REVIEW

TGF-beta in neural stem cells and in tumors of the central nervous system

Ludwig Aigner · Ulrich Bogdahn

Abstract Mechanisms that regulate neural stem cell activity in the adult brain are tightly coordinated. They provide new neurons and glia in regions associated with high cellular and functional plasticity, after injury, or during neurodegeneration. Because of the proliferative and plastic potential of neural stem cells, they are currently thought to escape their physiological control mechanisms and transform to cancer stem cells. Signals provided by proteins of the transforming growth factor (TGF)-beta family might represent a system by which neural stem cells are controlled under physiological conditions but released from this control after transformation to cancer stem cells. TGF-beta is a multifunctional cytokine involved in various physiological and patho-physiological processes of the brain. It is induced in the adult brain after injury or hypoxia and during neurodegeneration when it modulates and dampens inflammatory responses. After injury, although TGF-beta is neuroprotective, it may limit the self-repair of the brain by inhibiting neural stem cell proliferation. Similar to its effect on neural stem cells, TGF-beta reveals anti-proliferative control on most cell types; however, paradoxically, many brain tumors escape from TGF-beta control. Moreover, brain tumors develop mechanisms that change the anti-proliferative influence of TGF-beta into oncogenic cues, mainly by orchestrating a multitude of TGF-beta-mediated effects upon matrix, migration and invasion, angiogenesis, and, most importantly, immune escape mechanisms. Thus, TGF-beta is involved in tumor progression. This review focuses on TGF-beta and its role in the regulation and control of neural and of brain-cancer stem cells.

Keywords Neurogenesis · Smad signaling · Cancer · Stem cells · Immune system · Brain

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TGF-beta molecules

The TGF-beta superfamily includes more than 100 different proteins, more than 40 of them having been described in mammals. Members include proteins such as activin and inhibin, bone morphogenetic proteins (BMPs), one class of growth and differentiation factors (GDFs), and a small group of multifunctional cytokines, the TGF-beta molecules. Concerning mammals, the last-mentioned subfamily shares three isoforms, TGF-beta1, TGF-beta2, and TGF-beta3 (Massague 1998; Bottner et al. 2000). TGF-beta is synthesized as a precursor and subsequently processed. Being composed of three distinct domains (signal-peptide for secretion, pro-domain, and mature protein), TGF-beta is a typical example of a secreted signaling peptide. From the 391-amino-acid precursor form of TGF-beta1, the C-terminal 112 amino acids comprise the mature protein. The N-terminal peptide is the pro-domain, called the latency associated peptide (LAP). TGF-beta is secreted as a large latent complex composed of the active TGF-beta form covalently bound to LAP, which in turn is bound to a latent TGF-beta-binding protein (LTBP). Since the LTBP is linked to the extracellular matrix (ECM), the entire complex is stored in the extracellular space and provides a source of readily available ligand. Extracellular serine proteases cleave the LTBP and release the active ligand from LAP (Massague

1998; Annes et al. 2003). The biologically active form of TGF-beta consists of a homodimer built out of two peptides, 12.5 kD in size, which are linked through disulfide bonds (Bottner et al. 2000; Dennler et al. 2002).

TGF-beta was first described in 1981. The name of the protein was deduced from its transforming effect on rat kidney and fibroblast cell lines (Moses et al. 1981; Roberts et al. 1981). However, it soon became clear that TGF-beta has multiple functions. By regulating cell proliferation, migration, and differentiation, the apoptosis of a variety of cell types, ECM formation, and inflammatory responses, it controls developmental processes such as body plan and tissue formation and regulates homeostasis and repair in adult tissue, including the central nervous system (CNS; Border and Noble 1997; Roberts 1998; Bottner et al. 2000; Massague et al. 2000; Unsicker and Strelau 2000).

TGF-beta signal transduction pathways

Although TGF-beta signal transduction through its receptors and through Smad proteins seems to be fairly simple at first glance, signal divergence into other pathways and convergence from neighboring signaling pathways generate a highly complex network. Depending on the environmental and cellular context, TGF-beta signaling may result in a variety of different cellular responses (Massague et al. 2000; Dennler et al. 2002).
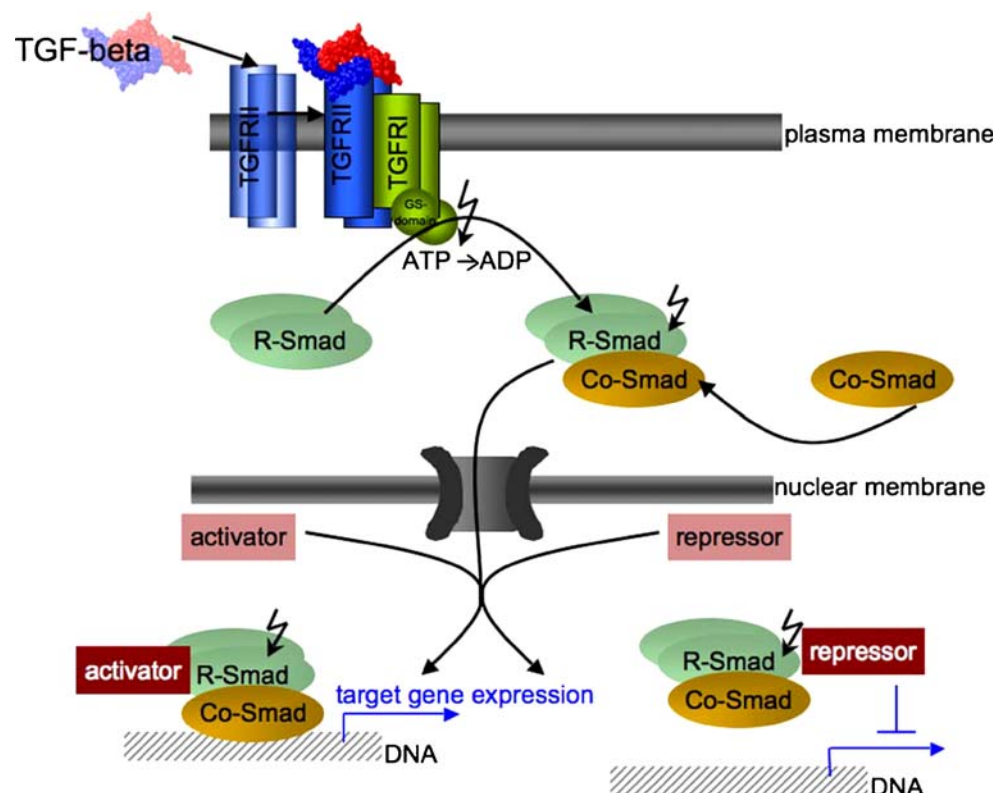
TGF-beta signals via Smad-dependent pathways

Activated TGF-betas exert their effects on the target cell via three different receptor classes: type I (TGFRI, also termed activin-like kinases (ALK; 53 kDa), type II (TGFRII; 70-100 kDa), and type III (TGFRIII; 200–400 kDa; Massague 1990). To date, seven different isoforms have been described for receptor type I and five for receptor type II (Bierie and Moses 2006). The cell-type-specific distribution of receptor isotypes plays a key role in differential signal transduction at the cellular level, together with additional modulating mechanisms (Shi and Massague 2003). Receptors of type I and II are glycoproteins and belong to the serine threonine kinase receptor group. They consist of a short cysteine-rich extracellular domain for ligand binding, a transmembrane segment, and an intracellular region with serine threonine kinase activity (Massague 1992, 1998; Wrana et al. 1994; Bottner et al. 2000; Massague and Chen 2000; Shi and Massague 2003). Receptor type III (betaglycan and endoglin) does not directly mediate a signal but increases the affinity of TGFRII for TGF-beta2 and thus enables the binding of this particular ligand. In contrast, TGF-beta1 and TGF-beta3 bind independently from TGFRIII to TGFRII (Bierie and Moses 2006).

Whereas type II receptor kinase is constitutively active, type I receptor needs to be activated. This process is initiated through the binding of the ligand to TGFRII; this triggers the transient formation of a complex that includes the ligand and receptor types I and II. Taking into account the dimeric composition of the ligand, the receptor complex most likely consists of a tetrameric structure formed by two pairs of each receptor type (I and II; Yamashita et al. 1994). Type I receptors contain a strongly conserved sequence rich in glycine and serine, the so-called GS-domain (Shi and Massague 2003). This domain is trans-phosphorylated by TGFRII kinase mediating the activation of TGFRI kinase (Wrana et al. 1994; Dennler et al. 2002). Subsequently, activated TGFRI interacts with a multitude of specific proteins within the cytoplasm. In this context, the family of Smad proteins (homologous proteins to the Sma and Mad proteins from *Caenorhabditis elegans* and *Drosophila melanogaster*) is essential (Gomes et al. 2005), although other effectors further downstream are also involved (see also next chapter; Fig. 1).

Characteristically, all Smad proteins possess two domains, the MH1 and MH2 (mad homology) domains, situated on the amino- and the carboxy-terminus, respectively, with MH1 being responsible for the protein-DNA interaction, and MH2 being responsible for the protein-protein interaction (Shi et al. 1998). Depending upon their structure and on their function, Smad proteins are divided into three groups: receptor-regulated "R-Smads" (Smad1, Smad2, Smad3, Smad5, Smad8), complex "Co-Smads" (Smad 4), and inhibitory "I-Smads" (Smad6, Smad7; Dennler et al. 2002). R-Smads are activated directly by trans-phosphorylation through the type I receptor kinase (Souchelnytskyi et al. 1997). With regards to the different ligands and to specificity, TGF-beta signals are mediated in general via Smad2 and Smad3, and the relevant BMP signals are mediated via Samd1, Smad5, and Smad8 (Feng and Derynck 2005). Activated "R-Smads" interact with Co-Smad 4, resulting in a complex that is trans-located to the nucleus where it directly regulates target gene transcription (Dennler et al. 2002). Contrary to this, inhibitory Smads work as antagonists by preventing the effects of activated "R-" and "Co-Smads" (Imamura et al. 1997; Nakao et al. 1997).

In summary, Smad-dependent cellular signal transduction initiated by activated TGF-beta consists of (1) the binding of the TGF-beta isoform to a specific TGFRI/II receptor pair, (2) the activation of the GS-domain in TGFRI by TGFRII, (3) the phosphorylation of intracellular Smads implemented by activated TGFRI, and (4) the translocation of an activated Smad complex into the nucleus in order to influence specific gene expression. Finally, the TGF-beta-mediated signals are interrupted by ubiquitinylation or proteasomal breakdown of the effectors (Massague 2000).

Fig. 1 Smad-mediated signal transduction of TGF-beta. TGF-beta binds to the TGFRII that complexes with and activates TGFRI. This induces the Smad cascade of signal transduction

TGF-beta triggers Smad-independent pathways: divergence

TGF-beta not only activates the Smad signaling pathway, but diverges into almost all other known classical signaling cascades (for reviews, see Derynck and Zhang 2003; Moustakas and Heldin 2005; Fig. 2). This high degree of divergence allows TGF-beta to modulate other signaling cascades, thus contributing to the multitude of cellular responses influenced by TGF-beta. However, since mutations in constituents of the various cascades might influence the TGF-beta response, this divergence also contributes to the metamorphosis of TGF-beta from a tumor-suppressor to a tumor promoter with respect to its role in tumor progression (Massague et al. 2000; Derynck et al. 2001; Roberts and Wakefield 2003; Bierie and Moses 2006; Seoane 2006).

Divergence into the Ras/Erk/MAPK pathway TGF-beta has been shown in a number of cell types to activate the MAPK (mitogen-activated protein kinase) pathway within a short time (minutes) suggesting a direct, Smad-, and transcription/translation-independent mechanism (Massague 2000). Results from experiments with Smad4-deficient cells and dominant-negative forms of Smads have supported the presence of Smad-independent mechanisms of the TGF-beta activation of the MAPK pathway (Engel et al. 1999). In addition, TGF-beta type I mutant receptors that are deficient in Smad activation are able to trigger MAPK

signaling in response to TGF-beta (Yu et al. 2002). More recently, the phosphorylation of p53 has been identified as the node that integrates TGF-beta and Ras/MAPK signals (Cordenonsi et al. 2007). Activation of Ras/Erk/MAPK signaling by TGF-beta can induce an autocrine amplification loop of TGF-beta1 expression (Yue and Mulder 2000).

Divergence into the JNK pathway JNK is rapidly activated by TGF-beta in a Smad-independent manner (Engel et al. 1999; Yamaguchi et al. 1999). TGF-beta-activated kinase (TAK)-1 and MAPK kinases mediate the TGF-beta and BMP activation of JNK and p38 MAPK (Yamaguchi et al. 1999).

Divergence into the Rho/ROCK pathway The small GTPases RhoA and RhoB have been implicated in TGF-beta signaling. For example, the TGF-beta1-induced epithelial to mesenchymal trans-differentiation and inhibition of cell proliferation is mediated via RhoA- and p160ROCK-dependent signaling (Bhowmick et al. 2001, 2003). In addition, TGF-beta stabilizes RhoB, which in turn downregulates TGF-beta signaling (Engel et al. 1998).

Divergence into the PI3K-Akt pathway In a number of cell types, TGF-beta activates the PI3K-Akt pathway. For example, in mammary epithelial cells expressing a constitutive active form of the TGF-beta receptor type I, the PI3K/Akt pathway is induced (Muraoka-Cook et al. 2006).

Fig. 2 Divergence and convergence of TGF-beta and other signaling cascades. The TGF-beta signaling cascade diverges into many other signaling cascades. Moreover, a number of signaling cascades are known to influence the Smad cascade. The final outcome of cellular responses might be balanced by the interaction between these cascades
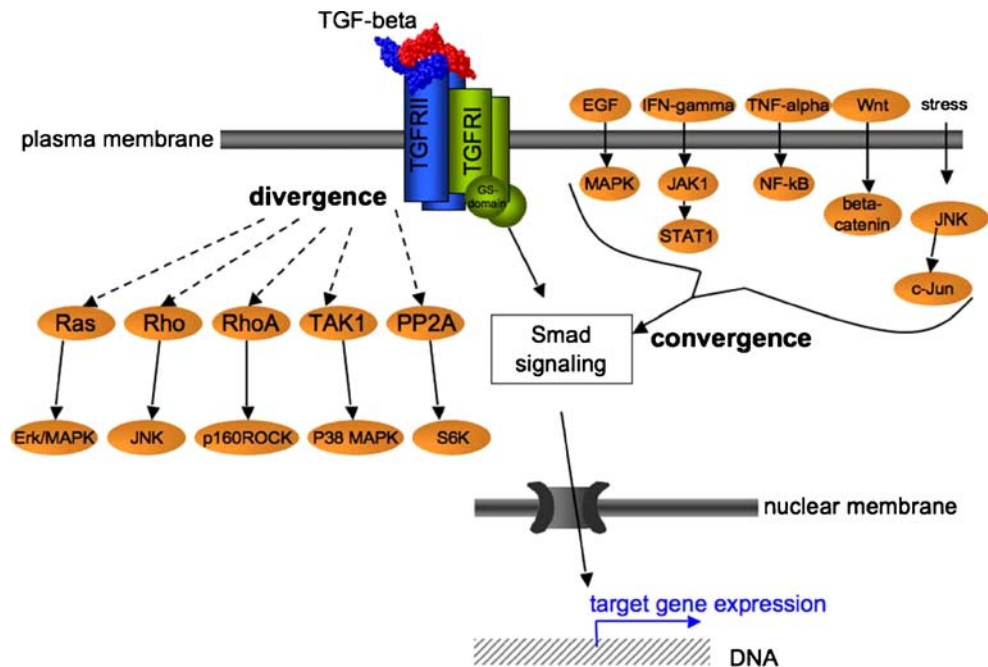
Moreover, the direct interaction of the TGF-beta receptors with p85, the regulatory subunit of PI3K, indicates a Smad-independent mechanism (Yi et al. 2005).

Divergence into the PP2A/S6 kinase pathway TGF-beta can induce the association of the TGF-beta receptor with protein phosphatase PP2A, which in turn results in the inhibition of S6-kinase and in the G1 arrest of the cell cycle (Petritsch et al. 2000).

Convergence of other signaling cascades in the TGF-beta/ Smad cascade and pathway cross-talk

The TGF-beta/Smad pathway is also modulated by many other signaling cascades, a phenomenon that contributes to the remarkable variety of context and cell-type-dependent TGF-beta responses (for reviews, see Derynck et al. 2001; Derynck and Zhang 2003; Fig. 2). Convergence into Smad signaling has been demonstrated, for example, for the Ras/ Erk/MAPK pathway (de Caestecker et al. 1998; Kretzschmar et al. 1999; Funaba et al. 2002), the JAK/STAT pathway (Ulloa et al. 1999), the JNK pathway (Engel et al. 1999), the Wnt pathway (Labbe et al. 2000; Letamendia et al. 2001), and the NF-kappaB pathway (Bitzer et al. 2000). The convergence of the signaling cascades may result in synergism; however, they may also inhibit and counteract each other (Kimura et al. 2000; Mazars et al. 2001; Pessah et al. 2002). Thus, the balance between Smad signaling and other signaling systems often defines the net cellular response to TGF-beta.

TGF-beta expression in the brain

All three isoforms of TGF-beta are expressed within the nervous system, in neurons and in glial cells (for a review, see Bottner et al. 2000). Most knowledge of the expression of TGF-beta in the CNS dates from work carried out on brain development. In general, TGF-beta2 and TGF-beta3 are found ubiquitously and are mostly co-expressed in the CNS, whereas TGF-beta1 is predominantly up-regulated and activated after CNS lesions or in cases of neuro-degeneration (Flanders et al. 1998). In the last-mentioned cases, it is involved in coordinating inflammatory responses and brain repair. TGF-beta1 and TGF-beta2 are also involved in brain-tumor development and progression, in particular of high-grade gliomas (Derynck et al. 1987; Jachimczak et al. 1993, 1995; Kjellman et al. 2000; Wick et al. 2001; Schlingensiepen et al. 2006).

TGF-beta2 und TGF-beta3 and their receptors can be found during the early development of the embryo in the chorda dorsalis and the subplate and during the establishment of the midbrain. Here, they work synergistically with other growth factors in order to promote the survival of dopaminergic neurons; in the same context, they might also be of importance for the regulation of neuronal migration and differentiation and for the proliferation and differentiation of glial cells (Poulsen et al. 1994; Krieglstein et al. 1998a, 1998c; Farkas et al. 2003; Roussa et al. 2004; Roussa and Krieglstein 2004). Glial cells (including radial glia) and neurons express TGF-beta2 and TGF-beta3 during development (Flanders et al. 1991; Pelton et al. 1991; Miller 2003). In the adult, TGF-beta2 and TGF-beta3 can

be found in all areas of the CNS, in glial and in neuronal cells (Flanders et al. 1998; Bottner et al. 2000; Unsicker and Strelau 2000).

Although some contradictory data exist with respect to the expression of TGF-beta1 in the CNS, TGF-beta1 is widely accepted as being found predominantly in the choroid plexus and in the meninges, whereas after lesions of the brain, it is also expressed by astroglial, neuronal cells, and most prominently, by microglia (Flanders et al. 1991; Unsicker et al. 1991; Constam et al. 1992; Bottner et al. 2000; Zhu et al. 2000; Unsicker and Krieglstein 2002). In addition, cultivated neurons and astrocytes have been shown to express TGF-beta1 (Lindholm et al. 1992; Morganti-Kossmann et al. 1992; Vivien et al. 1998; de Sampaio e Spohr et al. 2002; Mittaud et al. 2002; Sousa Vde et al. 2004). Moreover, the presence of TGF-beta1 has also been hinted at during cortical development in the proliferative zones and in the complete cortical plate (Miller 2003).

TGF-beta receptor expression in the brain

Receptors necessary for TGF-beta signal transduction, viz., TGFRI and TGFRII, are common in the developing and in the adult CNS (Bottner et al. 1996, 2000; Vivien et al. 1998). TGFRII mRNA can be found in the brain in many different areas including the cerebral cortex, midbrain, cerebellum, and brainstem. It is expressed in a multitude of different cells: neurons, astroglia, microglia, endothelial cells, and other non-neuronal cells, such as those of the choroid plexus (Morita et al. 1996; Ata et al. 1999; De Groot et al. 1999; Sousa Vde et al. 2006). TGFRI and TGFRII are also expressed by radial glia (Galter et al. 1999; Miller 2003), indicating a potential role of the TGF-beta system in this cell type, which has been shown to be a neural stem or precursor cell during brain development (Malatesta et al. 2003). Active and high TGF-beta signaling

in the brain has recently been demonstrated by using in vivo imaging with a Smad-responsive luciferase transgenic mouse (Lin et al. 2005). We have found the expression of TGFRI and II and the activation of downstream signaling by the presence of the phosphorylated form of Smad2 in the neurogenic regions of the adult rodent brain, the hippocampus (HC), and the subventricular zone (SVZ)-rostromigratory stream (RMS)-olfactory bulb (OB) axis (own unpublished observations). Moreover, the expression of TGFRI and II mRNA and of the TGFRII protein has been found in adult neural stem cells (aNSC) derived from rat SVZ in culture (Wachs et al. 2006), suggesting a role of TGF-beta signaling in the biology of these cells.

TGF-beta1 as a cytostatic factor of neural stem cells and inhibitor of neurogenesis

The following sections summarize the emerging scope of the different functions and roles of TGF-beta in the adult intact brain, in the degenerating brain, and in brain tumors. The variety of different effects that TGF-beta exerts in the brain provides TGF-beta with multiple faces: it is neuroprotective but limits endogenous cell replacement by inhibiting neural stem cell proliferation. On the other hand, during tumor progression, it is transformed into a mitogen for tumor cells. In addition, it exerts powerful protection of the tumor from the immune system (Fig. 3).

In addition to its other effects and probably depending upon its discrete cellular environment, TGF-beta1 possesses a strong anti-proliferative potential. The first CNS cell types in which TGF-beta was associated with an anti-proliferative activity, were astrocytes in culture (Johns et al. 1992; Lindholm et al. 1992; Morganti-Kossmann et al. 1992; Baghdassarian et al. 1993; Rich et al. 1999). In these experiments, TGF-beta1 either had a direct influence on the division rate or acted as an antagonist to other growth

Fig. 3 TGF-beta and its effects on neural stem cells, cancer stem cells, and brain tumors. TGF-beta inhibits neural stem cell proliferation. It may affect the transition from a neural to a cancer stem cell, which might escape from TGF-beta growth control. Later in tumor progression, TGF-beta acts as an oncogene; it further promotes tumor growth by promoting angiogenesis and suppressing the immune system. In addition, it promotes cellular migration, thereby driving cells into metastasis
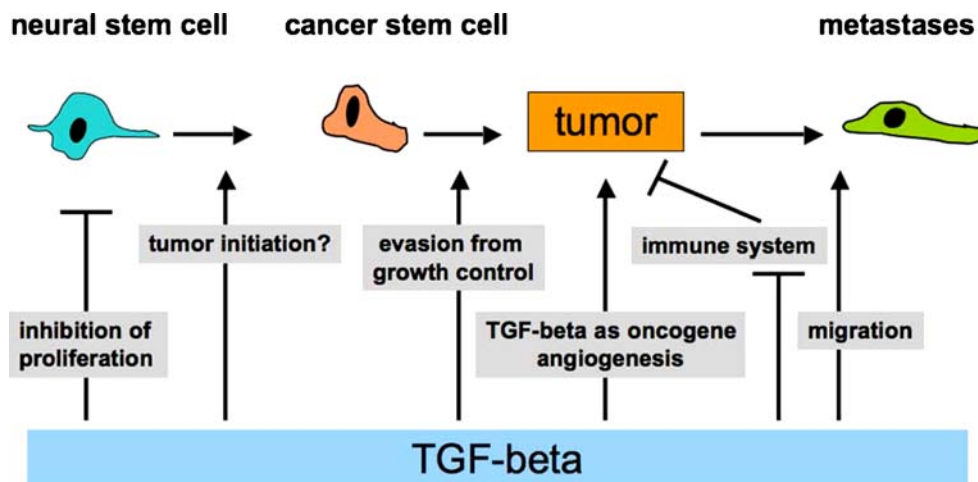
factors such as fibroblast growth factor, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), interleukin alpha, and interleukin 2 (Hunter et al. 1993; Vergeli et al. 1995). TGF-beta1 seemed not only to inhibit the proliferation of astrocytes, but also to accelerate their differentiation (de Sampaio e Spohr et al. 2002; Sousa Vde et al. 2004). In addition, TGF-beta1 has been shown to exert a negative effect on the proliferation of microglia and oligodendroglia (McKinnon et al. 1993; Suzumura et al. 1993). However, the growth-inhibiting effect of TGF-beta1 is not restricted to astroglia and microglia. It reduces the proliferation rate of fetal cortical, postnatal cerebellar, retinal neuroblastic cells, and neuronal precursor cells (Constam et al. 1994; Miller and Luo 2002; Close et al. 2005).

Recently, we have examined the influence of TGF-beta1 on neural stem and progenitor cells from the adult rodent hippocampus and lateral ventricle wall and the general impact of TGF-beta1 on neurogenesis (Wachs et al. 2006). According to our results, neural stem and progenitor cells express the receptor types TGFRI, II, and III (Wachs et al. 2006); in cell culture, TGF-beta1 decreases the expansion of neural stem and precursor cells in a dose-dependent manner. Clonal analysis has confirmed that TGF-beta1 have neither an impact on stem/progenitor cell identity, nor on the differentiation potential of the cells. Moreover, we have found no evidence that more cells undergo apoptotic cell death when treated with TGF-beta1. Instead, TGF-beta1 affects the proliferation potential of the cells, accompanied by an arrest in the cell cycle during the G0/G1 phase. These in vitro data have been confirmed in experiments in which TGF-beta1 is injected into the cerebrospinal fluid (Wachs et al. 2006). Upon infusion over 7 days, the number of proliferating cells in the hippocampus and in the lateral ventricle wall is substantially reduced; in addition, fewer neuronal precursor cells (as illustrated by doublecortin [DCX] staining) are present in the respective tissues after infusion. Confirmation of the latter results have come from transgenic animals over-expressing TGF-beta1 under the control of the glial fibrillary acidic protein promoter in astrocytes; the reduction in neural stem and precursor cell proliferation detected in these animals is comparable to the previously cited results with respect to in vitro and in vivo data (Buckwalter et al. 2006). The anti-proliferative effect of TGF-beta on neural stem cells and progenitors requires further molecular investigation, but we assume that the underlying mechanisms are similar or identical to those described in other cell types. In epithelial cells, TGF-beta regulates the expression of several genes involved in cell-cycle control and promoting cell-cycle arrest. In epithelial cells, TGF-beta rapidly induces p21Cip1 and p15Ink4b, two cyclin-dependent kinase inhibitors, and down-regulates the inhibitors of differentiation, Id1 and Id2, and the pro-proliferative transcription factor Myc (Siegel and Massague 2003).

Whether the TGF-beta-mediated inhibition of neural stem cell proliferation and of neurogenesis has physiological relevance remains to be determined. However, the increased expression of this growth factor in pathological conditions of neurodegenerative diseases, acute trauma, and neuro-inflammation and ageing has been demonstrated (Bye et al. 2001). Acute damage to the brain and hypoxic/ischemic lesions increase neurogenesis in SVZ and HC and can lead to the migration of the newborn cells toward the lesioned area (Arvidsson et al. 2002; Parent et al. 2002; Jin et al. 2006). However, to what extent these newborn neurons integrate functionally into the neuronal meshwork, and whether they are able efficiently to repair the damaged area remain unclear. In neurodegenerative diseases (e.g., Morbus Parkinson), fewer new neurons seem to be born in comparison with those in the healthy brain (Winner et al. 2004, 2007). The characterization of the various activities present in the different pathologies and the precise definition of their effects on neural stem and progenitor cells will be of importance. Neurogenesis in response to acute or chronic lesions of the brain might be a highly dynamic process; therefore, such analysis needs to include a temporal dimension.

In this context, TGF-beta1 might be a promising candidate among the molecules that are expected to exert an impact on neurogenesis under pathological conditions. A characteristic for both acute and chronic lesions in the CNS is the activation of microglia and of the immune system. Microglia seems to display both positive and negative effects upon the nervous parenchyma (Ming and Song 2005). On one hand, microglia increase the inflammatory response by secreting pro-inflammatory cytokines such IL-6, which inhibit the neuronal differentiation of neural stem and progenitor cells (Vallieres et al. 2002; Monje et al. 2003). On the other hand, microglia produce neurotrophic factors such as brain-derived neurotropic factor, which might promote neurogenesis (Benraiss et al. 2001). Microglial cells also release TGF-beta1 (Lehrmann et al. 1998; Krieglstein et al. 2002), which might contribute to the diverse roles of this cell type in the damaged brain. TGF-beta1 is well-known to play a major role in the survival of many neurons and to have a neuroprotective effect regarding the peripheral and central nervous systems (Krieglstein et al. 1998a, 1998b, 1998c; Roussa et al. 2004). In TGF-beta1-knockout mice, the loss of TGF-beta1 significantly reduces the potential of neurons for survival, as shown by data from both histochemistry and tissue culture (Brionne et al. 2003). Moreover, the brains of TGF-beta1-deficient animals are characterized by an increased amount of apoptotic neurons (Brionne et al. 2003). In contrast to these beneficial effects of TGF-beta1, its cytostatic activity on neural stem and progenitor cells clearly represents a limitation for the brain's capacity to

self-repair by inhibiting the proliferation of neural stem and progenitor cells.

An important role of TGF-beta arises from its effects on cells of the immune system. Any damage to the CNS is accompanied with the activation of microglia. This observation is true for all kinds of cellular loss, whether caused by acute inflammatory processes (as in multiple sclerosis or during encephalitis), by genetically determined and other forms of neuro-degeneration (such as Chorea Huntington, Morbus Parkinson, Morbus Alzheimer), or by ischemic/hypoxic events (such as stroke or global hypoxia during cardiac arrest). The possible stimuli for microglial activation are numerous. Amongst these are signaling molecules released by stressed or dying neurons, excessive deposits of protein aggregates, or the defective regulation of the immune response (Wyss-Coray and Mucke 2002). After activation, microglia secrete various signaling cytokines that provide a negative feedback loop and that might attenuate inflammation. TGF-beta belongs to such cytokines; it suppresses the activation and proliferation of microglia and limits inflammation and the resulting damage to the CNS (Suzumura et al. 1993; Boche et al. 2006).

Transformation of neural stem cells to cancer stem cells: a putative origin of brain tumors

Two hypotheses for the putative origin of solid tumors have been discussed. According to the stochastic model (Mendelsohn 1960), tumors consist of four different cell compartments: a pool of proliferating cells, a pool of quiescent cells that are transiently in G0, cells that have exited the cell cycle and are no longer competent to proliferate, and dying cells. In contrast, the concept of the hierarchical tumor model (Reya et al. 2001) describes solid tumors as tissue that consists of a small pool of self-renewing tumor stem cells, which have an infinite potential to proliferate and which generate progenitors with limited proliferation and self-renewal potential. They give rise to tumor cells that lack the capacity to proliferate. This hierarchical tumor model envisages a solid tumor resembling any other tissue or organ, but with de-regulated proliferation and differentiation (Reya et al. 2001). At present, the prime causes for the de-regulation of proliferation and differentiation are mostly unclear.

Brain-tumor cells develop mechanisms to escape from the cytostatic control of TGF-beta signaling, which may control neural stem cells proliferation under normal situations. Since brain tumors might originate from neural stem cells that have transformed into cancer stem cells (for reviews, see Reya et al. 2001; Jordan et al. 2006; Beier et al. 2007; Nicolis 2007), the mechanisms triggering such

transformation events and their correlation with the TGF-beta signaling pathway need to be addressed.

Initial data indicating that stem cells contribute to tumor formation derive from experiments demonstrating the existence of cells that have neural stem-cell-like characteristics (clonal growth, self renewal, neuronal/glial differentiation potential) and that can be derived from glioma, medulloblastoma, and ependymoma (Ignatova et al. 2002; Hemmati et al. 2003; Singh et al. 2003; Taylor et al. 2005). The brain-tumor-derived stem cells have been exclusively detected in the fraction of cells expressing stem cell marker CD133 (Singh et al. 2003). One hundred CD133-positive cells are sufficient to generate brain tumors in the host (Singh et al. 2003). In comparison with non-tumor-derived stem cells in the brain, however, the stem-cell-like cells derived from brain tumors differ in their unusual proliferative and multiple differentiation capacity, which is presumably associated with the transformed phenotype (Hemmati et al. 2003). A second block of information on stem cells contributing to brain-tumor formation is derived from experiments involving the implantation of glioblastoma-derived and clonally grown, stem-cell-like cells. These cells have the capacity to establish glioblastomas through serial transplantations and have therefore been termed tumor-initiating cells (Galli et al. 2004). The cancer or brain-tumor-initiating stem cells have been identified by their expression of CD133 (Singh et al. 2004). Injection of brain-tumor-derived CD133-positive cells produces tumors of the original phenotype in serial transplantations (Singh et al. 2004). More recent experiments have demonstrated that cancer or brain-tumor stem cells are not confined to the CD133-positive pool of cells (Beier et al. 2007). Both CD133-positive and CD133-negative glioblastoma-derived cells generate neurospheres in vitro and brain tumors in vivo after transplantation, albeit with different growth and molecular properties (Beier et al. 2007). Finally, a third block of correlative and experimental evidence should be mentioned. (1) Genes that are mutated in brain tumors are often genes associated with stem cells or involved in regulation of their fate (for a review, see Nicolis 2007). These include genes from the Wnt/beta-catenin and the SHH pathway in the case of medulloblastomas (Marino 2005), and genes of the EGF, PTEN and p53 signaling cascades in the case of glioblastoma (Ohgaki and Kleihues 2005). (2) Over-expression or deletion of these genes in neural stem cells generates brain tumors. For example, deletion of p53, a tumor-suppressor gene expressed in stem and progenitor cells, promotes the transformation of slow-proliferating SVZ cells to give rise to glial tumors in the adult brain (Gil-Perotin et al. 2006). Mice lacking p53 and expressing a conditional allele of the NF1 tumor suppressor that negatively regulates the signaling of Ras develop malignant astrocytomas (Zhu et al. 2005). In these animals,

the earliest evidence of tumor formation is found in neurogenic regions suggesting the involvement of neural stem and progenitor cells (Zhu et al. 2005). In another example, over-expression of PDGF in neural progenitors induces the formation of oligodendrogliomas (Dai et al. 2001), and PDGF-R activation in the SVZ in stem cells is sufficient to induce cytological hallmarks of the early stages of tumor formation (Jackson et al. 2006). Targeted expression of activated forms of Ras and Akt induces high-grade gliomas in mice, when expressed in neural progenitors, but not after transfer to differentiated astrocytes (Holland et al. 2000). Moreover, the treatment of rats with N-ethyl-N-nitroso-urea, a substance used to induce glioma formation in experimental animals, results in the transformation of neural stem cells, further suggesting that brain stem cell transformation might generate cancer stem cells (Savarese et al. 2005).

As an alternative hypothesis, cancer stem cells might derive from progenitors that have de-differentiated into a stem-cell-like status. In the rodent and human adult brain, normal stem cells generating new neurons and glia are located in the SVZ and HC. However, the astroglial character of CNS stem cells ((Heins et al. 2002); for a review, see Gotz and Huttner 2005) and the finding that cells with neural stem cell characteristics can be obtained from progenitors located in non-neurogenic regions (Palmer et al. 1999; Kondo and Raff 2000; Nunes et al. 2003; Vroemen et al. 2003) imply that the pool of potential cellular targets for transformation events might not be restricted to stem cells of the classic neurogenic regions. Considering that, with the exception of ependymomas, most brain tumors are not located in the classic neurogenic regions, the latter idea might become even more relevant. Along the same lines, targeted deletion or over-expression of stem cell and cancer-related genes might induce brain tumors, even when the targeted cell is not a stem cell. For example, the deletion of Ink4a and Arf results in glioblastoma formation from astrocytes and enhances tumor incidence in neural progenitor cells (Uhrbom et al. 2002).

In summary, whether brain tumors arise for the stem cell pool, from progenitor cells, or from differentiated cells is presently unclear, although the cancer stem cell theory still has its limitations (Fan et al. 2007; Tysnes and Bjerkvig 2007). Differentiated cells might de- or trans-differentiate to generate cancer stem cells. Moreover, cell fusion, which has been demonstrated between microglia or bone-marrow-derived cells with pyramidal neurons or Purkinje cells (Alvarez-Dolado et al. 2003; Ackman et al. 2006) and/or horizontal gene transfer, which may occur in tissue repair processes, might also be involved in tumor initiation and progression (Tysnes and Bjerkvig 2007). An additional feature arguing against neural stem cells being the prime source of cancer stem cells is the possibility that some of the cells with stem-cell-like properties isolated from brain tumors are indeed non-transformed neural stem cells invading the tumor. This is supported by the finding that brain tumors are highly attractive for neural stem cells and that they induce the targeted migration of these cells toward the tumor (Aboody et al. 2000). However, as this study used the neural stem cell line C17.2, its relevance is not clear at present. Tropism of neural stem cells toward brain tumors still needs to be confirmed by using primary non-transformed neural stem cells. Nevertheless, the hypothesis that transformed neural stem cells provide the basis for brain-tumor development is highly intriguing and of enormous clinical relevance. It therefore needs further exploration.

Molecular and cellular mechanisms of brain-tumor initiation: de-regulation of self-renewal, asymmetric division, and chromosomal segregation with a role for TGF-beta?

Any mutation, amplification, or alteration in the number of chromosomes including aneuploidy (summarized as genetic instability), and epigenetic modifications that arise in stem cells might be the first step in tumor initiation or the consequence of metabolic or cell environmental alterations. This cannot be dissected at the moment, but the consideration of the mechanisms that regulate stem cell biology might give some indications. A central hallmark of neural stem cells is the capability of asymmetric cell division, a process that is ultimately linked to chromosomal co-segregation and to the self-renewal capacity of stem cells. Stem cells divide to generate two daughter cells, one retaining stem cell characteristics and the other becoming a progenitor that might, even at this early stage, be restricted in its fate. Possibly in order to protect themselves and their gene pool from mutations, stem cells have developed a mechanism selectively to retain the older set of template DNA within the daughter cell destined to become the stem cell, a process termed immortal strand co-segregation (Cairns 1975, 2006; Merok et al. 2002; Rambhatla et al. 2005; Shinin et al. 2006; Conboy et al. 2007). The mechanisms that control the co-segregation of chromosomes are probably associated with centrosomal proteins and with the mechanisms that regulate asymmetric versus symmetric cell division. In this respect, the involvement of the proteins p53 and Numb and signaling via the Notch, Wnt, SHH, and TGF-beta pathways might be relevant.

Studies in *Drosophila* have shown that centrosomal function is involved in the regulation of the asymmetric division of stem cells and in the self-renewal of the stem cell pool (Yamashita et al. 2003). By an as yet non-identified mechanism, the mother centrosome remains

anchored in the region of the future stem cell, whereas the daughter centrosome migrates to the opposite side of the cell before spindle formation (Yamashita et al. 2007). Defects in the regulation of centromere function that involve p53 function may contribute to aneuploidy in various tumors including brain tumors (Weber et al. 1998). Moreover, p53 has been implicated in the regulated co-segregation and retention of parent chromatids in stem cells during asymmetric cell division. For example, the over-expression of p53 in non-stem cells results in the co-segregation of the original DNA strand into one daughter cell (Merok et al. 2002). Since p53 is a key factor between TGF-beta and the Ras/MAPK pathway (Cordenonsi et al. 2007), TGF-beta might modulate chromosomal segregation under certain cellular and microenvironmental conditions.

Another protein that seems to be implicated in centro-some integrity and chromosomal stability is the nucleolar protein nucleophosmin. Mutations in nucleophosmin have been found in a number of different tumors and deletion of this gene leads to unrestricted centrosome duplication, genomic instability, and oncogenesis (Grisendi et al. 2005). Interestingly, nucleophosmin is phosphorylated by CDK2/cyclin E, and its expression is regulated by myc, all proteins involved in the Wnt, SHH, and TGF-beta signaling pathways.

In diverse stem cell systems, such as in retinal or cortical development, asymmetric localization of Numb determines both the cleavage plane during mitosis and the daughter cell destined to become the future stem cell in asymmetric cell division (Cayouette et al. 2001; Cayouette and Raff 2002; Shen et al. 2002). Moreover, Numb is required for the maintenance of self-renewal of various neural progenitor cells (Petersen et al. 2002). The loss of Numb and of the related molecule Numbl causes premature progenitor-cell depletion (Petersen et al. 2004). Numb function can be directly linked to the Notch signaling pathway, a pathway that regulates stem cell self-renewal (Guo et al. 1996). The first evidence that Notch might maintain stem cell self-renewal in mammals was derived from experiments in which an activated form of Notch1 was overexpressed in the embryonic nervous system, thereby promoting radial glia cell identity (Gaiano et al. 2000). Later, Notch signaling was demonstrated as being required for the expansion of the stem cell pool by symmetric division during development and for maintaining the stem cell pool in the adult by controlling asymmetric cell division (Alexson et al. 2006). In addition to Notch, other signaling mechanisms have been implicated in neural stem cell self-renewal. These include the Bmi-1 and the Wnt pathways (Molofsky et al. 2003; Willert et al. 2003; Lie et al. 2005). Noteworthy, mutations in components of the Notch signaling pathway have been identified in brain tumors (Modena et al. 2006).

The Notch signaling cascade carries out cross-talk with all other signaling cascades involved in stem cell identity and fate, such as the Wnt, TGF-beta/BMP, SHH, and growth-factor-receptor tyrosine kinase pathways (Carlson and Conboy 2007). With regard to epithelial cell prolifer-ation, TGF-beta and Notch are well-established cytostatic factors. Moreover, the two factors act in cooperation through the cell-cycle inhibitor p21, and TGF-beta induces the expression of the Notch ligand Jagged1 (Zavadil et al. 2004; Niimi et al. 2007). Although antagonistic effects between TGF-beta and Notch signaling have also been described (for a review, see Kluppel and Wrana 2005), we might speculate that TGF-beta1 regulates neural stem cell self-renewal and eventually asymmetric cell division and chromosomal segregation by modulating Notch signaling.

Another aspect that needs to be considered is the tight control of the transition between cell proliferation and migration in neurogenesis. De-regulation of proteins in-volved in the regulation of neuronal migration might be involved in chromosomal segregation and centrosomal function. Evidence supporting this hypothesis derives from experiments in which proteins originally associated with functions in neuronal migration, such as the family of DCX proteins, have recently been implicated in the control of nucleokinesis, the orientation of spindle apparatus, mitotic checkpoint control, and chromosome separation (Faulkner et al. 2000; Couillard-Despres et al. 2004; Siller et al. 2005; Toyo-Oka et al. 2005). Moreover, DCX expression has been correlated with the invasiveness of brain tumors, although it suppresses proliferation and the malignant phenotype in glioblastoma (Santra et al. 2006). TGF-beta might be involved in such processes, since it regulates DCX expression (Karl et al. 2005).

TGF-beta in brain tumor and tumor progression

In healthy tissue and in low-grade epithelial tumors, TGF-beta inhibits cell proliferation and therefore is considered a classical tumor-suppressor protein. During tumor progres-sion, TGF-beta transforms into an oncogene by an autocrine mechanism of growth stimulation (for reviews, see Derynck et al. 2001; Wakefield and Roberts 2002; Roberts and Wakefield 2003; Siegel and Massague 2003; Seoane 2006). In addition, TGF-beta is a key mediator in other aspects of pathobiology of malignant gliomas: (1) tissue invasion and metastasis (Platten et al. 2000; Hau et al. 2006; Arslan et al. 2007), (2) angiogenesis (Stiles et al. 1997), and (3) evasion from immune attack (Cordenonsi et al. 2007). Therefore, TGF might become a major molecular target in brain-tumor therapy, especially as it is frequently and highly expressed in brain tumors, in particular gliomas (Derynck et al. 1987; Samuels et al. 1989; Constam et al.

1992; Jachimczak et al. 1996; Kjellman et al. 2000; Platten et al. 2001).

TGF-beta and growth control in brain tumors

In most cell types, including neural stem cells, TGF-beta has cytostatic activity. However, paradoxically, many brain tumors escape from TGF-beta control. In some tumors, cells acquire somatic mutations in molecules of the TGF-beta-Smad signaling pathway in order to evade the tumor-suppressor and anti-proliferative functions of TGF-beta. In addition, some malignant tumors, in particular gliomas, selectively lose the capacity to respond to TGF-beta but maintain the TGF-beta signaling pathway intact (Derynck et al. 2001; Wakefield and Roberts 2002; Roberts and Wakefield 2003; Siegel and Massague 2003; Seoane 2006). In these cases, TGF-beta transforms into an oncogenic factor and promotes proliferation. Most of the data available are derived from tumors and cancers outside the brain, but similar mechanisms probably drive TGF-beta to act as an tumor promoter in the various tumors. These data have been reviewed extensively by others (Derynck et al. 2001; Wakefield and Roberts 2002; Roberts and Wakefield 2003; Siegel and Massague 2003). Considering the high degree of divergence into and convergence form other signaling pathways (Fig. 2), TGF-beta signaling is, not surprisingly, capable of conversion from a tumor-suppressor to a tumor-promoter effect. The most relevant signaling cascade cross-talk in this respect is most probably the one between the TGF-beta-Smad and MAPK pathway (Derynck et al. 2001; Wakefield and Roberts 2002; Roberts and Wakefield 2003; Siegel and Massague 2003; Seoane 2006). A dysbalance between the Smad and MAPK pathways, as is associated with the evasion from TGF-beta cytostatic control and with the oncogenic activity of TGF-beta, has been demonstrated in a number of malignant cell types and has recently been shown also to be involved in malignant gliomas (Nickl-Jockschat et al. 2007).

A number of inactivating mutations in the TGF-beta signaling pathway that could explain the release from the cytostatic TGF-beta effect have been identified in brain tumors. These include mutations and altered gene expression in TGF-beta-RI and TGF-beta-RII in pituitary adenomas and gliomas (Izumoto et al. 1997; Fujiwara et al. 1998; D'Abronzo et al. 1999), physiologically supporting TGF-beta receptors as tumor suppressors. Mutations in Smad molecules seem not to play a major role in brain tumors; such mutations are in general associated with colon, lung, and pancreatic carcinomas (for a review, see Derynck et al. 2001). Furthermore, we need to determine whether other TGF-beta downstream elements, which have been demonstrated as being mutated and involved in some cancers, are also mutated in brain tumors.

In addition to mutations in TGF-beta and other signaling components, autocrine mechanisms for TGF-beta growth-promoting effects have been described. Tumors in which TGF-beta acts as a tumor promoter usually express high levels of TGF-beta, often because TGF-beta is able to induce its own expression, thereby generating a malignant autocrine loop (Jachimczak et al. 1996). Recently, the growth-promoting effects of TGF-beta in some cases of glioma have been demonstrated to be mediated via the enhanced expression of PDGF. In many gliomas, the PDGF-B gene has been found to be non-methylated. Depending on the methylation status of the PDGF-B gene, TGF-beta induces PDGF-B and thereby promotes glioma cell proliferation and angiogenesis (Bruna et al. 2007).

TGF-beta1 and its role in cellular migration, invasion, and metastasis

TGF-beta influences cell migration in the healthy brain and in tumors. The physiological effects of TGF-beta in CNS cell migration have been demonstrated for a number of different cell types. For example, TGF-beta improves cell-cell contacts of astrocytes and also the focal adhesion of cells, resulting in an increase in cell mobility and also in changes in cell shape (Baghdassarian et al. 1993; Siegenthaler and Miller 2004; for a review, see Gomes et al. 2005). In cases of malignant glioma, evidence is increasing for a prominent role of TGF-beta in glioma cell mobility and migration, both into the stroma and in and out of blood vessels (Platten et al. 2001). Several TGF-beta-mediated mechanisms seem to be involved: (1) the TGF-beta-mediated epithelial to mesenchymal transition, which is associated with the loss of TGF-beta mediated growth control (see above), (2) the TGF-beta-mediated changes in ECM components that ultimately influence cell migration, and (3) the direct effects of TGF-beta on the motility of glioma cells (for a review, see Platten et al. 2001). The ECM components that are altered by TGF-beta comprise molecules such as collagen, fibronectin, laminin, L1, tenascin, vitronectin, and versican (Uhm et al. 1999b; Platten et al. 2001; Hau et al. 2006; Arslan et al. 2007). In association with ECM function, changes in ECM metalloproteases MMP9 and MMP2 and/or integrin expression have been related to glioma cell migration and tumor invasion (Uhm et al. 1999a; Miyake et al. 2000; Rooprai et al. 2000). TGF-beta via its influence on the ECM and on the cytoskeleton might help to produce changes in cell shape and mobility; the mechanism of transition is complex and is thought to be accompanied by Ras/PI-3-K signaling and the TGF-beta-induced activation of Smad and RhoA signaling (Bhowmick et al. 2001). The described changes in MMPs might provide a positive feedback mechanisms in TGF-beta action: the ECM, hosting the latent form of TGF-

beta, is the reservoir from which substantial amounts of active TGF-beta can be mobilized quickly, and activation of the latent form is aided by proteases such as MMP-9 and MMP-2. MMPs are frequently present in areas with malignant cell masses, promoting latent TGF-beta activation (Derynck et al. 2001).

TGF-beta and its role in angiogenesis and tumor progression

A unique prerequisite of brain-tumor growth is the formation of new blood vessels by capillary sprouting (angiogenesis). The vascular endothelial growth factor (VEGF) and its receptor Flk-1 signaling cascade trigger endothelial growth and angiogenesis during developmental growth and in brain tumors (Machein and Plate 2004). Typically, high levels of VEGF are present in brain tumors providing the tumor with a pro-angiogenic and immuno-suppressive environment (Machein and Plate 2004). In the context of a role for TGF-beta in brain-tumor angiogenesis, Stiles et al. (1997) have demonstrated that its expression correlates with tumor vascularity. Moreover, and most importantly, TGF-beta induces VEGF expression by vascular endothelial cells and glioma cells (Koochekpour et al. 1996; Breier et al. 2002). Thus, VEGF provides a mechanism that mediates the TGF-beta-induced effects on angiogenesis. As in tumor cell migration, TGF-beta might contribute to angiogenesis and endothelial cell invasion by modulating the ECM (see above).

TGF-beta and its role in evasion from the immune system

A central hallmark of malignant gliomas is their potential to escape from immune surveillance by active immune suppression, a finding that currently presents the limiting issue encountered in brain-tumor therapy. TGF-beta plays the key role in this process because of its activity as a highly potent physiological immune suppressor. In malignant brain tumors, TGF-beta is highly expressed and provides the tumor with a protective strategy against an attack by the immune system (for reviews, see Fontana et al. 1991; Platten et al. 2001). In vitro experiments have demonstrated that TGF-beta inhibits the proliferation and differentiation of T-cells (Siepl et al. 1988), in particular of CD8-positive cytotoxic T-cells (Thomas and Massague 2005). Differentiation of the cytotoxic T-cells is inhibited by specific inhibition of the expression of perforin, granzyme A, granzyme B, Fas ligand, and interferon gamma, molecules that are known to be responsible for cytotoxic T-cell-mediated tumor cytotoxicity (Thomas and Massague 2005; Li et al. 2006). The role of TGF-beta in regulating T-cell activity has further been established in mice with a targeted deletion in the TGF-beta1 gene. These mice die because of systemic inflammation and an auto-immune phenotype early in life (Diebold et al. 1995).

TGF-beta and implications for brain-tumor therapy

The notion that TGF-beta is a key mediator of the various pathological characteristics of gliomas, such as escape from cytostatic control, malignant growth, metastasis, angiogenesis, and evasion from immune attack, has resulted in attention being focused on TGF-beta as a potential target in brain-tumor therapy. Several approaches have been designed experimentally and in part translated into clinical practice. Concerning the question of choosing either TGF-beta1 or TGF-beta2 as the therapeutic target, the initial focus was on TGF-beta1. TGF-beta1 stimulates the migration and invasion of glioma cells (Merzak et al. 1994; Platten et al. 2000), and the inhibition of glioma invasion can be achieved by using a specific antisense oligonucleotides against TGF-beta1 (Paulus et al. 1995). The relevance of TGF-beta2 as a therapeutic target seems to be higher, since antisense molecules targeted against TGF-beta2 are more potent in inhibiting tumor cell growth compared with those targeting TGF-beta1 (Jachimczak et al. 1996). Consequently, the modulation of TGF-beta2 and associated pathways is the focus of current preclinical and clinical development. Initial clinical studies with intratumoral infusion of TGF-beta2 antisense molecules to suppress the levels of TGF-beta 2 have provided evidence for the clinical value of such strategies (Schlingensiepen et al. 2005, 2006). Alternatively, the targeting of TGF-beta1 and TGF-beta2 expression by RNA interference has also been evaluated in preclinical models (Friese et al. 2004). Recently, the scope of TGF-beta as a therapeutic target for brain tumor has been extended to other members of the TGF family, in particular the BMPs. These molecules are able to inhibit tumor-initiating stem cells to generate glioblastoma (Piccirillo et al. 2006).

Concluding remarks

In summary, the many different effects that TGF-beta has on the various cell types within the brain make it a highly interesting molecule with respect to basic principles arising during development and later in adult life. Moreover, because of its possible involvement in neural repair and neurogenesis and its role in brain tumors, TGF-beta is a highly attractive molecular target for the development of therapies. Here, we have reviewed the different aspects of TGF-beta in CNS repair, in neural stem cell biology, and in brain-tumor development and progression.

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