6

Transforming Growth Factor Beta in the Central Nervous System

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1. Introduction

By definition, growth factors are polypeptides that modulate the proliferation of mammalian cells by acting on their receptors at low concentration. Based on similarities in their sequences and their receptors, growth factors can be divided into several superfamilies including platelet-derived growth factors, epidermal growth factors, insulin-like growth factors, the transforming growth factor-beta (TGF-β) family, fibroblast growth factors, nerve growth factors (neurotrophins), erythropoietin, and hemopoietic colony stimulating factors. Transforming growth factors were originally named by their capacity to induce oncogenic transformation in rat kidney fibroblasts (Roberts et al., 1981). Transforming growth factor alpha has a structure and action similar to epidermal growth factor (Wells, 1999) and is not a subject of the present chapter. The TGF-β superfamily includes products of over 25 distinct genes. Comparison of the deduced amino acid sequences led to the definition of several groups within the superfamily, such as TGF-βs, bone morphogenetic proteins, multiple isoforms of activins and inhibins, anti-Mullerian hormone, decapentaplegic protein in *Drosophila*, and Vg1 protein in *Xenopus* (Burt & Law, 1994). There are five TGF-β sequences including three mammalian isoforms (TGF-β1, β2 and β3), which are encoded by unique genes located on different chromosomes (Lawrence, 1996). Besides the regulation of cell growth and division, *TGF-βs* can control the proliferation, survival, differentiation, migration, or function of cells depending on the circumstance. The best established activities of TGF-βs are the following: they inhibit proliferation of most cells, but can stimulate the growth of some mesenchymal cells; they enhance the formation of extracellular matrix; and they exert immunosuppressive effects (Roberts, 1998). Based on their effects on cells of the immune system, TGF-βs can also be considered cytokines (Kiefer et al., 1995).

2. Biochemistry of transforming growth factor-βs (TGF-βs)

2.1 Release and activation of TGF-βs

A characteristic feature in the biology of TGF-βs is that they are usually secreted from cells in latent forms. TGF-βs are synthesized as homodimeric proproteins (proTGF-βs). These

precursor proteins are modified intracellularly prior to secretion. The C-terminal pro-regions are cleaved from the N-terminal portion of the protein and in the trans Golgi to provide mature TGF-β and the latency-associated protein (LAP) which remain non-covalently associated to form the small latent complex (Clark & Coker, 1998; Khalil, 1999). In turn, disulfide bridges bind the so-called latent TGF-β binding proteins (LTBPs) to this complex to result the TGF-β large latent complex, in which TGF-βs are present in the extracellular space (Koli et al., 2001; Saharinen et al., 1999). LTBPs are large multidomain proteins belonging to the fibrillin-LTBP family of extracellular matrix proteins. LTBPs have a typical repeated domain structure consisting mostly of epidermal growth factor (EGF)-like repeats and characteristic eight cysteine (8-Cys) repeats. They are required for the proper folding and secretion of TGF-βs (Sinha et al., 1998; Todorovic et al., 2005). Following secretion, TGF-β is deposited to the extracellular matrix in the pericellular space covalently via the N-termini of the LTBPs. LTBPs contain multiple proteinase sensitive sites, providing means to solubilize the large latent complex from the extracellular matrix structures (Keski-Oja et al., 2004; Rifkin, 2005).

2.2 Latent TGF-β binding proteins

There are four mammalian LTBP isoforms encoded by distinct genes, including LTBP-1, -2, -3, and -4 and different splice variants for each of them (Mangasser-Stephan & Gressner, 1999; Oklu & Hesketh, 2000). The significance of this structural diversity is mostly unclear at present. The potential selective binding of different LTBPs to different proTGF-β types is not well characterized yet. *In vitro* studies suggest that LTBP-1, and -3 can bind to all three types of proTGF-β types efficiently whereas LTBP-2 does not bind to proTGF-βs (Saharinen & Keski-Oja, 2000). TGF-β associated with the large latent complex cannot interact with its receptor and has no biological effect. Therefore, TGF-β activity is regulated by the release of mature TGF-β from the large latent complex. Alternatively, the large latent complex undergoes a conformational change, which exposes the TGF-βs to their receptor binding sites. Many potential activators of the extracellular TGF-βs have been proposed (Annes et al., 2003; Gumienny & Padgett, 2002) including proteases, thrombospondin-1, integrins, reactive oxygen species, and pH. The activation of the 3 different isoforms of TGF-βs may be different. Furthermore, the type of LTBPs may affect the way of activation of TGF-βs (Rifkin, 2005).

2.3 Release of TGF-βs from neurons

Apart from various peripheral cell types, the model neuron chromaffin cell has also been demonstrated to possess regulated secretion of TGF-β and LTBPs (Krieglstein & Unsicker, 1995). Cholinergic stimulation of bovine chromaffin cells leads to the release of storage vesicles. The released content of the vesicles was shown to contain TGF-β but not other members of the TGF-β superfamily suggesting that TGF-β is stored in chromaffin granules and can be released by exocytosis (Krieglstein & Unsicker, 1995). In addition, the level of active TGF-β has been suggested to be increased by elevated neuronal activity (Lacmann et al., 2007). In primary cell culture of embryonic hippocampal neurons, various treatments leading to increased neuronal activity resulted in tetrodotoxon-dependent elevation of active TGF-β levels (Lacmann et al., 2007).

2.4 Receptors and signal transduction pathways

With regard to mediation of TGF-β actions, different TGF-β receptors have been identified (Massague, 1992). Type I and type II TGF-β receptors bind TGF-βs with high-affinity. Ligand binding induces the assembly of type I and type II receptors into complexes. The exact stoichiometry in the TGF-β-induced heteromeric type I and type II receptor complex is likely to be a heterotetramer comprising two TGF-β type I and two TGF-β type II receptors. Following activation, type II receptors phosphorylate type I receptors in the juxtamembrane region. This phosphorylation is both essential and sufficient for TGF-β signalling (ten Dijke & Hill, 2004). In addition, the type III TGF-β receptor also binds TGF-βs with high affinity. However, it is an extracellular protein, which does not lead to signal transduction. In fact, it may be a negative regulator of TGF-β function (Chu et al., 2011).

Both type I and type II receptors are single-pass transmembrane proteins with a serine/threonine kinase domain on the cytosolic side of the plasma membrane (Arighi et al., 2009; Attisano & Wrana, 2002). The activated type I kinase propagates the signal inside the cell through the phosphorylation of receptor-regulated Smads (R-Smads: Smad1, Smad2, Smad3, Smad5 and Smad8). Access of the R-Smads to the type I receptors is facilitated by auxiliary proteins such as Smad anchor for receptor activation. Activated R-Smads form heteromeric complexes with Smad4. These complexes accumulate in the nucleus, where they control gene expression in a cell-type-specific and ligand dose-dependent manner. Inhibitory Smads (I-Smads: Smad6 and Smad7) form a distinct subclass of Smads that act in an opposing manner to R-Smads and antagonize signalling (Padgett et al., 1998; Schmierer & Hill, 2007).

TGF-β also uses non-Smad signaling pathways such as the p38 and Jun N-terminal kinase (JNK) mitogen-activated protein kinase (MAPK) pathways to convey its signals. Other potential TGF-β-induced non-Smad signaling pathways include the phosphoinositide 3-kinase-Akt-mTOR pathway, the small GTPases Rho, Rac, and Cdc42, and the Ras-Erk-MAPK pathway (Mu et al., 2011).

3. Distribution of TGF-βs, their binding proteins and receptors in the central nervous system

The distribution pattern of TGF-βs established using immunohistochemistry at the protein level (Unsicker et al., 1991) and by means of in situ hybridization histochemistry at the mRNA level (Vincze et al., 2010) was similar in several brain regions. TGF-β2 and β3 immunoreactivities were present constitutively in cerebral cortical layers II, III and V and their expression depended on the cortical layer rather than the areas within the cerebral cortex. Furthermore, different regions of hippocampus, as well as widely distributed cells in the hypothalamus and amygdala contained both TGF-ß2 and ß3. Intense labeling of these isoforms was also described in brainstem monoaminergic neurons, and motor nuclei (Unsicker et al., 1991; Vincze et al., 2010). In turn, the striatum, most thalamic nuclei, and the superior colliculus were almost devoid of TGF-β2 and ß3 mRNA and immunoreactivities. However, considerable differences between the distribution of mRNAs and immunoreactivities of TGF-βs have also been reported. Most importantly, TGF-β1 immunoreactivity was reported to be constitutively present only in meninges and the choroid plexus in the brain (Komuta et al., 2009 ; Unsicker et al., 1991) while a more

widespread expression of the mRNA of this isoform was described including intense labeling in some cortical and hippocampal cells, the medial preoptic area, the paraventricular hypothalamic nucleus, the central amygdaloid nucleus, and the superior olive. Furthermore, TGF-β2 and β3 immunoreactivities entirely overlapped and, in general, were found in large multipolar neurons (Unsicker et al., 1991) with the level of TGF-ß2 being considerably higher (Bottner et al., 2000). In some areas, including brainstem motoneurons and the area postrema, the 2 isoforms had similar mRNA expression patterns with high intensity labeling suggesting that different isoforms of TGF-βs may be co-expressed in the same cell. In most brain areas, however, the distributions of TGF-ß2 and-ß3 mRNAs were markedly different. In the cerebral cortex, TGF-βs were expressed in different layers. In the hippocampus, TGF-β2 was abundantly expressed only in the dentate gyrus while TGF-β3 in the CA2 region and the dentate gyrus. In the cerebellum, TGF-β2 was present in the Purkinje cell layer while TGF-β3 mRNA was absent in the cerebellum. In addition, the medial mamillary nucleus, the parafascicular thalamic nucleus and the choroid plexus expressed predominantly TGF-β2 while the reticular thalamic nucleus, the superior colliculus, and the inferior olive contained almost exclusively TGF-β3 mRNA (Vincze et al., 2010). An important future question is the type of cells that express TGF-β in the central nervous system. Most previous studies examined the cell type of TGF-β expression following some type of induction. TGF-β1 upregulation in astrocytes and microglia has been reported to be a predominant response to lesion and during pathology (Krohn, 1999; Wu et al., 2007; Wu et al., 2008) that results in the induction of reactive phenotypes (Flanders et al., 1998; Morgan et al., 1993). Under basal conditions, astrocytes were also shown to express TGF-β1 in the preoptic area (Bouret et al., 2004; Dhandapani & Brann, 2003). However, neuronal expression of TGF-β1 has also been reported (Battaglia et al., 2011; Lacmann et al., 2007; Wu et al., 2007). The available data on the cell type specific expression of other TGF-β isoforms is scarce. However, their distributions suggest a dominant neuronal expression (Unsicker et al., 1991; Vincze et al., 2010).

The four types of LTBPs also had distinct distribution patterns in the brain based on the localization of their mRNAs (Dobolyi & Palkovits, 2008). The dominant form in the brain was LTBP3 while LTBP4 also had high level of expression in a variety of forebrain areas. LTBP1 had considerable level of expression in only some brain regions including the choroid plexus, the cerebral cortex, the medial amygdaloid nucleus, the anteromedial and midline thalamic nuclei, the medial preoptic area, the arcuate and dorsomedial hypothalamic nuclei, the superior olive and the area postrema. LTBP2 expression was restricted to the cerebral cortex, the hippocampus, and the lateral hypothalamus (Dobolyi & Palkovits, 2008). Comparison of the distribution of TGF-β and LTBP subtypes suggested that all 3 isoforms of TGF-βs are co-expressed with LTBP3 in the brain. In addition, TGF-βs might also bind to other types of LTBPs in certain brain regions. For example, the distribution of TGF-β1 and LTBP-4 is similar in the supraoptic nucleus and the central nucleus of the amygdala. The choroid plexus, where TGF-β2 expression is dominant contains LTBP1 and 3. The inferior olive and the arcuate nucleus, brain areas with dominant TGF-β3 expression contain large amount of LTBP4 and LTBP1, respectively (Dobolyi & Palkovits, 2008). Nevertheless, further double labeling studies are needed to actually establish co-expression of different isoforms of TGF-βs and LTBPs in single cells of the nervous system.

Although the topographical distribution of TGF-β receptors in the central nervous system has not been systematically described, the available data suggest widespread localization. When TGF-β receptor mRNA was detected by RT-PCR in rats at different stages of development similar levels were found in several regions of the CNS, including cortex, midbrain, cerebellum, brain stem and hippocampus (Bottner et al., 1996).

4. The role of TGF-βs in neural functions

Many of the investigations of TGF-β functions did not differentiate between the isoforms of TGF-βs. In many cases, TGF-β1 was applied, which, when exogenously applied, can mimick the effects of other endogenous TGF-β isoforms. Therefore, we will only mention TGF-β in these cases.

4.1 Neuronal differentiation and survival

Distributional data were the first to suggest a role of TGF-βs in the regulation of neuronal differentiation. During the development of the central nervous system, TGF-β immunostaining was most prominent in zones where neuronal differentiation occurs and less intense in zones of active proliferation (Flanders et al., 1991). Subsequent in vitro experiments using quail neural crest cell demonstrated that TGF-β inhibits proliferation of neural crest cells while neurogenesis increased significantly in the presence of TGF-β (Zhang et al., 1997). Subsequent experiments using brains supported an inhibitory role of TGF-βs on neuronal stem cell proliferation (Aigner & Bogdahn, 2008). TGF-β had an antimitotic effect on progenitors and increased expression of neuronal markers in hippocampal and cortical primary cell cultures of developing mouse (Vogel et al., 2010). These effects were dependent upon Smad4. Furthermore, in vivo loss-of-function analyses using TGF-β2(-/-)/TGF-β3(-/-) double mutant mice showed the opposite effect of increased cell proliferation and fewer neurons in the cerebral cortex and hippocampus (Vogel et al., 2010). TGF-β may also play a role in the regulation of adult neurogenesis as it had a pro-neurogenic effect in the dentate gyrus in a model of increased neurogenesis by adrenalectomy as well as in the subventricular zone when administered chronically with adenoviral vectors expressing TGF-β (Mathieu et al., 2011). Furthermore, adrenalectomy increased TGF-β levels in the dentate gyrus while blockade of TGF-β biological activity by administration of an anti-TGF-β type II receptor antibody diminished neurogenesis (Battista et al., 2006).

Apart from playing a role in the adoption of neuronal cell fate, TGF-β may also be involved in the differentiation of selected neuronal isoforms at the expense of other isoforms. Within the intermediate and ventral domains, Smad3 promoted differentiation of ventral interneurons at the expense of motoneuron generation. Consequently, the absence of Smad3 expression from the motoneuron progenitor domain during pattern formation of the neural tube was a prerequisite for the correct generation of spinal motoneurons (Garcia-Campmany & Marti, 2007). In turn, the survival of motoneurons may also depend on TGF-βs as a potentially continous trophic support factor from muscle fibres or other cell types. Using cultures of purified chick embryonic motoneurons, TGF-βs acted synergistically with basic fibroblast growth factor to keep motoneurons alive (Gouin et al., 1996). Indeed, motoneurons were shown to synthesize TGF-β receptors and to transport them anterogradely, where they were inserted into the axonal membrane and nerve terminal

(Jiang et al., 2000a) Furthermore, TGF-β2 was detected in the synaptic portions of muscle fibres, motoneurons and in injured nerves, indicating that motoneurons may be exposed to multiple and potentially redundant sources of transforming growth factor-beta 2 (Jiang et al., 2000a). In addition, double-ligation experiments were used to demonstrate that motoneurons transport transforming growth factor-beta 2 up and down their axons (Jiang et al., 2000a). To test the effect of TGF-β on motoneuron survival in vivo, TGF-β2 was administered to the hypoglossal nucleus following the avulsion of the hypoglossal nerve in adult rats, which caused a significant attenuation of the motoneuron cell death in a low dose (Jiang et al., 2000b). TGF-β2 was, however, unable to prevent or reduce the axotomy-induced down regulation of choline acetyltransferase suggesting that TGF-β2 is only one of the growth factors regulating the homeostasis of motoneurons (Jiang et al., 2000b).

In addition to motoneurons, TGF-βs may also be required for the differentiation of midbrain dopaminergic neurons influencing motor activity, emotional behavior, and cognition and being involved in the generation of Parkinson's disease, a neurodegenerative disorder of dopaminergic neurons (Markus, 2007). Treatment of cells dissociated from the rat embryonic day 12 midbrain floor with TGF-β significantly increased the number of tyrosine hydroxylase (TH)-positive dopaminergic neurons within 24 h. Neutralization of TGF-β in vitro completely abolished the induction of dopaminergic neurons (Farkas et al., 2003). In addition to the development, the survival of midbrain dopaminergic neurons may also depend on TGF-β. Administration of TGF-β2 and TGF-β3, prevented the death of cultured rat embryonic midbrain dopaminergic neurons at picomolar concentrations (Poulsen et al., 1994). Furthermore, they provided protection against N-methyl-4-phenylpyridinium ion (MPP+) toxicity of dopaminergic neurons (Krieglstein et al., 1995). In contrast to some other cytokines affecting dopaminergic neurons the mechanism of action of the TGF-βs did not involve cell proliferation or delivery of growth factors from astroglial cells (Krieglstein et al., 1995).

Since TGF-β is only one of the factors regulating the differentiation and survival of motoneurons and midbrain dopaminergic cells, their interactions with other regulatory molecules has been examined. For example, glial cell line-derived neurotrophic factor (GDNF) is also a potent survival factor for dopaminergic neurons in culture whose effect can be potentiated by TGF-βs (Poulsen et al., 1994). However, while TGF-β is required for the induction of dopaminergic neurons, GDNF is only required for regulating and/or maintaining a differentiated neuronal phenotype (Roussa et al., 2008). A cooperative role of TGF-β2 and GDNF with regard to promotion of survival has also been demonstrated within the peripheral motor system (Rahhal et al., 2009).

Finally, it has to be emphasized that motoneurons and midbrain dopaminergic cells are 2 neuronal cell types whose development has been demonstrated to be affected by TGF-β. A role of TGF-β in the differentiation and survival of other, as yet unexplored neuronal cell types might also be possible. As far as glial cells, data are available that in the peripheral nervous system, TGF-β regulates the degree of Schwann cell proliferation induced by neuronal contact (Guenard et al., 1995; Parkinson et al., 2001).

TGF-βs are also involved in apoptosis, the genetically regulated form of cell death. Apoptosis enables the balance between growth and elimination of cells and occurs physiologically during the embryonal development or involution processes. Furthermore,

infectious agents and other cell-damaging circumstances (e.g., traumatic or ischemic conditions) can lead to apoptosis. TGF-β1 has been recently characterized as an antiapoptotic factor in a model of staurosporine-induced neuronal death through a mechanism involving activation of the extracellular signal-regulated kinase 1/2 and a concomitant increase phosphorylation of the antiapoptotic protein Bad. 5 (Buisson et al., 2003). This action of TGF-β may be involved in its neuroprotective actions (see below).

4.2 Synaptic transmission and plasticity

TGF-β2 was demonstrated to influence synaptic transmission, rather than synaptogenesis, at some central synapses (Heupel et al., 2008). TGF-β2 was found to be essential for proper synaptic function in the pre-Botzinger complex, a central rhythm organizer located in the brainstem while it was not crucial for the morphology and function of the neuromuscular junction of the diaphragm muscle. Genetic deletion of TGF-β2 in mice strongly impaired both GABA/glycinergic and glutamatergic synaptic transmission in the pre-Botzinger complex area, while numbers and morphology of central synapses of knock-out animals were indistinguishable from their wild-type littermates at embryonic day 18.5 (Heupel et al., 2008). The role of TGF-β in synaptic transmission might be the basis of its proposed function in synaptic facilitation. Prolonged treatment with TGF-β2 induced facilitation of evoked postsynaptic currents in hippocampal neurons suggesting that it may play a role in the cascade of events underlying long-term synaptic facilitation (Fukushima et al., 2007). The long-term electrophysiological changes may be associated with cAMP response element-binding protein (CREB) because TGF-β2 enhanced the phosphorylation of CREB previously implicated in long-term potentiation (Fukushima et al., 2007).

The effect of TGF-β on synaptogenesis has also been proposed. In particular, TGF-β1 was identified as the molecule responsible for the synaptogenesis promiting effect of Schwann cell-conditioned medium in Xenopus nerve-muscle cocultures (Feng & Ko, 2008). TGF-β1 increased agrin expression and synaptogenesis were along nerve-muscle contacts while immunodepletion of TGF-β1 with a specific antibody abolished the synaptogenic effect of Schwann cell-conditioned medium (Feng & Ko, 2008). These results indicate that TGF-β1 may be a glial signal that instructs neurons to switch from a "growth state" to a "synaptogenic state".

4.3 Involvement in inflammatory and neuroendocrine functions

In an induced inflammatory model, the concentration of TGF-β increased in cerebrospinal fluid. This increase occurred earlier than those in the concentrations of other proinflammatory cytokines (Matsumura et al., 2008). In another inflammatory model, systemic injection of complete Freund's adjuvant, TGF-β1 and TGF-β receptor II both markedly increased in the leptomeninges and the parenchymal cells (Wu et al., 2007). Double-staining immunohistochemistry demonstrated TGF-β1 to be induced in both glial cells and cortical neurons, whereas TGF-βRII was induced only in cortical neurons. The intracisternal administration of an anti-TGF-β antibody partially inhibited the resulting fever (Matsumura et al., 2007). Furthermore, intracisternal administration of TGF-β dose-dependently raised the body temperature (Matsumura et al., 2008). These findings suggest a novel function of TGF-β as a proinflammatory cytokine in the central nervous system

The potential involvement of TGF-β in central reproductive regulation is also an emerging topic. Gonadotropin-releasing hormone neurons in the preoptic area contain TGF-β receptors as well as SMAD2/3 suggesting that they are fully capable of responding directly to TGF-β1 stimulation (Prevot et al., 2000). Subsequent double-labeling experiments showed that astrocytes in the preoptic area expressed TGF-β1 mRNA and that GnRH perikarya were often found in close association with TGF-β1 mRNA-expressing cells (Bouret et al., 2004). Incubation of preoptic explants with TGF-β1 caused a significant, dose-dependent decrease in GnRH mRNA expression in individual neurons. This effect was inhibited by addition of the soluble form of TGF-β-RII to the incubation medium (Bouret et al., 2004). These results support that astrocyte-derived TGF-β1 may directly influence GnRH expression and/or secretion in vivo by acting on the perikarya of GnRH neurons.

Intracisternal administration of TGF-β induces an increase in fat oxidation while intracisternal administration of anti-TGF-β antibody partially inhibits an increase in fat oxidation during treadmill running in rats indicating a regulatory role of TGF-β in the brain on fat oxidation during exercise (Fujikawa et al., 2007). Since TGF-β3 increased noradrenaline levels in the paraventricular and ventromedial hypothalamic nuclei and chemical lesion of noradrenaline input to these nuclei completely abolished the regulatory effect of TGF-β on fat oxidation it has been suggested that TGF-β in the brain enhances fat oxidation via noradrenergic neurons in the paraventricular and ventromedial hypothalamic nuclei (Fujikawa et al., 2007). An inhibitor of FA oxidation could induce an activation of TGF-β in the CSF suggesting that shortage of energy derived from fatty acids leads to the activation of TGF-β (Fujikawa et al., 2011).

TGF-β1 and 3 also co-localize with arginine vasopressin in magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus suggesting that TGF-β secreted by the neurohypophysis might regulate the proliferation and secretion of certain anterior pituitary cells (Fevre-Montange et al., 2004). So far, the regulatory role of TGF-β on hormone secretion, gene transcription, and cellular growth of prolactin-producing cells has been shown. TGF-β inhibited the transcriptional activity of the estrogen receptor although estrogens had no effect on TGF-β-specific Smad protein transcriptional activity (Giacomini et al., 2009). A diurnal pattern of expression of TGF-β as well as SMAD3 was found in the suprachiasmatic and paraventricular nuclei of young animals, a rhythm that was not onserved in older mice suggesting a diurnal and age-dependent function of the TGF-β system in these nuclei (Beynon et al., 2009). These expressional data indicate numerous yet unexplored functions of TGF-βs in the hypothalamus. Therefore, promising future investigations on the role of TGF-βs in endocrine regulations are eagerly awaited.

5. Pathophysiological functions of TGF-βs in the nervous system

In addition to their role in normal functioning of the nervous system, TGF-βs have also been implicated in different mechanisms under pathophysiological conditions. TGF-βs have been shown to be injury-related proteins. They were suggested to be neuroprotective following ischemia as well as in various neurological diseases. Furthermore, TGF-βs were implicated in glial scar formation. Finally, their role in brain tumor formation will be discussed.

5.1 Neuroprotective function in brain ischemia

A number of studies have documented that TGF-β1 levels are enhanced in the brain following cerebral ischemia (Dhandapani & Brann, 2003). The expressions of other isoforms are also enhanced albeit with a different pattern around a focal lesion. Following middle cerebral artery occlusion, TGF-β1 expression was elevated in the penumbra around the lesion site while TGF-β2 and 3 expressions showed increases in particular cortical layers throughout the ipsilateral cerebral cortex (Vincze et al., 2010).

TGF-β1 administered into the brain reduced the infarct size dose dependently in experimental models of ischemia including permanent occlusion of the left middle cerebral artery by microbipolar electrocoagulation in mice (Prehn et al., 1993), autologous clot embolus injection into the right internal carotid artery in rabbit (Gross et al., 1993), and transient middle cerebral artery occlusion in rat (Zhu et al., 2002). In turn, antagonizing the endogenous action of TGF-β1 with a soluble TGF-β type II receptor resulted in a dramatic increase in infarct area (Ruocco et al., 1999). An intracortical injection of the soluble antagonsi in rats subjected to a 30-minute reversible cerebral focal ischemia aggravated the volume of infarction (Ruocco et al., 1999). These results suggest that, in response to an ischemic insult, brain tissue responds by the synthesis of TGF-β1, which is involved in the limitation of the extent of the injury.

Despite the accumulating knowledge on the signal transduction of TGF-βs, the signaling pathway mediating its protective effect is not fully understood. Bad is a proapoptotic member of the Bcl-2 family and is inactivated on phosphorylation via mitogen-activated protein kinase (MAPK). A gradual activation of extracellular signal-regulated kinase 1/2 and MAPK-activated protein kinase-1 and a concomitant increase in Bad phosphorylation in mouse brains after adenovirus-mediated TGF-β1 transduction under nonischemic and ischemic conditions induced by transient middle cerebral artery occlusion (Zhu et al., 2002). Consistent with these effects, the ischemia-induced increases in Bad protein level and caspase-3 activation were suppressed in TGF-β1-transduced brain. Consequently, DNA fragmentation, ischemic lesions, and neurological deficiency were significantly reduced. Furthermore, inhibitors of the MAPK signal transduction pathway abolished the neuroprotective activity of TGF-β1 in staurosporine-induced apoptosis, indicating that activation of MAPK is necessary for the antiapoptotic effect of TGF-β1 (Zhu et al., 2002). These data suggest that TGF-β1 regulates the expression and ratio of apoptotic (Bad) and antiapoptotic proteins, creating an environment favorable for cell survival of death-inducing insults (Dhandapani & Brann, 2003).

5.2 TGF-β in astrogliosis

The physiological role of astrogliosis remains controversial with respect to the beneficial or detrimental influence of reactive astrocytes on CNS recovery. On the one hand, the very dense network of processes built up in the scar by reactive astrocytes suggests that the scar tissue may fulfill important functions as a barrier isolating and protecting the intact tissue from the lesions, from which toxic molecules could be released. On the other hand, molecules expressed in lesion scars on the astroglial cell surface or secreted molecules render the reactive astrocyte a less favorable substrate, which could be inhibitory to neuritic outgrowth. Nevertheless, scar formation in the nervous system begins within hours after

traumatic injury and is characterized primarily by reactive astrocytes depositing proteoglycans that inhibit regeneration. A fundamental question in CNS repair has been the identity of the initial molecular mediator that triggers glial scar formation. Recent evidence suggests that one of the gliosis signaling molecules is TGF-β. TGF-β up-regulates the biosynthesis of keratin sulphate and chondroitin sulphate (Yin et al., 2009). Local injection of TGF-β antagonists into cerebral wounds reduces glial scarring (Lagord et al., 2002). Inhibition of the TGF-β receptor pathway abolished the fibrinogen-induced effects on glial scar formation in vivo and in vitro (Schachtrup et al., 2011) pointing to TGF-β as a molecular link between vascular permeability and scar formation. Furthermore, TGF-β expression increases immediately after injury e.g. in the injured segment in an animal model using an impactor (Wang et al., 2009). There are, however, differences in the expression pattern of individual TGF-β isoforms. Levels of TGF-β1 mRNA were most elevated over the acute inflammatory phase after transection of the dorsal funiculi in the spinal cord, while TGF-β2 mRNA levels were raised locally about the wound, particularly in astrocytes and neovascular endothelial cells, over the subacute period of scarring. TGF-β protein production also increased after injury. Both TGF-β1 and TGF-β2 were found in hematogenous inflammatory cells, while TGF-β1 was also neuron-associated, and high levels of TGF-β2 were localized to multiple cell types in the wound, including reactive astrocytes, during the period of glial/collagen scar formation (Lagord et al., 2002). More recently, TGF-β levels were also reported in the human spinal cord after traumatic injury. Sections from human spinal cords from 4 control patients and from 14 patients who died at different time points after traumatic spinal cord injury were investigated immunohistochemically. In control cases, TGF-β1 was confined to occasional blood vessels, intravascular monocytes and some motoneurons, whereas TGF-β2 was only found in intravascular monocytes (Buss et al., 2008). After traumatic spinal cord injury, TGF-β1 immunoreactivity was dramatically upregulated by 2 days after injury and was detected within neurons, astrocytes and invading macrophages. The staining was most intense over the first weeks after injury but gradually declined by 1 year. TGF-β2 immunoreactivity was first detected 24 days after injury. It was located in macrophages and astrocytes and remained elevated for up to 1 year. In white matter tracts undergoing Wallerian degeneration, there was no induction of either isoform (Buss et al., 2008). The conclusion from these studies is that TGF-β1 modulates the acute inflammatory and neural responses and formation of the glial scar, while the later induction of TGF-β2 may indicate a role in the maintenance of the scar.

5.3 The role of TGF-βs in brain tumor formation

TGF-β reveals anti-proliferative control on most cell types including an inhibitory effect on the proliferation of normal astrocytes. Thus, upon TGF-β treatment, primary rat astrocytes show a significant decrease in DNA synthesis upon thymidine incorporation with a cell cycle arrest in the G(1) phase and the expression of the cyclin-dependent kinase inhibitor (CdkI) p15(INK4B) is up-regulated (Rich et al., 1999). The SMAD signal transduction pathway is likely to be involved as Smad3 null mouse astrocytes show a loss of both TGF-β-mediated inhibition of growth (Rich et al., 1999). Analysis of Smad3 null mouse astrocytes showed a significant loss of both TGF-β-mediated growth inhibition and p15(INK4B) induction compared with wild-type mouse astrocytes.

Paradoxically, many brain tumors escape from normal TGF-β inhibitory control. High-grade human gliomas secrete TGF-β and can activate latent TGF-β (Sasaki et al., 2001). Yet, they are resistant to its growth inhibitory effects. In fact, they develop mechanisms that change the anti-proliferative influence of TGF-β into oncogenic cues. Thus, TGF-β is involved in tumor progression (Aigner & Bogdahn, 2008). The dominant hypothesis of TGF-β's pathogenetic association with malignant transformation has been predicated upon acquisition of resistance to its growth inhibitory effects. However, the lack of obvious correlation with TGF-β receptor expression between hyperdiploid glioblastoma multiforme and TGF-β-inhibited glioblastoma cultures suggests the existence of intrinsically opposed regulatory mechanisms influenced by TGF-β (Jennings & Pietenpol, 1998). The mechanism of conversion might be explained either by the loss of a putative tumor suppressor gene, which mediates TGF-β's inhibition of growth or by enhancement of an active oncogenic pathway among hyperdiploid glioblastoma multiforme. Experimental evidence supports the involvement of several factors including inactivating mutation/loss of the TbetaR type II, alterations in post-receptor signal transmission or the cyclin/cyclin dependent kinase system. The expression of the Smad2 and Smad3 proteins is lowered in many glioma cell lines. The phosphorylation and nuclear translocation of Smad2 and Smad3 are also impaired (Zhang et al., 2006). The loss of p15(INK4B) may also explain the selective loss of growth inhibition by TGF-β in gliomas to form a more aggressive tumor phenotype (Rich et al., 1999). TGF-β also induced expression of Sox2, a stemness gene, and this induction was mediated by Sox4, a direct TGF-β target gene. Inhibitors of TGF-β signaling drastically deprived tumorigenicity of glioblastoma cells identifying the relevance of the TGF-β-Sox4-Sox2 pathway, too (Ikushima et al., 2009). Among TGF-β isoforms, TGF-β2 has been identified as the most important factor in the progression of malignant gliomas. TGF-β2, originally described as "glioblastoma-derived T-cell suppressor factor", was particularly associated with the immuno-suppressed status of patients with glioblastoma. Furthermore, elevated TGF-β2 levels in tumors and in the plasma of patients have been associated with advanced disease stage and poor prognosis (Hau et al., 2011).

High-grade gliomas are the most common primary tumors in the central nervous system (CNS) in adults. Despite efforts to improve treatment by combination therapies (neurosurgery, radio- and chemotherapy), high-grade glioma patients still have a grim prognosis, indicating an urgent need for new therapeutic approaches. Since TGF-β is intimately involved in the regulation of several processes characteristic of human malignant glioma including excessive proliferation, infiltrative growth, angiogenesis and suppression of anti-tumor immune surveillance, TGF-β promises to become a novel target for the experimental therapy of human malignant glioma (Platten et al., 2001). Several in vitro paradigms and rodent glioma models have been used to demonstrate that the antagonism of TGF-β holds promise for the treatment of glioblastoma, employing antisense strategies, inhibition of pro-TGF-β processing, scavenging TGF-β by decorin, or blocking TGF-β activity by specific TGF-β receptor I kinase antagonists (Naumann et al., 2008; Wick et al., 2006). Among these possibilites, the antisense oligonucleotide trabedersen (AP 12009) that specifically blocks TGF-β2 mRNA has the highest potential at present to treat gliobastomas (Hau et al., 2011). In three phase I/II studies and a randomized, active-controlled dose-finding phase IIb study, trabedersen treatment of high-grade glioma patients with recurrent or refractory tumor disease led to long-lasting tumor responses and so far promising

survival data. On the basis of these data the currently ongoing phase III study SAPHIRRE was initiated (Hau et al., 2011). In addition, TGF-β inhibition may also be used as a supplementary treatment as it can enhance the therapeutic efficacy of glioma-associated antigen vaccines (Ueda et al., 2009).

5.4 Neuroprotective function in additional neurological diseases

Apart from ischemia, trauma, or tumors, deafferentation and neurodegeneration also induce TGF-β expression in the central nervous system (Morgan et al., 1993). Therefore, it is not surprising that TGF-βs were implicated in a variety of neurodegenerative diseases.

Alzheimer's disease (AD) is characterized by the presence of amyloid (Abeta) plaques, neurofibrillary tangles, and neuronal loss. The disorder is also frequently associated with cerebrovascular changes, including perivascular astrocytosis, amyloid deposition, and microvascular degeneration, but it is not known whether these pathological changes contribute to functional deficits in AD. TGF-β1 expressed in the astrocytes of transgenic mice induced a prominent perivascular astrocytosis, followed by the accumulation of basement membrane proteins in microvessels, thickening of capillary basement membranes, and later, around 6 months of age, deposition of amyloid in cerebral blood vessels. At 9 months of age, various AD-like degenerative alterations were observed in endothelial cells and pericytes. These results suggest that chronic overproduction of TGF-β1 triggers a pathogenic cascade leading to AD-like cerebrovascular amyloidosis, microvascular degeneration, and local alterations in brain metabolic activity (Wyss-Coray et al., 2000). A specific impairment of TGF-β1 signaling pathway has also been demonstrated in AD brain. The deficiency of TGF-β1 signaling has been shown to increase both Abeta accumulation and Abeta-induced neurodegeneration in AD models. The loss of function of TGF-β pathway also seems to contribute to tau pathology and neurofibrillary tangle formation (Caraci et al., 2009). Growing evidence suggests a neuroprotective role for TGF-β1 against Abeta toxicity both in vitro and in vivo models of AD. Different drugs, such as lithium or group II mGlu receptor agonists are able to increase TGF-β1 levels in the central nervous system. The combined Abeta- and TGF-β1-driven pathology recapitulates salient cerebrovascular, neuronal, and cognitive AD landmarks and yields a versatile model toward highly anticipated diagnostic and therapeutic tools for patients featuring Abeta and TGF-β1 increments (Ongali et al., 2011). Thus, TGF-β1 might be considered as new neuroprotective tools against Abeta-induced neurodegeneration.

A defective expression or activity of neurotrophic factors, such as brain- and glial-derived neurotrophic factors, is known to contribute to neuronal damage in Huntington's disease (HD). Asymptomatic HD patients also showed a reduction in TGF-β1 levels in the peripheral blood, which was related to trinucleotide mutation length and glucose hypometabolism in the caudate nucleus. Immunohistochemical analysis in post-mortem brain tissues showed that TGF-β1 was reduced in cortical neurons in HD patients. In mouse models of HD, the animals showed a reduced expression of TGF-β1 in the cerebral cortex, localized in neurons, but not in astrocytes. In these mice, glutamate receptor agonist failed to increase TGF-β1 formation in the cerebral cortex and corpus striatum, suggesting that a defect in the regulation of TGF-β1 production is associated with HD. Accordingly, reduced TGF-β mRNA and protein levels were found in cultured astrocytes transfected with mutated exon 1 of the human huntingtin gene, and in striatal knock-in cell lines expressing

full-length huntingtin with an expanded glutamine repeat (Battaglia et al., 2011). These data suggest that serum TGF-β1 levels are potential biomarkers of HD development during the asymptomatic phase of the disease, and raise the possibility that strategies aimed at rescuing TGF-β1 levels in the brain may influence the progression of HD.

Additional neurodegenerative diseases were also associated with an alteration of the TGF-βs. Using immunohistochemistry, the expression of TGF-β2 appeared in neurofibrillary tangle bearing neurons and tangle-bearing glial cells in progressive supranuclear palsy and in neurons with age-related neurofibrillary tangle formation (Lippa et al., 1995). Widespread staining of reactive astrocytes for TGF-β2 was observed in all degenerative diseases. TGF-β1 and -3 staining was not selectively altered in these diseases (Lippa et al., 1995). These data suggest that the induction of TGF-β2 may be an intrinsic part of the processes that underlie neurofibrillary tangle formation and reactive gliosis in a variety of neurodegenerative diseases.

Activation of the TGF-β pathway was identified as the underlying mechanism behind the epileptogenic effect of albumin following the compromise of the blood brain barrier (Cacheaux et al., 2009). TGF-β1 resulted in epileptiform activity similar to that after exposure to albumin. Coimmunoprecipitation revealed binding of albumin to TGF-β receptor II, and Smad2 phosphorylation confirmed downstream activation of this pathway. Transcriptome profiling demonstrated similar expression patterns after blood brain barrier breakdown, albumin, and TGF-β1 exposure, including modulation of genes associated with the TGF-β pathway, early astrocytic activation, inflammation, and reduced inhibitory transmission. Importantly, TGF-β pathway blockers suppressed most albumin-induced transcriptional changes and prevented the generation of epileptiform activity. Based on these data, the TGF-β pathway was suggested to be a novel putative epileptogenic signaling cascade and therapeutic target for the prevention of injury-induced epilepsy (Cacheaux et al., 2009).

6. Conclusion

TGF-βs are a class of growth factors and cytokines with a special biochemistry and range of actions thoughout the organs of the body. Our knowledge on their roles in the central nervous system is accumulating fast in the last years. Neverthless, their neurochemistry is not well described, and often we can only anticipate that their synthesis, activation, and signal transduction pathways is similar to that in other tissues. The potential differences are to be determinded in future studies. Our understanding of the physiological functions of endogenous TGF-βs is also limited despite recent significant progress in the field. An increasing body of evidence suggests the otherwise logical assumption that TGF-βs play a role in the development of the nervous tissue. Recent studies revelased that TGF-βs are also involved in the physiological functions of the adult nervous system as well. So far, the best established functions include synaptic transmission and neuronal plasticity. Somewhat surprisingly, however, the direct involvement of TGF-βs in neuroendocrine functions has also been supported. The experiments often did not differentiate between the 3 different isoforms of TGF-β. Therefore, future studies are needed to elaborate their specific functions. Based on differences in the distribution of TGF-β1, TGF-β2, and TGF-β3, they possess separate neural functions.

TGF-βs also participate in a number of pathophysiological processes. It has been long established that they are neuroprotective during excitotoxicity and ischemia. Strong evidence supports that TGF-βs constitute part of an endogenous neuroprotective system involved in ischemic preconditioning. This action of TGF-βs may or may not be related to their role in astroglial scar formation following injury. Nevertheless, the pharmacologic potentiation of this endogenous defensive mechanism might represent an alternative and novel strategy for the therapy of hypoxic-ischemic cerebral injury. TGF-β also play a pivotal role in brain tumor formation. The anti-proliferative actions of TGF-βs on astrocytes can be converted in tumor cells. Therefore, TGF-β-antagonistic treatment strategies are among the most promising of the current innovative approaches for glioblastoma, particularly in conjunction with novel approaches of cellular immunotherapy and vaccination.

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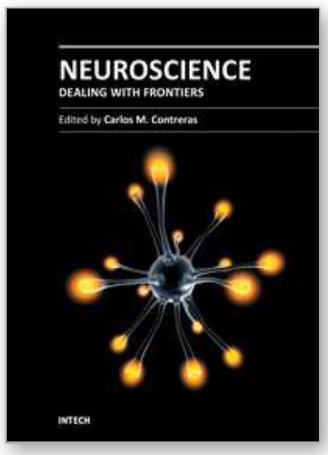

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The Neuronal Doctrine recently reached its 100th year and together with the development of psychopharmacology by the middle of 20th century promoted spectacular developments in the knowledge of the biological bases of behavior. The overwhelming amount of data accumulated, forced the division of neuroscience into several subdisciplines, but this division needs to dissolve in the 21st century and focus on specific processes that involve diverse methodological and theoretical approaches. The chapters contained in this book illustrate that neuroscience converges in the search for sound answers to several questions, including the pathways followed by cells, how individuals communicate with each other, inflammation, learning and memory, the development of drug dependence, and approaches to explaining the processes that underlie two highly incapacitating chronic degenerative illnesses.

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