prevalence is consistent with the numerous activational states found in peripheral macrophages [Adams and Hamilton,

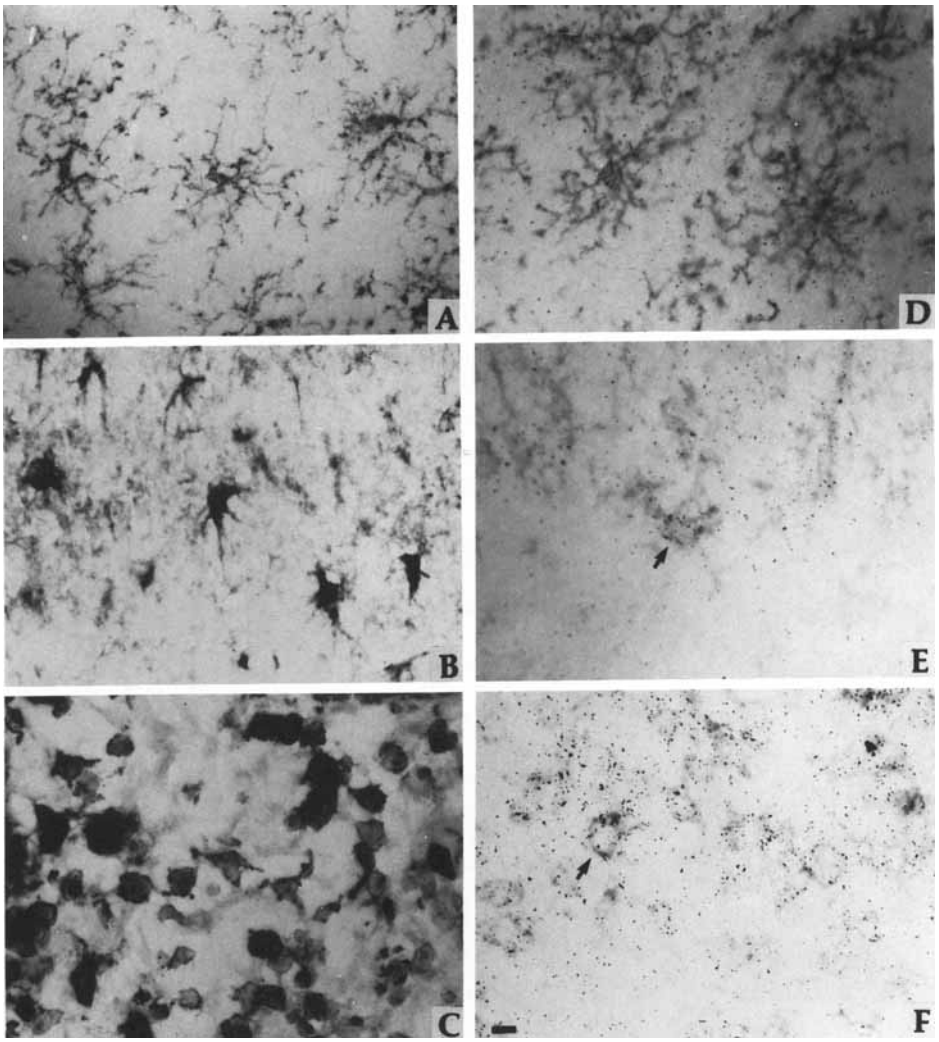

Fig. 1. Microglia in the adult rat brain display three major morphotypes. **A–C** show cells stained by immunocytochemistry for the macrophage/microglial antigen OX-42, using nickel intensification. **D–F** show in situ hybridization for TGF-β1 mRNA, in combination with immunocytochemistry without nickel intensification. **A,D:** Molecular layer of the dentate gyrus of unlesioned rats, in which most microglia have spidery processes (resting morphotype) but do not show signals for TGF-β1 mRNA; this could mean that TGF-β1 mRNA is at low prevalence. **E:** Responses 4 days after deafferenting lesions of the perforant path,which lead to the appearance of microglia with short stubby processes (reactive morphotype) and localized signals for TGF-β1 mRNA. **C,F:** Ameboid macrophage/microglial cells with TGF-β1 mRNA. These cells are another OX-42 immunopositive morphotype and probably represent infiltrating hematogenous macrophages; this morphotype is not common in the unlesioned brain and was found only at the edges of the surgical wound in the temporal cortex made by the surgical lesion. [From Morgan et al., 1993.]

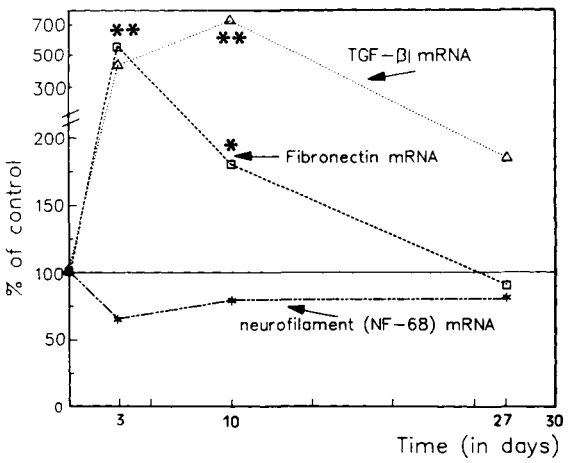

Fig. 2. TGF-β1 and fibronectin mRNA increase together in the striatum after deafferenting lesions of the rat cortex. By contrast, neurofilament mRNA did not increase. A further experiment showed that intraventricular infusions of TGF-β1 from porcine platelets induced fibronectin mRNA in astrocytes. These findings suggest that TGF-β1 is released after lesions to regulate extracellular matrix molecules like fibronectin that are implicated in reactive synaptogenesis. [From Pasinetti et al., 1993]

1992]. The failure to detect TGF-β1 mRNA in a resting microglial/macrophage morphotype [Morgan et al., 1993] suggests that the mRNA of TGF-β1, together with that of other cytokines, may distinguish microglial activational states at the transcriptional level.

Besides microglia, other brain cells also express TGF-β1 mRNA in responses to injury. Astrocytes near to the lesions [Logan et al., 1992; Morgan et al., 1993] did not show definitive TGF-β1 mRNA, whereas those in AIDS brains did [da Cunha et al., 1993]. Neuronal expression of TGF-β1 mRNA was detected after auditory nerve axotomy [Lefebvre et al., 1992] and in occasional neurons near a penetrating wound [Logan et al., 1992]. Although β2 and β3 proteins are found in neurons of normal brains, there are no reports on how these molecules respond to lesions. We may conclude that, as observed in non-neural tissues, any brain cell type may contain abundant TGF-β1 mRNA in response to injury, in culture, or other particular conditions. This conditionality is a basic feature of the biology of the TGF-βs and their target cell responses.

ACTIVITIES IN BRAIN TISSUES AND CELLS

TGF-β's have broad influences on cellular proliferation, differentiation, migration, and the extracellular matrix. Through these properties, the TGF-βs participate in numerous mechanisms of wound healing and tissue repair in the periphery, including the modulation of diverse immune cell functions which is discussed later. The presence of mRNAs for three mammalian TGF-βs in the adult brain implies analogous roles during responses to neurodegenerative diseases and experimental lesions.

Receptors

Actions of TGF-β are mediated by receptors of different affinity that are encoded by at least three genes with distinct sized mRNAs [Lin and Lodish, 1993; Tsuchida et al., 1993]. Two high-affinity receptors occur in most tissues, including brain: types I and II, which bind TGF-β1 and β3 better than β2. Both show signal transduction, with different effector pathways [Chen et al., 1993]. Interactions between receptor types I and II in the cell membrane may influence the binding of TGF-βs and synergistically activate different signal transduction pathways. Data suggest that type I promotes synthesis of extracellular matrix proteins, while type II inhibits DNA synthesis. Type III receptors have slightly lower affinity and have not shown signal transduction; this receptor may mediate interactions with extracellular matrix and TGF-β storage or clearance. Binding studies of membranes from primary cultures of astrocytes show three proteins corresponding to these receptors [Morganti-Kossman et al., 1992].

TGF-β As a Neurotrophin and Neuroprotectant

In several cell culture systems, TGF-β1 enhances survival of neurons and other brain cells obtained from embryos, e.g., spinal neurons [Martinou et al., 1990]. Moreover, TGF-β1 can prevent degeneration of rat neurons after treatment with glutamate at neurotoxic levels [Prehn et al., 1993]. TGF-β2 and -β3 were less effective at the same doses. Similar effects were observed with chick embryo neurons in protecting against either hypoxia or glutamate. These studies imply a direct neuroprotectant action on neurons, because the neuron cultures lacked glia. As discussed below, astrocytes and fibroblasts can secrete NGF in response to TGF-β [Lindholm et al., 1990; Yoshida and Gage, 1992].

TGF-β also has other activities that give indirect neuroprotection. Cerebral infusions of TGF-β1 reduced infarct size after cerebral ischemia [Gross et al., 1993], whereas in experimental pneumococcal meningitis, systemic TGF-β1 and -β2 inhibited brain edema and increased

cerebrovascular flow [Pfister et al., 1992]. As discussed by Pfister et al. [1992], the mechanisms may include inhibition of NO and of oxygen radicals, as well as modulating adhesion molecules in vessels.

Interactions With Other Growth Factors

TGF-β2 and -β3, but not -β1, may block actions of other neurotrophins, depending on the cell type [Flanders et al., 1991]. Moreover, TGF-β1 acts cooperatively with other cytokines to increase NGF synthesis in fibroblasts and astrocytes [Yoshida and Gage, 1992]. Other inducers of TGF-β1 include FGF, EGF, IL-1β, and TNF-α [Martinou et al., 1990]. These effects on growth factors may also have effects on chemotaxis, because many growth factors are associated with extracellular matrix (ECM) during development.

Neurotransmitters

Direct interactions with neurotransmitters have not been reported. The induction of TGF-β1 mRNA in microglia after excitotoxin lesions [Morgan et al., 1993] could be entirely attributed to the macrophage activation by a range of factors released by damaged cells. However, macrophages, like many immune cells, have receptors for neurotransmitters (e.g., NE, 5-HT, vasopressin), which could be released by local neurons to influence the expression of TGF-β1.

Cytokines

In astrocytes, TGF-β1 is antiproliferative [Lindholm et al., 1992; Morganti-Kossmann et al., 1992]. Data on interactions with other cytokines are divergent. For example, activities of bFGF were inhibited by TGF-β1 according to Lindholm et al. [1992], while Labourdette et al. [1990] observed enhancement. In oligodendroglial cultures, TGF-β1 is mitogenic [Martinou et al., 1990]. However, the outcome is contingent on the growth state, since TGF-β1 stimulates DNA synthesis in short-term cultures of Schwann cells, but had the opposite effect if the culture was long-standing [Eccleston et al., 1989]. The antimitotic effects of TGF-β1 imply important anti-inflammatory roles during responses to injury, such as limiting the proliferation of local astrocytes or those of invading hematogenous cells. Also recall from above that there are increases of TGF-β1 mRNA and protein in the meninges and choroid plexus after injury.

Chemotaxis

TGF-β1 is chemotactic for cultured astrocytes [Morganti-Kossmann et al., 1992] and microglia [Yao et al., 1990], which suggests a role for attracting the astrocytes and microglia that surround senile plaques. Chemotactic roles for TGF-β2 and -β3 have been proposed during development, where these proteins are transiently associated with glia fibers that appear to guide neural processes [Flanders et al., 1991]. In avian neural crest cells, TGF-β enhances migration and substrate adhesion [Delannet and Duband, 1992]. Complex effects are observed on neural adhesion molecules in cultured astrocytes: TGF-β1 and -β2 increased L1, but decreased N-CAM [Saad et al., 1991]. It is thus plausible that TGF-βs could be local factors for chemotaxis and cell adhesion during reactive synaptogenesis, as well as in ongoing synaptic remodeling.

Regulation of the Extracellular Matrix

In peripheral tissues, TGF-β1 induces the synthesis of fibronectin and of other macromolecules that modify the extracellular matrix (ECM) during responses to injury. Similarly in brain, fibronectin mRNA is induced in striatum by infusion of TGF-β1 [Pasinetti et al., 1993]. In non-neural cells, synthesis of fibronectin is mediated by type I TGF-β receptors [Chen et al., 1993].

Cytoskeleton and Sprouting

Little is known about the factors governing the rapid and numerous changes in shape of astrocytes, microglia, and neurons that are observed during responses to brain lesions. TGF-β may be among those factors on the basis of recent evidence. TGF-β1 infusions in the unlesioned brain induce mRNAs encoding two astrocyte intermediate filaments: GFAP [Laping et al., in press] and vimentin [Krohn K et al., unpublished observations]. Other cytokines also influence GFAP expression [reviewed in Nichols et al., 1993] and might also be local regulators of synaptic plasticity. For example, TNF induces neurofilament and MAP expression in neuroblastoma cells [Ponzoni et al., 1992]. Of particular interest is the embryonic and neuron-specific isoform of tubulin, Tα1, which also increases in

adult brains during synaptic remodeling. [Poirier et al., 1991]. As observed for GFAP in astrocytes, infusions of TGF-β1 induce increases of tubulin-α1 mRNA [Laping et al., in press]. Moreover, TGF-β alters Schwann cell functions to enhance neurite outgrowth [Rogister et al., 1993]. The presence of TGF-β1 protein in senile plaques [van der Wal et al., 1993] could be a factor in promoting the growth of neurites found in senile plaques during AD and DS.

Role in Glial Scaring

TGF-β1 may facilitate the formation of the glial/mesodermal scars (glia limitans externa) after penetrating brain wounds [Logan et al., 1992]. In view of the long-recognized association of the limitation of central nervous system (CNS) regeneration with glial scarring, Logan et al. [1992] suggested that antagonists to block matrix deposition might enhance recovery from CNS injury. Increases of TGF-β1 in microglia and other cells around surgical wounds (previous section) could stimulate activities, as described above, that are consistent with its roles in peripheral wound healing and that could provide a neuroprotective microenvironment against influx of proinflammatory blood cells and proteins.

INTERACTIONS WITH IMMUNE AND INFLAMMATORY MECHANISMS

Anti-inflammatory Versus Pro-inflammatory Actions

The ubiquitous TGF-βs may serve as local anti-inflammatory or pro-inflammatory agents [Wahl, 1992]. Either outcome may be found, immunosuppression or promotion of inflammatory responses, depending on the conditions. For example, TGF-β induces naive T cells to proliferate, but inhibits proliferation of mature T cells. This conditionality of responses implies sensitivity to the sets of genes that are expressed at a given time.

In responses to brain lesions, it is important that TGF-β can deactivate macrophages and microglia. With cultured microglia, effector cells and oligodendroglia targets, TGF-β inhibited basal ("natural") cytotoxicity against the oligo's, as well as that induced by IFN-γ [Merrill and Zimmerman, 1991]. As another example of anti-inflammatory actions in the brain, TGF-β1 infusions modulated several complement (C) factor mRNAs, including decreases of C1q mRNA [T. Morgan et al., unpublished] and increases of clusterin mRNA [Laping et al., in press]; clusterin is an inhibitor of the membrane attack complex (MAC) of the C-system [May and Finch, 1992] and is secreted by astrocytes [Pasinetti et al., in press]. Effects of TGF-β1 on receptors for C factors in brain cells are also likely, in view of the up-regulation of the C1q receptor in primary fibroblast cultures [Luddington et al., 1993]. Interactions of TGF-β with C-system mRNAs are not well described in general and are an intriguing new feature of TGF-β1 as an inflammatory mediator.

We recently showed that brain neurons and microglia contain relatively abundant mRNAs for several C factors (C1qB, C4a) [Lampert-Etchells et al., 1993; Pasinetti et al., 1992] and that certain C mRNAs are increased in response to lesions [Pasinetti et al., 1992]. These findings suggest that the numerous C factors found in the senile plaques of AD brains, including those of the MAC [references cited in Lampert-Etchells et al., in press; Pasinetti et al., 1992] may be made by resident brain cells. These early findings suggest that TGF-β1 has a neuroprotective role, by downregulating the activity of the C-system. It is pertinent to the activities of resident microglia/macrophages that TGF-β acts directly on monocytes to increase the numbers of immunoglobulin receptors (Fc_γ RIII, or CD16); other lymphokines were inactive [Welch et al., 1990]. Microglia have not been tested for this action.

It is not well understood why so few B and T cells penetrate the blood-brain barrier, except under special conditions. This is a major puzzle to researchers on inflammation. For example, infusions of monocyte chemotaxins that cause massive immigration in other tissues, activated local microglia/macrophages and induced accumulations of monocytes at vessel margins, but did not enhance their immigration into the brain [Andersson et al., 1992]. We note that the TGF-β's are well known to inhibit numerous immune cell reactions, including the production of IL-2 and its proliferative effects on B- and T-cells, and the production of polyclonal antibodies. Moreover, some of these activities also are found in brain cells, e.g., the suppression of Mhc class II antigen expression in astrocyte after activation by IFN-γ, on the basis of which Schluesener [1990] suggested that TGF-β is a regulator of

inflammation in the brain. We suggest further that the induction of TGF-β1 mRNA in the choroid plexus after invasive wounds [Logan et al., 1992] could be part of the brain's defense against invading lymphocytes.

Autoinduction

The autoinduction of TGF-β1 mRNA by TGF-β1 has been well documented as a possible local amplifying mechanism for autocrine effects of TGF-β1 [Van Obberghen-Schilling et al., 1988]. Autoinduction was recently extended to neural cells through studies of cultured astrocytes [Lindholm et al., 1990; Morganti-Kossmann et al., 1992] and in vivo in the hippocampus after infusion (Young-Chan et al., unpublished observations). These findings suggest that TGF-β1 is a mediator of early responses to neurodegeneration.

Hormonal Interactions

TGF-β1 mRNA was found in the hippocampus by screening a cDNA library for sequences that were regulated by glucocorticoids; the elevations after adrenalectomy and suppression by glucocorticoids was mediated by type II glucocorticoid receptors that respond to the type II agonist RU28362 [Nichols and Finch, 1991]. Thus, it seems likely that TGF-β mediated brain responses are integrated with systemic homeostatic mechanisms. Direct involvement with endocrine control is also indicated for TGF-β1 in the adrenal cortex, where it inhibits corticosteroid production [Keramidas et al., 1991], and the pituitary, where it inhibits prolactin secretion [Sarkar et al., 1992].

Interactions With Other Cytokines

IL-1α, but not IL-1β, released TGF-β1 from the primary brain cultures of astrocytes more than from microglia or oligodendroglia [da Cunha et al., 1993]. Initially released IL-1 could thereby stimulate the release of TGFβ-1 by local brain cells. In primary astrocyte cultures, TGFβ-1 induces transcription of NGF mRNA [Lindholm et al., 1990]. Thus, there is a potential for self-amplifying cascades of TGF-β which could be triggered by IL-1, with numerous pleiotropic effects on the surrounding cells in regions of tissue damage or deafferentation. These interactions during responses of non-neural tissues to injury are characterized by considerably redundancy and complexity. No less complexity should be anticipated for cytokine-growth factor interactions in the brain.

CONCLUSIONS

The TGF-βs have remarkably broad activities that were first described for non-neural tissues and that, by analogy, now may be considered as pertinent to the brain. So far, nearly all activities of TGF-β1 in the brain are precedented by activities elsewhere in the body. Of particular importance is that TGF-β1 down-regulates many inflammatory activities. In particular, the inhibition by TGF-β1 of actions by interleukins on T cells may be how it has therapeutic effects in models of MS, meningitis, and stroke. There is also evidence that TGF-β1 modulates several complement (C) system mRNAs (C1q and clusterin) in the brain. Other important activities are chemotaxis, and effects on fibronectin and other extracellular matrix and cell adhesion molecules, as shown for astrocytes. TGF-β1 also induces cytoskeletal mRNAs in astrocytes and neurons that are germane to synaptic remodelling during AD and to the formation of glial scars. While TGF-β1 does influence cytoskeleton gene expression in bone and other non-neural cells, the induction of Tα1 mRNA is specific to the brain, since this is a neuron-specific isoform [Laping et al., in press]. Moreover, TGF-β1 can act directly on neurons as a neuroprotectant during responses to hypoxia and excitatory amino acids. Among actions of TGF-β1 known in non-neural tissues that are worth studying in the brain are the stimulation of angiogenesis and the regulation of superoxide anions.

While the TGF-βs are considered primarily as local paracrine and autocrine agents, they also interact with systemic hormones. Adrenal steroids inhibit TGF-β secretions, whereas TGF-β1 mRNA is down-regulated by glucocorticoids in the brain. When considered with the autoinduction of TGF-β1 mRNA in the brain, we can discern interactions of TGF-β1 at numerous points in the autocrine, paracrine, and endocrine networks. These actions suggest additional mechanisms in the interactions of adrenal steroids and stress with aging and neurodegeneration, besides the direct effects of glucocorticoids on neurons [Sapolsky, 1992; Kerr et al., 1991]. For example, chronic elevations of glucocorticoids may elevate C-system gene expression and therefore promote C-mediated aspects of

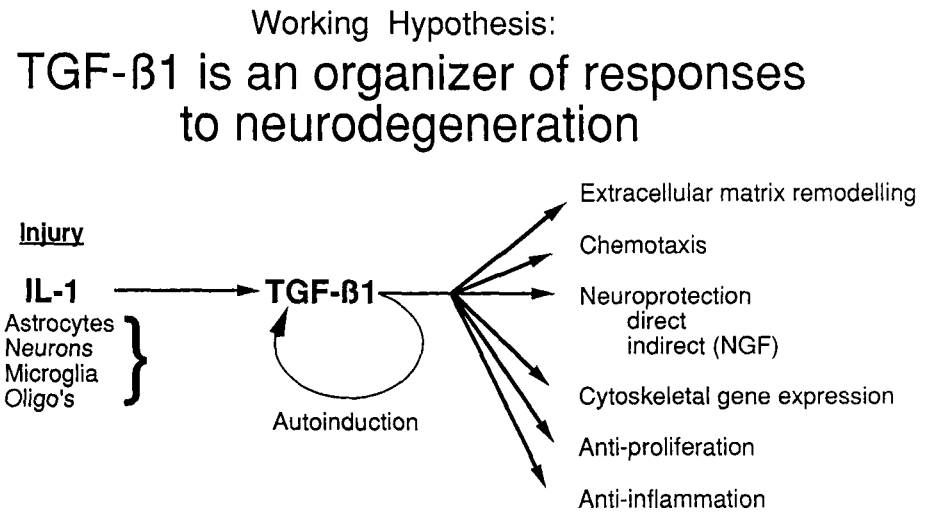

Fig. 3. Scheme of TGF-β1 involvement during responses to neurodegeneration.

neurodegeneration by inhibiting antagonists such as TGF-β1.

To help consolidate these complex actions, we propose an exploratory hypothesis: that the TGF-β peptides have roles in organizing responses to neurodegeneration and brain injury (Fig. 3). Of particular importance to the brain is protection against invading B and T cells. Here the brain differs importantly from most other tissues, because of the greater importance of invading B and T cells during inflammatory processes. B or T cells are rare in the brain except under unusual conditions, such as MS or meningitis. Testing the features of this schema could identify new therapies for AD, AIDS, and MS.

Information needed to evaluate the potentially far-reaching roles of TGF-β1 in the brain includes the involvement of TGF-β2 and β3 in responses to lesions; interactions of the TGF-β's with other cytokines and growth factors; the uniqueness of TGF-β actions; controls on secretion and activation of TGF-βs; cellular specificities and functions of TGF-β receptors; and the extent of coordinated transcription and signal transduction events to the TGF-βs by astrocytes, cerebrovascular endothelia, oligodendroglia, microglia, and neurons.

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