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TGF-β Family Signaling in Neural and Neuronal Differentiation, Development, and Function

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Signaling by the transforming growth factor β (TGF-β) family is necessary for proper neural development and function throughout life. Sequential waves of activation, inhibition, and reactivation of TGF-β family members regulate numerous elements of the nervous system from the earliest stages of embryogenesis through adulthood. This review discusses the expression, regulation, and function of TGF-β family members in the central nervous system at various developmental stages, beginning with induction and patterning of the nervous system to their importance in the adult as modulators of inflammatory response and involvement in degenerative diseases.

The transforming growth factor β (TGF-β) family plays a central role in multiple aspects of nervous system development and function. During embryogenesis, TGF-β family members regulate the initial formation of the nervous system, dorsalization and establishment of rostrocaudal boundaries, patterning of the central nervous system (CNS), stem-cell lineage commitment to neurons and glia, cell migration and axon guidance, synaptogenesis, and cell survival (see Table 1). During adulthood, TGF-β family members modulate inflammatory responses, influence quiescence in neural stem cells of the hippocampus, and have a role in neurodegenerative disease. This review will cover the expression, regulation and function of TGF-β family members in the CNS from early development to adult life.

NEURAL INDUCTION

Formation of the neural plate, the first step in the genesis of the nervous system, is triggered during gastrulation by signals produced by an organizer region on the dorsal blastophore lip (Fig. 1) (Spemann and Mangold 1924). These signals act primarily by inhibiting signaling by TGF-β family members including bone morphogenetic proteins (BMPs), nodal, and activin (Hemmati-Brivanlou and Melton 1992, 1994). Noggin, follistatin, and chordin, the first neural inducers that were identified (Hemmati-Brivanlou et al. 1994; Sasai et al. 1994, 1995), act by suppressing BMP signaling (Piccolo et al. 1996; Zimmerman et al. 1996; Fainsod et al. 1997). Additional BMP antagonists secreted from the organizer include Cerberus, Gremlin,

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Table 1. Summary of some known actions of transforming growth factor β (TGF-β) family members in the nervous system

TGF-β family member	Effects of antagonism	Synergistic effects
BMPs	Induction of nervous system Floor plate induction (BMP-4 and BMP-7) Oligodendrogenesis (BMP-2/BMP-4) Neurogenesis in olfactory epithelium	Roof plate induction (BMP-4 and BMP-7) Anterior neural tissue specification (BMP-5 and BMP-7) Dorsoventral patterning of the nervous system (BMP-4, BMP-6, and BMP-7) Neurogenesis (BMP-2, BMP-4, and BMP-6) Astrocytogenesis (BMP-2 and BMP-4) Cholinergic neuron specification (BMP-9) Guidance of commissural axons (BMP-7) Dendritic growth Neuronal migration Induction of neurotrophin dependence Apoptosis of stem/progenitor cells
Nodal	Induction of nervous system	Induction of floor plate Differentiation of hypothalamic neurons
Activins	Induction of nervous system	Specification of rod photo receptors
GDFs	Neurogenesis in olfactory epithelium (GDF-11)	Specification of dorsal neurons (GDF-7) Neurogenesis in olfactory epithelium (GDF-7) Guidance of commissural axons (GDF-7)
TGF-βs	Microglial activation (TGF-β1)	Neurotrophic for dopaminergic and Purkinje neurons (TGF-β2 and TGF-β3) Neuronal differentiation in olfactory epithelium (TGF-β1 and TGF-β2) Differentiation of oligodendrocytes Neuronal migration (TGF-β1 and TGF-β2) Axon elongation (TGF-β1 and TGF-β2) Synaptogenesis Astrogliosis after injury (TGF-β1)

Dan, Drm, Coco, and Ogon/Sizzled (sFRP) (Wagner and Mullins 2002; Yabe et al. 2003).

Targeted inactivation of any one neural inducer does not prevent formation of the CNS. For example, most mice have a normal CNS after inactivation of the *Chordin* gene (Bachiller et al. 2000; Anderson et al. 2002), and *Noggin*$^{-/-}$ mice also have normal gastrulation and neural plate formation (McMahon et al. 1998). However, *Chordin*$^{-/-}$; *Noggin*$^{-/-}$ double-mutant mouse embryos have a severe neural phenotype with a loss of the prosencephalic vesicle and lack of anterior notocord, because of ventralization of the mesoderm (Bachiller et al. 2000). Similarly, antisense oligonucleotides targeting *Noggin, Chordin,* and *Follistatin* cause nearly complete loss of the neural plate in *Xenopus tropicalis* embryos (Khokha et al. 2005). Thus, chordin, noggin and follistatin have redundant functions in the BMP inhibition required for neural formation and patterning of the embryonic axis.

Nodal antagonists secreted from the organizer are also required to induce neural development. Although gastrulation is normal after targeted inactivation of expression of either of the nodal antagonists, *Cerberus-like* gene or *Lefty1*, *Cerberus*$^{-/-}$; *Lefty1*$^{-/-}$ double-mutant mice have severe developmental impairment of the anterior embryo (Perea-Gomez et al. 2002; Yamamoto et al. 2004). In *Xenopus laevis*, the asymmetry of nodal signaling is partially regulated by two microRNAs (miRNAs), miR-15 and miR-16. These miRNAs are enriched at the ventral side of the embryo and attenuate the nodal signaling gradient by targeting the nodal

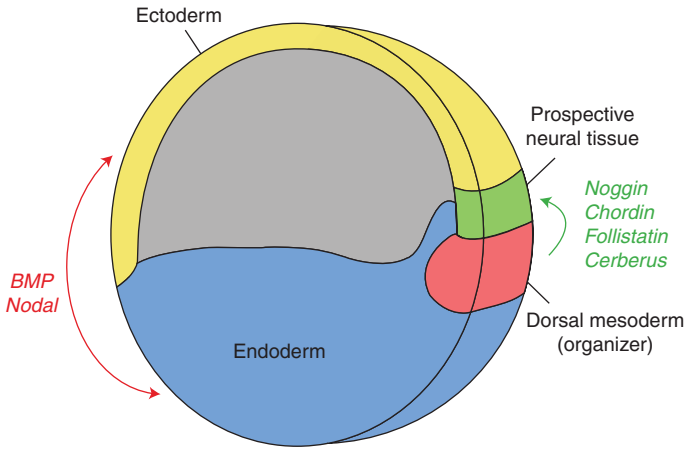

Figure 1. Role of the transforming growth factor-β (TGF-β) family in neural induction. During late gastrulation, the neural tube is specified within ectoderm at the expense of epidermis. Bone morphogenetic proteins (BMPs) and nodal antagonists are secreted by the dorsal mesoderm (organizer) to allow for neural differentiation. BMP, nodal, and their cofactors are secreted from the ventral center to specify prospective epidermis.

receptor activin receptor type 2A (ACVR2A, also known as ActRII) (Martello et al. 2007). Zebrafish use a different miRNA, miR-430, to target nodal signaling (Choi et al. 2007). Taken together, these studies identify a fundamental role for BMP and nodal signaling in neural induction and indicate that these families of antagonists act in a redundant or compensatory manner (Piccolo et al. 1999; Niehrs 2001; Wu and Hill 2009).

Epidermal fate is determined by the expression of the BMP-related Decapentaplegic (Dpp) in *Drosophila* and BMP-4 in *Xenopus* explants (Wilson and Hemmati-Brivanlou 1995). Numerous experimental methods have been used to impair BMP signaling, promoting neural induction of the epidermis (Hemmati-Brivanlou and Melton 1994; Hawley et al. 1995; Sasai et al. 1995; Wilson and Hemmati-Brivanlou 1995; Xu et al. 1995). Targeted silencing experiments for BMP-2, BMP-4, and BMP-7 in *Xenopus* indicate a redundancy in neural tissue specification; however, BMP-4 inhibition has the strongest dorsalized phenotype and is sufficient for neuralization (Reversade et al. 2005). Inactivation of BMP-2, BMP-4, and BMP-7 expression combined with inactivation of the expression of the BMP family member antidorsalizing morphogenetic protein (ADMP), which is expressed in the dorsal gastrula organizing center (Moos et al. 1995), causes complete neuralization of the ectoderm in *Xenopus* experiments. Restoring signaling by BMP-2, -4, -7 and/or ADMP in embryos with silenced BMP-2, BMP-4, and BMP-7 expression allows for an impressive return of epidermal patterning (Reversade and De Robertis 2005). Further, ADMP competes with nodal for the ACVR2A receptor, which may be a method for self-regulation in the organizer (Inui et al. 2012).

Manipulation of BMP signal transducers and inhibitors of downstream signaling further validates their roles in regulation of epidermal formation. Expression of Smad1 and Smad5, along with the BMP target gene *Msx1* prevents neuralization in *Xenopus* animal caps (Suzuki et al. 1997a,b; Wilson et al. 1997). Interfering with inhibitors of BMP signaling, for example, silencing the expression of the BMP decoy receptor BAMBI, the Smad ubiquitin ligase Smurf1, or the Smad4 E3 ubiquitin ligase ectodermin (also known as TIF1-γ or TRIM33), impair neural induction (Onichtchouk et al. 1999; Zhu et al. 1999b; Dupont et al. 2005). Additionally, BMPs and their antagonists are regulated by extracellular metalloproteinases; specifically *Twisted gastrulation* (Tsg) binds both BMPs and chordin to modulate BMP sig-

naling toward or against neural induction (Oelgeschläger et al. 2000, 2003; Larraín et al. 2001). This regulation is further complicated by expression of the Tolloid metalloproteinase that cleaves chordin, and Sizzled (sFRP) metalloproteinase, which inhibits Tolloid proteases (Oelgeschläger et al. 2003; Lee et al. 2006; Zakin and De Robertis 2010). Thus, inhibition of BMP signaling during neural induction is tightly regulated at many levels by BMP ligands, signal transducers, target genes, and extracellular metalloproteinases.

Wnt/β-catenin signaling regulates the BMP pathway during early induction by inducing the expression of noggin and chordin in the dorsal organizer region. Activation of β-catenin signaling reduces BMP-4 expression leading to neurulation, which can be inhibited by a constitutively active BMPRIA (BMP type IA receptor, also known as ALK-3), linking both Wnt/β-catenin and BMP signaling (Baker et al. 1999; Kuroda et al. 2004). BMP and Wnt signaling converge later in development when both signaling pathways are integrated through Smad1 phosphorylation of glycogen synthase kinase 3 (GSK3) in gastrulation (Fuentealba et al. 2007). In zebrafish, β-catenin induces a homeobox gene *bozozok/dharma* that directly represses the expression of *BMP2b*, which encodes BMP-4 (Leung et al. 2003). *Bozozok*$^{-/-}$; *Chordin*$^{-/-}$ zebrafish mutants show synergistic losses of neural tissue and dorsal structures (Gonzalez et al. 2000). Taken together, Wnt/β-catenin signaling acts to inhibit BMP transcripts and increase BMP antagonists to block their function and promote neural induction.

Additional signals regulate BMP activity to influence proper neural induction in the embryo (Lamb and Harland 1995; Fürthauer et al. 1997; Kretzschmar et al. 1997; Wilson et al. 2000; Pera et al. 2001). In particular, fibroblast growth factor (FGF) signaling down-regulates the expression of BMP-4 and BMP-7, and FGF together with insulin-like growth factor (IGF) activate the mitogen-activating protein (MAP) kinase cascade that regulates BMP signaling (Ishimura et al. 2000; Wilson et al. 2000). FGF and IGF obstruct BMP signal transduction by phosphorylating the linker region of Smad1 that blocks translocation of Smad to the nucleus (Pera et al. 2003; Sapkota et al. 2007). The relationship between BMP and FGF is necessary for proper neural development (Khokha et al. 2005); however, FGF signaling has additional roles in development of the embryo that are independent of BMP activity (Linker and Stern 2004; Delaune et al. 2005; Dorey and Amaya 2010).

In conclusion, loss- and gain-of-function experiments in multiple species show that antagonism of BMP signaling is required for proper induction of the nervous system. The importance of this signaling is further represented by the redundancy of BMP ligands and the need of double or triple knockdowns to fully elucidate the role of the TGF-β family.

NEURAL PATTERNING

Following neural induction, organizing centers are responsible for patterning the complex structure of the nervous system (Fig. 2). The roof plate in the dorsal midline and the floor plate and notochord in the ventral midline establish dorsoventral identities. Proper development is induced by the TGF-β family members nodal and BMP, whereas nodal signaling and BMP inhibition form the floor plate and specify ventral patterning. BMP signaling is instrumental in inducing the roof plate and specifying dorsal patterning (Placzek and Briscoe 2005; Lupo et al. 2006; Kiecker and Lumsden 2012).

Nodal signaling is crucial for proper formation and differentiation of the floor plate cells, as impairment of nodal signaling in the zebrafish mutant *Cyclops* and inhibition of nodal receptors yield severely depleted or absent floor plate cells (Hatta et al. 1991; Feldman et al. 1998; Rebagliati et al. 1998; Dougan et al. 2003). Malformation of the floor plate in the *Cyclops* mutant could be because of the effects on prechordal mesoderm differentiation that lead to a reduction in other signals, like sonic hedgehog (Shh). In *Nodal*$^{-/-}$ mutants, the floor plate is prematurely induced in the anterior epiblast in mouse embryos (Camus et al. 2006), whereas inactivation of the gene encoding the nodal antagonist Lefty increases induction of mesendoderm in formerly ectodermal tissue (Meno et al.

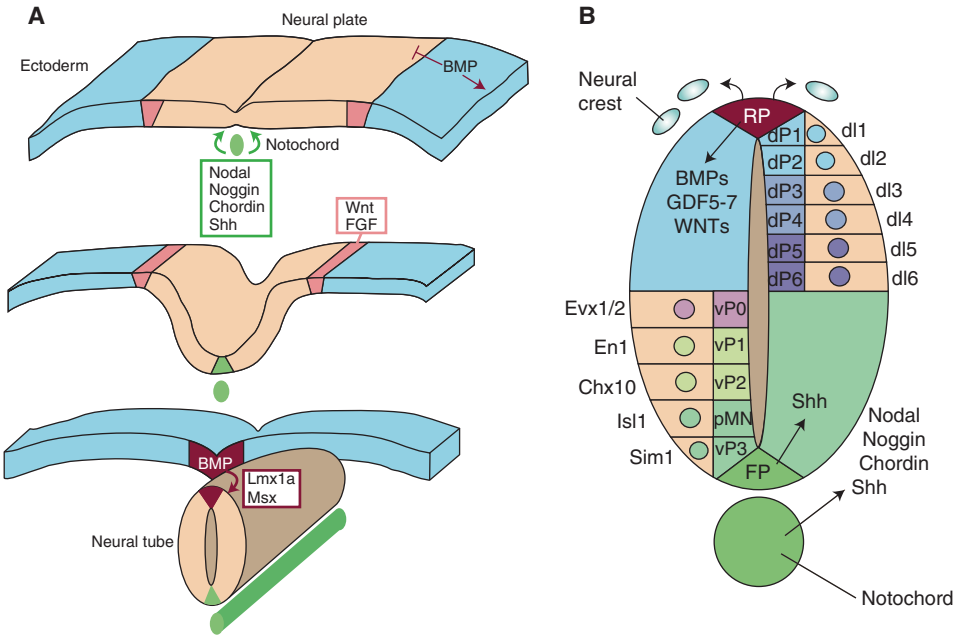

Figure 2. Role of the transforming growth factor-β (TGF-β) family in forming the neural tube and patterning the spinal cord. (*A*) Antagonism from the notochord inhibits bone morphogenetic proteins (BMPs) signaling to specify the floor plate (FP) (green), whereas the neural plate folds to form the neural tube. The FP and roof plate (RP) (red) form on the ventral and dorsal midline of the neural tube, respectively. Wnt and fibroblast growth factor (FGF) help to regulate BMP signaling to aid in neurulation, and BMP signaling through Lmx1a and Msx forms the RP. (*B*) BMPs, GDF-5, GDF-6, GDF-7, and Wnts are secreted from the RP to specify neural crest and dorsal interneuron (dI) subtype. Nodal and BMP antagonists are secreted from notochord to specify ventral neuron (vP) subtype. Nodal instructs ventral identity either in parallel or through sonic hedgehog (Shh) signaling.

1999; Perea-Gomez et al. 2002). Nodal-deficient mutants show late recovery of midline floor plate cells in the trunk and tail, identifying signaling pathways that ameliorate these effects, specifically Shh and Gli activity (Albert et al. 2003; Norton et al. 2005). This late recovery, however, is not observed in the brain. Variable cycloptic phenotypes are observed in *Nodal*$^{-/+}$ mice, as well as heterozygous or homozygous mutants that inactivate downstream nodal signaling, including *Smad2* or *Acvr2a*/*Actr2* (Nomura and Li 1998; Song et al. 1999). Shh is required for floor plate development in many species (Chiang et al. 1996; Wijgerde et al. 2002), and nodal potentiates the ability of Shh to induce floor plate identity in addition to inducing the expression of ventral genes encoding Shh and the forkhead box A2 (FOXA2) transcription factor (Müller et al. 1999, 2000; Rastegar et al. 2002; Patten et al. 2003). Taken together, the role of nodal in ventral patterning may be to (1) sensitize cells to the action of Shh or to enhance Shh signaling (Chen and Schier 2001; Norton et al. 2005), (2) operate in parallel with Shh to trigger the expression of floor-plate-specific genes, or (3) foster expression of floor-plate-specific genes, including *Shh*, that require Shh for their maintenance (Norton et al. 2005).

In addition to nodal activation, inhibition of BMP signaling is required for proper floor plate induction. Noggin, chordin, and follistatin are expressed in the notochord, prechordal mesoderm, and floor plate that extends from the presumptive anterior diencephalon into the hindbrain (Furuta et al. 1997; Dale et al. 1999; Chapman et al. 2002). Impairments in Shh-expressing ventral midline cells are ob-

served in *Noggin*$^{-/-}$ mutant mice (McMahon et al. 1998), whereas the combined actions of Shh and Chordin are able to induce ectopic Shh-expressing floor plate cells in the chick embryo in vivo (Patten and Placzek 2002). *Chordin*$^{-/-}$; *Noggin*$^{+/-}$ mice have a dorsalized ventral telencephalon (Anderson et al. 2002), and similar phenotypes are observed in mice lacking *Megalin/Lrp2*, which encodes a protein responsible for endocytic uptake and lysosomal degradation of BMP-4 (Spoelgen et al. 2005). Further, *Bmpr1a*$^{-/-}$; *Bmpr1b*$^{-/-}$ mice fail to form two hemispheres, known as holoprosencephaly, and also fail to form the dorsal midline cell types (Fernandes et al. 2007). Taken together, inhibition of BMP signaling, together with nodal and Shh signaling, is required for proper induction of the floor plate.

Following formation of the floor plate, inhibition of BMP signaling induces normal ventralization of the neural tube (Fig. 2B). This is observed in *Noggin*$^{-/-}$ mice, which results in the loss of ventral interneurons and depletion of motor neurons (McMahon et al. 1998; Liem et al. 2000), whereas overexpression of chordin and follistatin expands the motor neuron population at the expense of dorsal populations (Liem et al. 2000; Patten and Placzek 2002). Localized inhibition of BMP signaling confines expression during patterning. The homeodomain protein, Six3, represses BMP-4 expression in the forebrain near the anterior neural plate and is able to restore the size of neural plate in *Chordin*$^{-/-}$ mice (Gestri et al. 2005). Meanwhile, Smad7, an inhibitory-Smad, is expressed in the intermediate spinal cord and confines BMP signaling to the dorsal spinal cord (Yan et al. 2009; Hazen et al. 2011). Thus, control of BMP signaling in the spinal cord, through inhibition of signaling or repression of gene expression, is necessary for proper ventral patterning.

The roof plate forms along the dorsal midline of the neural tube and is induced by BMP signaling (Chizhikov and Millen 2004b). BMP-4 and BMP-7 are expressed in the chick epidermal ectoderm at the time of roof plate specification and can induce roof plate cells from cultured chick neural plate, whereas noggin and follistatin inhibit this induction (Liem et al. 1997). *Bmp2*, *Bmp4*, and *Bmp7* as well as *Gdf7* (encoding GDF-7, growth and differentiation factor 7, also known as BMP-12), activin and dorsalin are expressed in the roof plate (Basler et al. 1993; Dickinson et al. 1995; Lee et al. 1998). BMP signaling is necessary and sufficient for chick roof plate development in vivo (Chizhikov and Millen 2004b; Liu et al. 2004) and ectopic activation of BMP signaling expands the roof plate domain to include almost the entire dorsoventral axis of the spinal cord. *Bmp5*$^{-/-}$; *Bmp7*$^{-/-}$ double mutants develop an abnormally patterned forebrain, whereas *Bmp5*$^{-/-}$ or *Bmp7*$^{-/-}$ single mutants do not show developmental defects in the brain (Solloway and Robertson 1999). These studies show the crucial role of the TGF-β family, particularly BMP signaling, in the development of the dorsal organizer.

BMP signaling activates expression of LIM and Msx homeodomain transcription factors to induce the roof plate. Gain- and loss-of-function experiments in chick and mouse models show that expression of Lmx1a is activated by BMP signaling from epidermal ectoderm (Millonig et al. 2000; Chizhikov and Millen 2004a). Interestingly, Lmx1a induces expression of *Gdf7/Bmp12* and *Bmp4* when ectopically expressed in the developing chick spinal cord or in caudal neural tube explants in vitro (Chizhikov and Millen 2004a). Lmx1a is the main regulator of BMP signaling, as BMP-4 is unable to induce roof plate in explants from *Lmx1a*$^{-/-}$ mutants. By itself, Lmx1a can induce roof plate only in the most dorsal region of the neural tube, suggesting that cofactors are necessary for its dorsalizing effects (Chizhikov and Millen 2004a; Liu et al. 2004). These observations indicate a feedback regulation of BMP and Lmx1a signaling. BMP signaling also induces the expression of the Msx family transcription factors (*Msx1*, *Msx2*, and *Msx3*) in the dorsal spinal cord (Timmer et al. 2002; Liu et al. 2004). Single loss-of-function studies have not been informative, likely because of redundancy; however, overexpression of *Msx1*, but not *Msx3*, in early chick developing spinal cord is sufficient to induce expression of roof plate markers (Liu et al. 2004). Together, Msx and Lmx1a mediate aspects of BMP signaling effects on roof plate development.

After specifying the roof plate, BMP signaling acts as a morphogen to pattern specific dorsal subtypes in a posterior-caudal to anterorostral direction (for review, see Chizhikov and Millen 2005). BMP signals induce interneuron populations in the dorsal (dI1-dI3), but not more ventral (dI4-dI6) spinal cord (Liem et al. 1995, 1997). Addition of BMP-4, BMP-6, BMP-7, or GDF-7 to naïve caudal neural plate explants mimics roof-plate-mediated induction of dI1 and dI3 interneurons (Liem et al. 1997; Lee et al. 1998; Butler and Dodd 2003), and complete ablation of the roof plate results in failure to form dI1-dI3 interneurons leading to expansion of dI4-dI6 interneurons (Lee et al. 2000). Deletion of both BMPRIA and BMPRIB from the dorsal spinal cord leads to a complete loss of the dorsal-most dI1 interneurons (Wine-Lee et al. 2004), whereas activation of BMPRIA and BMPRIB expands dI1 interneurons at the expense of other interneuron types (Timmer et al. 2002; Chizhikov and Millen 2004a; Liu et al. 2004). Use of small interfering RNA (siRNA) to silence the expression of the downstream BMP signaling mediator, *Smad4,* has similar effects on dorsal phenotypes (Chesnutt et al. 2004). Thus, BMP signaling is necessary for patterning of dorsal interneurons, and this role is mediated in part by Lmx1a and Msx3 (Millonig et al. 2000; Chizhikov and Millen 2004a; Liu et al. 2004).

Beyond the spinal cord, BMP signaling from the roof plate contributes to the development of the dorsal hindbrain and diencephalon. Hindbrain roof plate cultures express *Bmp6*, *Bmp7*, and *Gdf7* and these factors are sufficient to induce cerebellar granule neurons (Alder et al. 1999; Machold et al. 2007). BMP-4 and BMP-6 stimulate differentiation and promote survival of granule neurons (Angley et al. 2003; Barneda-Zahonero et al. 2009), whereas targeted inactivation of *Bmpr1a* and *Bmpr1b* in mice results in fewer cerebellar granule neurons, causing a smaller cerebellar cortex without foliation (Qin et al. 2006). Application of noggin to the developing midbrain–hindbrain border results in complete loss or dorsal shift of Phox2-positive neurons. The varying response of Phox2-positive neurons indicates that they form in response to a graded BMP signal from either the roof plate or adjacent epidermal ectoderm (Vogel-Höpker and Rohrer 2002). Downstream BMP signaling through Lmx1a plays a unique role in segregating roof plate epithelium lineage from adjacent cerebellar rhombic lip cell lineage. *Lmx1a*$^{-/-}$ mouse embryos induce the roof plate normally; however, cells that belong to the roof plate epithelium lineage migrate and adopt fates of neuronal rhombic lip derivatives (Chizhikov et al. 2010). Msx1 signals downstream of BMP in the more rostral roof plate, and targeted inactivation of *Msx1* causes a specific loss of the diencephalic roof plate and compromises the dorsal subcommissural organ (Bach et al. 2003). Expression of BMP ligands and receptors both dorsally and ventrally in the diencephalon enhances the complexity of this signaling pathway. Activation of BMPRIA and BMPRIB results in a disruption of proper gene expression patterns in the diencephalon, in addition to an increase in programmed cell death (Lim et al. 2005). However, dominant-negative BMPRIA and BMPRIB did not perturb diencephalic nuclear patterning, suggesting that signaling via BMPRI receptors may not be necessary for patterning in the diencephalon. Thus, BMP signaling functions as a dorsalizing factor in the hindbrain to specify the cerebellum as well as in the spinal cord.

The cerebral hemispheres of the telencephalon surround and dwarf the dorsal midline (roof plate) as it differentiates into the choroid plexus and cortical hem. The dorsomedial telencephalon expresses BMP-2, BMP-4, BMP-6 and BMP-7, as well as the BMP target genes *Msx1* and *Msx2* (Furuta et al. 1997; Grove et al. 1998). Ablation of the roof plate fails to induce the dorsal telencephalic midline tissue, and gene expression is reduced, including diminished adjacent *Lhx2* expression (Monuki et al. 2001; Cheng et al. 2006). Similarly, inactivation of BMP signaling leads to specific loss of the roof-plate-derived choroid plexus, and the cortical hem fails to form (Hébert et al. 2003; Fernandes et al. 2007). Expression of activated BMPRIA in the telencephalon or ectopic expression of BMP-4 can rescue the choroid plexus epithelium without affecting the ventral

neural tube (Hébert et al. 2002; Cheng et al. 2006). When BMP signaling is ablated after neural tube closure, holoprosencephaly does not occur, but formation of the dentate gyrus of the hippocampus is affected (Caronia et al. 2010). Indirect evidence suggests a larger role for BMP signaling in the telencephalon. Mutual antagonism exists between BMPs and Wnts in the cortical hem and between BMPs and FGF-8 in the anterior telencephalon. Additionally, there are significant forebrain patterning defects in embryos treated with exogenous BMPs, mice lacking both *Bmp5* and *Bmp7*, and mice lacking *Chordin* and *Noggin* (Bachiller et al. 2000). These models are complicated to interpret because they include phenotypes that span multiple regions beyond the roof plate. Thus, understanding the role of BMP signaling in telencephalon patterning (and all patterning along the anterior–posterior axis) must be seen in the context of other signaling cascades and transcriptional networks. However, in general BMP signaling specifies dorsal structures, and its role in ventral instruction is less well known.

CELL FATE SPECIFICATION

Stem and progenitor cells in the proliferative ventricular zone (VZ) and later the subventricular zone (SVZ) generate neurons throughout the CNS, followed by sequential waves of astrocyte and oligodendroglia generation. Remarkably, BMP signaling is critical for progenitor cell fate specification in both neurogenesis and astrogliogenesis, although it inhibits oligodendrogliogenesis at all stages of development.

Neurons

Forebrain

Neural stem cells in the VZ and SVZ have the potential to differentiate into all major neural cell types, and the influence of BMP signaling on lineage commitment shifts during development. At early stages of neurogenesis, exposing stem cells and progenitor cells in the telencephalic VZ to BMP-2 or BMP-4 increases apoptosis and inhibits proliferation, whereas at later stages BMP-2 or BMP-4 signaling promotes neuronal differentiation by inducing the expression of the neuron-specific class II β-tubulin (Tuj1) through activation of the Erk mitogen-activated protein kinase (MAPK) pathway (Li et al. 1998; Mabie et al. 1999; Mehler et al. 2000; Moon et al. 2009). Forebrain explants exposed to BMP-4 downregulate anterior neural gene expression, and deletion of BMP antagonists causes loss of anterior brain structures (Furuta et al. 1997; Anderson et al. 2002). BMPs are strong inducers of both *Id* and *Hes* family members, which inhibit actions of basic helix–loop–helix (bHLH) transcription factors (Ross et al. 2003) and mediate many of the negative effects of BMPs on commitment and differentiation of neuronal precursors (Takizawa et al. 2003; Imayoshi et al. 2008). The peak of expression of neurogenin (Ngn1), a proneuronal bHLH transcription factor, coincides with the time course of neurogenesis and gradually declines with the transition to gliogenesis (Ma et al. 1996). During neurogenesis, Ngn1 suppresses BMP-mediated astrocyte differentiation by sequestering downstream transcriptional regulators away from glial gene promoters, such as the promoter of the gene encoding glial fibrillary acid protein (GFAP) (Sun et al. 2001). BMP-2 expression in the VZ results in differentiation and migration of neuroblasts away from the VZ (Li et al. 1998). It also promotes survival and differentiation of cultured FGF-2-primed ventral progenitor cells of the SVZ into GABAergic striatal neurons (Hattori et al. 1999; Yung et al. 2002).

Further cell-type specification is guided by BMP expression, where a balance between BMP-4 and Shh is necessary for determining the proportion of interneurons generated in vivo. This is evident in the greater number of GABAergic interneurons that are derived from progenitor cells in the dorsolateral versus the dorsomedial wall of the telencephalon, where BMP expression is highest (Furuta et al. 1997; Mehler et al. 1997; Grove et al. 1998). Exogenous Shh expression in the dorsomedial wall enhances the number of GABAergic interneurons (Gulacsi and Lillien 2003), whereas BMP signaling determines the fate of GABAergic interneuron pre-

cursors, promoting differentiation of parvalbumin-positive interneurons and blocking differentiation of calbindin- and somatostatin-positive interneurons (Samanta et al. 2007; Mukhopadhyay et al. 2009). Induction of basal forebrain cholinergic neurons (BFCNs) requires BMP-9 expression (López-Coviella et al. 2000, 2005) and, interestingly, human embryonic stem-cell cultures confirm that BMP-9 induces expression of transcription factors that are necessary and sufficient for BFCN induction (Bissonnette et al. 2011).

BMP signaling continues to regulate neurogenesis in two niches of the adult telencephalon that maintain populations of neural stem cells, the SVZ in the lateral ventricles, and the subgranular zone (SGZ) of the hippocampus. BMP-2, BMP-4, and BMP-7 are expressed in the SVZ and promote astroglial lineage commitment, whereas noggin suppresses it (Lim et al. 2000; Colak et al. 2008). In the SGZ, exogenous expression of noggin and BMP-4, or inactivation of either *BMPRIA* or *Smad4* show the role of BMP signaling in the regulation of quiescence and activation of neural stem cells (Bonaguidi et al. 2008; Colak et al. 2008; Mira et al. 2010; Bond et al. 2014; Meyers et al. 2016).

Midbrain

The TGF-β family regulates development of dopaminergic neurons (DNs) in the substantia nigra, the neuronal population that degenerates in Parkinson's disease. TGF-β and Shh cooperatively induce DNs from ventral midbrain floor cells in vitro and in chick embryo in vivo (Krieglstein et al. 2000; Farkas et al. 2003; Roussa and Krieglstein 2004), whereas *Tgfb2*$^{-/}$; *Tgfb3*$^{-/-}$ mice have a severe reduction in DNs at E14.5 (Roussa et al. 2006). Glial-derived neurotrophic factor (GDNF) promotes survival of embryonic DNs and inhibits the apoptotic death in postnatal midbrain DNs in vitro (Apostolides et al. 1998; Burke 2003). Together, TGF-β2 and TGF-β3 synergize with GDNF to facilitate its signaling (Peterziel et al. 2002), whereas TGF-β neutralizing antibodies abolish the survival-promoting effects of GDNF in vitro and in vivo (Krieglstein et al. 1998; Schober et al. 2007). GDF-5 (also known as BMP-14 and CDMP-1) expression occurs during differentiation of DNs in the ventral midbrain and increases the number of DNs in E14 rat ventral midbrain cultures (Krieglstein et al. 1995b; Wood et al. 2005; O'Sullivan et al. 2010). GDF-5 and GDF-15 (also known as NAG-1 and MIC-1) promote adult DN survival and GDF-5 further increases neurite growth from DNs in ventral midbrain transplants into adult striatum (Sullivan et al. 1998; O'Sullivan et al. 2010; Costello et al. 2012). GDNF-deficient mice show normal DN development; however, *Gdnf*$^{-/-}$; *Tgfb2*$^{-/-}$ mice show a loss in midbrain DNs at E14.5 (Roussa et al. 2008; Rahhal et al. 2009).

Hindbrain

Mice lacking expression of both *Bmp5* and *Bmp7* have delayed closure of the cranial neural tube and the size of the hindbrain roof plate is compromised (Solloway and Robertson 1999), whereas ectopic expression of *Bmp7* in the hindbrain causes dorsalization and expansion of the hindbrain neuroectoderm (Arkell and Beddington 1997). Cerebellar granule neurons originate in the rhombic lip and many BMPs, including BMP-6, BMP-7, and GDF-7, are expressed in the midline cells adjacent to the rhombic lip and induce cerebellar granular progenitors in vitro (Alder et al. 1999). Conditional *Bmpr1a*$^{-/-}$; *Bmpr1b*$^{-/-}$ mutants show a dramatic repression of granule cell specification markers along with a loss in the number of granule neurons, whereas the number of Purkinje cells remains unaltered in vivo (Qin et al. 2006). Purkinje and granule cells in the cerebellum express TGF-β2, which regulates the proliferation of cerebellar neurons in vitro (Constam et al. 1994; Kane et al. 1996). Down-regulation of TGF-β family signaling by a reduction in *Smad4* during embryogenesis is required for proper temporal and spatial development of granule progenitor cells (Fernandes et al. 2012). However, inactivation of *Smad4* in the mouse CNS results in a marked decrease in the number of Purkinje cells and parvalbumin-positive interneurons in the cerebellum (Zhou et al. 2003). Taken together, members of the TGF-β family

directly regulate various cell types in the cerebellum.

The Retina and Olfactory Epithelium

TGF-β2 and TGF-β3 are expressed in the central retina but are restricted to the zones of optic nerve head and optic fiber layer, whereas the TGF-β type I and TGF-β type II receptors (TβRI and TβRII) are expressed in the inner retina, cornea and lens (Dünker and Krieglstein 2003). *Tgfb2*$^{-/-}$ mice show inhibition of apoptosis in the neuroblastic layers of the retina, whereas *Tgfb3*$^{-/-}$ mice show no phenotype in the eye (Kaartinen et al. 1995; Proetzel et al. 1995; Sanford et al. 1997; Dünker et al. 2001). However, *Tgfb2*$^{-/-}$; *Tgfb3*$^{-/-}$ mice have their retina detached from the underlying pigment epithelium along with a dose-dependent reduction in the thickness of the cornea, the corneal stroma, and the lens epithelium, resulting from enhanced apoptosis (Dünker and Krieglstein 2003).

TGF-β family members exert both positive and negative regulation of olfactory receptor neuron differentiation. BMP-4 and BMP-7 are expressed by embryonic neurons in the olfactory epithelium, whereas BMP-2 is expressed by stromal fibroblasts (Shou et al. 2000; Peretto et al. 2002). Olfactory epithelial cell cultures treated with BMP-2, BMP-4, or BMP-7 reduce olfactory receptor neurons (Shou et al. 1999), whereas low concentrations of BMP-4 in vitro promote survival of newly generated olfactory receptor neurons (Shou et al. 2000). These opposing effects are likely controlled by activation of different receptors. Inactivation of *Bmpr1b* prevents the reduction of neurogenesis induced by BMP-7, whereas the effects of BMP-4 remain unaltered (Calof et al. 2002). Both BMPRIA and BMPRIB are expressed in the olfactory epithelium and, whereas BMP-4 and BMP-7 signal through BMPRIB, BMP-4 signals through BMPRIA (ten Dijke et al. 1994), suggesting that BMPRIA exerts a survival effect. Neurogenesis in olfactory epithelial cell cultures is stimulated by GDF-7, and targeted inactivation of *Gdf7* reduces the number of MASH1-positive progenitor cells (Kawauchi et al. 2004). GDF-11 (also known as BMP-11), its receptors, and its antagonist follistatin, are expressed by progenitors and olfactory receptor neurons in the olfactory epithelium. GDF-11 is a negative growth regulator of olfactory receptor neurons and impairs proliferation of neuronal precursors, whereas follistatin reverses this effect (Wu et al. 2003; Lander et al. 2009; Gokoffski et al. 2011). Thus, the TGF-β family regulates persistent neurogenesis in the adult olfactory system, stimulating production of olfactory receptor neurons when necessary.

Astrocytes

During late embryonic and postnatal periods, BMP signaling strongly induces astrocyte differentiation (Gross et al. 1996; Mehler et al. 1997; Fukuda et al. 2007; See et al. 2007). In culture, BMP signaling promotes astrogliogenesis in SVZ progenitor cells, cortical progenitor cells, and oligodendrocyte precursor cells (Gross et al. 1996; Mabie et al. 1999; Grinspan et al. 2000). In the adult brain, BMP signaling promotes astroglial lineage commitment and blocks neuron and oligodendrocyte differentiation, whereas noggin suppresses the number of stellate astrocytes (Gomes et al. 2003a). Cultured neural stem cells express the astrocyte intermediate filament protein, GFAP, in response to the leukemia inhibitory factor (LIF)/ciliary neurotrophic factor (CNTF) family proteins as well as BMPs. LIF/CNTF proteins, which activate Jak-STAT pathways, cooperate with BMPs to promote astrogliogenesis by activating the expression of astrocyte-specific genes through a STAT3-p300/CBP-Smad1 complex (Nakashima et al. 1999). Because induction of GFAP-expressing cells through LIF and BMP signaling acts through different pathways, this may explain in part why LIF and BMP generate different types of astrocytes. LIF-induced astrogliogenesis generates more immature GFAP-positive progenitor cells, whereas BMP signaling promotes more mature GFAP-positive astrocytes that lack stem/progenitor cell properties (Bonaguidi et al. 2005). BMP-mediated astroglial fate commitment can also occur by noncanonical STAT signaling through the serine-thre-

onine kinase FKBP12/rapamycin-associated protein (FRAP), also known as mammalian target of rapamycin (mTOR), in high-density conditions (Rajan et al. 2003). In this signaling pathway, FKBP12 binds to BMPRIA and after BMP-4 binding, detaches to activate FRAP, which in turn phosphorylates STAT causing astrocytic gene expression. Recent studies have identified the histone acetylation/deacetylation machinery as the means through which BMP and STAT3 promote astrocytic differentiation (Scholl et al. 2012). TGF-β2 and TGF-β3, as well as their receptors, are expressed in astrocytes, and TGF-β1 expression is induced in astrocytes, in culture of after injury (Toru-Delbauffe et al. 1990). Thus, whereas BMPs are required for specification of astrocytes, a role for TGF-βs in astrocytes is primarily linked to neural injury.

Oligodendrocytes

Oligodendrocyte differentiation occurs in the subcortical white matter, whereas BMP signaling is inhibited by noggin (Li et al. 1998; Mabie et al. 1999). In early embryogenesis, inactivation of BMP signaling in the chick dorsal neural axis results in an increase in oligodendrogenesis (Mekki-Dauriac et al. 2002). BMP-2 or BMP-4 treatment of cultured neural stem/progenitor cells inhibits oligodendrogenesis at all stages of development, whereas noggin treatment increases it (Mehler et al. 1995; Gross et al. 1996; Zhu et al. 1999a). Diminished oligodendrocyte differentiation is also observed in transgenic mice overexpressing BMP-4, whereas overexpression of noggin increases oligodendrogenesis (Gomes et al. 2003b). BMPs regulate oligodendrogenesis through up-regulation of the expression of Id2 and Id4 in neural progenitors, which sequesters Olig1 and Olig2, preventing them from binding to their targets (Samanta and Kessler 2004). BMP signaling may also have a role in myelin protein expression, as seen in myelin injury and disease models (See and Grinspan 2009; Weng et al. 2012). In contrast, noggin treatment increases the number of mature oligodendrocytes and increases remyelination of injured axons in the corpus callosum (Sabo et al. 2011; Wu et al. 2012; Sabo and Cate 2013). Further, Sip1 (Smad-interacting protein 1, also known as Zeb2) has been identified as an essential modulator of myelination through transcriptional repression of downstream BMP signaling (Weng et al. 2012). It should be noted that oligodendrocyte precursors also express TGF-β, and that the combination of TGF-β and activin signaling promotes oligodendrogenesis and CNS myelination (McKinnon et al. 1993; Dutta et al. 2014).

Microglia

Microglia are quiescent macrophages that are activated in response to injury and disease in the CNS. Microglia synthesize and secrete TGF-β1 in response to inflammatory cytokines such as type I interleukin (IL-1), IL-6, nerve growth factor (NGF) and tumor necrosis factor-α (TNF-α) (Lindholm et al. 1992b; da Cunha et al. 1993; Chao et al. 1995a,b). TGF-β1 inhibits free radical induction and induces apoptosis, and TGF-β signaling through Smad2 and/or Smad3 is necessary for maintaining quiescent microglia populations after injury (Suzumura et al. 1993; Lodge and Sriram 1996; Herrera-Molina and von Bernhardi 2005; Abutbul et al. 2012). Extensive microgliosis is observed in the neocortex and hippocampus in *Tgfb1*$^{-/-}$ mice, whereas one allele of *Tgfb1* is sufficient to reverse the phenotype (Brionne et al. 2003). These studies identify TGF-β1 as an anti-inflammatory cytokine in the CNS through inactivation of microglia.

MIGRATION AND AXON GUIDANCE

Following neurogenesis, the formation of cell layers in the nervous system depends on interactions between neurons, glia, and the extracellular matrix for spatial and temporal migration. The expression patterns of TGF-β ligands and receptors in the cerebral cortex are indicative of their involvement in neuronal migration. TGF-β1 is primarily expressed in the meninges, TGF-β2 and TGF-β3 are expressed by neurons and radial glia, and BMP-6 is expressed by radial glia (Schluesener and Meyermann 1994; Murphy

et al. 2004; Ozdamar et al. 2005). TβRI is expressed in the developing murine cortex, and is found postnatally along radial glial fibers, whereas TβRII is primarily expressed by neurons (Tomoda et al. 1996; Miller 2003). Low concentrations of TGF-β1 in culture promote neuronal migration of immature neurons and neuroblastoma cells, whereas high concentrations impair migration. TGF-β1 acts by upregulating the expression of cell-adhesion molecules, like neural cell-adhesion molecule (N-CAM), and the integrin subunits α_3, α_5, and β_1 (Siegenthaler and Miller 2004). Cell-adhesion molecules assist in cell migration by mediating cell attachments through hemophilic interactions, and integrins act as essential links between the extracellular environment and cytoskeleton. In glioma brain tumors, TGF-β1 and TGF-β2 stimulate migration of glioma cells by inducing the expression of α5β3 integrins, whereas anti-TGF-β neutralizing antibodies reduce glioma cell migration (Paulus et al. 1995; Platten et al. 2000; Wick et al. 2001). TGF-β1, TGF-β2, and TGF-β3 have also been shown to increase the number and length of neurites (Unsicker et al. 1996). Together, these findings indicate that TGF-β signaling is required to induce axon formation and neuronal migration (Yi et al. 2010).

BMP and activin are responsible for migration and axon guidance in the developing brain. BMPs act as inductive signals to promote growth cone guidance, axonal orientation and path finding. During spinal cord development, BMP-6, BMP-7, and GDF-7 are expressed in the rodent roof plate and direct commissural neuron axon extension through the spinal cord toward the floor plate (Lee et al. 1998; Augsburger et al. 1999; Butler and Dodd 2003). Explant cultures treated with BMP-7 mimic the repellent activity of the roof plate for commissural axons and directly act to collapse their growth cones (Augsburger et al. 1999), whereas *Bmp7*$^{-/-}$ and *Gdf7*$^{-/-}$ explant cultures show very little repellent activity in vitro. Studies show that BMP-7 and GDF-7 form a heterodimer and act cooperatively in vivo for the guidance of commissural axons (Butler and Dodd 2003). Interestingly, BMP-6 and BMP-7 both induce differentiation of commissural neurons, but only BMP-7 is necessary to orient axons (Perron and Dodd 2011, 2012). The fast-acting repellent action of BMP-induced axonal orientation suggests signaling through cytoskeletal actin remodeling and c-Jun amino-terminal kinase (JNK)-mediated microtubule stabilization (Wen et al. 2007; Podkowa et al. 2010; Perron and Dodd 2011). Additional signaling from activin aids in organizing neural circuitry, and the expression of the activin βA subunit at E17 in the telencephalon indicates a possible role in topographical wiring between the neocortex and neostriatum (Andreasson and Worley 1995). In vitro cultures of rat cortical neurons show that activin signaling promotes dendritic complexity through disinhibiting specific signaling factors (Ishikawa et al. 2010). Thus, multiple members of the TGF-β family are highly involved in migration and axon outgrowth and guidance.

SYNAPTOGENESIS AND PLASTICITY

Neurons communicate through synapses that allow for two-way signal transmission from presynaptic and postsynaptic targets. Strengthening synapses is necessary for learning and memory and for regenerating neuronal circuits after injury. BMP signaling regulates neurite outgrowth and dendritic development throughout the CNS, including cortical neurons (Li et al. 1998; Le Roux et al. 1999; Lee-Hoeflich et al. 2004; Podkowa et al. 2010), hippocampal neurons (Withers et al. 2000), and cerebellar neurons (Matsuura et al. 2007). In culture, treatment of sympathetic neurons with BMP-2, BMP-5, BMP-6, or BMP-7 enhances dendritic development (Lein et al. 1995, 1996; Guo et al. 1998; Beck et al. 2001; Horbinski et al. 2002). However, in cerebellar granule neurons, BMP-2 inhibits neurite outgrowth by LIMK-dependent mechanisms (Matsuura et al. 2007). Treatment of cultured rat hippocampal neurons with TGF-β1 or TGF-β2 results in extension of axon-like processes with no effect on dendritogenesis (Ishihara et al. 1994). The postulated role of TGF-β in synapse formation and plasticity in vertebrates is based to a large extent on expres-

sion patterns. Inactivation of *Tgfb1* in mice results in lower levels of the presynaptic protein synaptophysin in the neocortex and hippocampus, leading to decreased synaptic density (Brionne et al. 2003). TGF-β1 is also necessary for normal expression of the extracellular matrix protein laminin, which has been implicated in learning and memory (Venström and Reichardt 1993; Luckenbill-Edds 1997). Transgenic overexpression of TGF-β1 in astrocytes leads to increased production of laminin, whereas loss of *Tgfb1* results in a reduction in laminin expression (Brionne et al. 2003).

Direct evidence for the role of TGF-β family proteins in synaptic differentiation and maturation comes from the study of the glutamatergic neuromuscular junction (NMJ) in *Drosophila* (for review, Darabid et al. 2014). Evidence of this involvement in synapse development and plasticity has also been provided by studies of the mollusk *Aplysia* (Schuman 1997; Zhang et al. 1997). During long-term sensitization of the gill- and siphon-withdrawal reflex in this organism, long-term facilitation also results in an increase in TGF-β1 mRNA in sensory neurons (Liu et al. 1997; Zhang et al. 1997). Application of TGF-β1 strengthens the sensory-motor-neuron synaptic connections, whereas a TGF-β receptor antagonist blocks this effect (Zhang et al. 1997; Chin et al. 1999). In the mouse, TGF-β2 treatment in cultured hippocampal neurons alters evoked postsynaptic currents (ePSCs), indicating a role in hippocampal synaptic plasticity (Fukushima et al. 2007). The TGF-β family member activin also affects hippocampal neurons by modifying spine morphology and increasing synaptic contacts (Shoji-Kasai et al. 2007). Thus, the TGF-β family has an important role in both synaptogenesis and in plasticity of the nervous system.

CELL SURVIVAL AND DEATH IN THE NERVOUS SYSTEM

Programmed cell death in the developing vertebrate nervous system is responsible for loss of a large number of neurons. Neuron survival is dependent on competition for a limited supply of survival factors (neurotrophins) provided by target cells. TGF-βs are not independently neurotrophic; however, treatment with TGF-β enhances neurotrophic signaling in cultured neurons grown with low and subthreshold concentrations of neurotrophins. Meanwhile, blocking endogenous TGF-βs lowers the survival-promoting activity of neurotrophin (Krieglstein and Unsicker 1996; Krieglstein et al. 1998). The biological relevance of this synergy is also shown by the increase in TGF-β synthesis and release from neurons in response to neurotrophins (Krieglstein and Unsicker 1996; Krieglstein et al. 1998). Unlike the cotrophic effects of TGF-β signaling, BMP signaling in the developing nervous system triggers apoptosis. BMPs are expressed in the chick embryo in the dorsal regions of the odd-numbered rhombomeres (r3 and r5) and induce segmental apoptosis in these areas (Graham et al. 1994). Loss of BMP antagonists in *Chordin*$^{-/-}$; *Noggin*$^{+/-}$ embryos, as well as conditional activation of BMPRIA or BMPRIB expression, increases cell death in the rostral neuroepithelium (Anderson et al. 2002). BMP signaling induces apoptosis of neocortical progenitors, forebrain precursor explants, trigeminal neurons, sympathoadrenal cells, sympathetic neuroblasts, and postmigratory enteric neurons (Chalazonitis et al. 2004). In vitro, treatment of SVZ neurospheres with BMP-4 promotes apoptosis in a dose-dependent manner through Msx2 and the cyclin-dependent kinase inhibitor p21^{Cip1} (Israsena and Kessler 2002). BMP signaling can also promote survival through indirect mechanisms such as induction of neurotrophin receptors (Zhang et al. 1998).

The TGF-β family has an essential role in midbrain DN survival. TGF-β1, TGF-β2, and TGF-β3 promote survival of mesencephalic DNs, whereas neutralizing antibodies against TGF-β in the developing chick (E6-10) impairs survival (Krieglstein and Unsicker 1994; Poulsen et al. 1994; Roussa et al. 2004). The effects of TGF-β signaling on DN survival are mediated by HIPK1 (homeodomain interacting protein kinase 1) interacting with Smad3 to regulate target genes (Zhang et al. 2007). In contrast, BMP signaling acts indirectly on dopaminergic neuron survival by stimulating astrocyte differ-

entiation (Jordan et al. 1997; Farkas et al. 2003). BMP-7 induces dopamine neuron differentiation in culture, and promotes survival in the adult nigrostriatal pathway against dopamine toxins in vivo (Lee et al. 2003; Harvey et al. 2004; Chou et al. 2008). Although the direct role of BMP signaling on dopamine neuron induction is unknown, Msx1 and Lmx1a are key determinants of midbrain DNs and are both induced by BMP-Smad activation (Tríbulo et al. 2003; Chizhikov and Millen 2004a; Andersson et al. 2006). Thus, TGF-βs together with BMPs are key regulators in survival and programmed cell death within the developing nervous system.

THE NORMAL AND PATHOLOGICAL ADULT NERVOUS SYSTEM

Injury and Repair

The expression of several TGF-β family ligands and receptors is increased following neural injury. In the normal adult rat brain TGF-β1 is expressed at low levels primarily in the meninges; however, following brain injury, the expression of TGF-β1 and the TGF-β receptors, TβRI and TβRII, is up-regulated (Lindholm et al. 1992a; Tomoda et al. 1996; McTigue et al. 2000; Zhu et al. 2000; Sometani et al. 2001; Fee et al. 2004). The temporal pattern of TGF-β1 induction and neuronal death suggests that TGF-β1 is predominantly expressed by activated microglia infiltrating the ischemic region (Lehrmann et al. 1995). TGF-β1 expression increases following cerebral infarcts and spinal cord injury and mediates microglial activation to control inflammation following injury (Krupinski et al. 1996; Brionne et al. 2003; Makwana et al. 2007; Buss et al. 2008). A unique TGF-β-dependent population of microglia is present in both mouse and human (Butovsky et al. 2014), and treatment with TGF-β1 before or within 2 hours after cerebral ischemia reduces the volume of infarct and neuronal death in several animal models (McNeill et al. 1994; Prehn and Krieglstein 1994; Henrich-Noack et al. 1996). However, in a neurodegenerative disease model, transgenic overexpression of TGF-β1 in astrocytes exacerbates the disease pathology (Wyss-Coray et al. 1997). In patients with multiple sclerosis, high levels of TGF-β1 mRNA expression in mononuclear peripheral cells have been associated with reduced disability, disease duration, and disease brain activity (Link et al. 1994; Söderström et al. 1995; Bertolotto et al. 1999), although clinical trials of TGF-β treatment of patients with multiple sclerosis were terminated because of non-neurological toxicity (Wiendl et al. 2000).

BMP signaling has been shown to promote astrocyte reactivity and glial scar formation after spinal cord injury. Expression of BMPs increases in the spinal cord after injury, and inhibition of BMP signaling in injured cords expands the lesion volume and shows poor functional recovery (Enzmann et al. 2005). However, there is evidence that BMP inhibition enhances axonal outgrowth and locomotor activity (Setoguchi et al. 2004; Matsuura et al. 2008). BMP receptor signaling following injury show a beneficial effect of BMPRIA, and not BMPRIB for wound repair (Sahni et al. 2010). *Bmpr1b*$^{-/-}$ mice have reduced lesion volumes and an increase in GFAP-expressing cells 1 week postinjury, whereas this result is not apparent in *Bmpr1a*$^{-/-}$; *Bmpr1b*$^{-/-}$ mice. These results indicate a specific role of BMPRIA in the initial injury response; however, *Bmpr1a*$^{-/-}$ mice show better recovery 5 weeks postinjury, suggesting that BMPRIB regulates glial scar progression (Sahni et al. 2010). Further, miR-21, a posttranscriptional regulator of gene expression induced by BMP signaling, mediates the astrocytic response after spinal cord injury (Sahni et al. 2010; Bhalala et al. 2012). Thus, many members of the TGF-β family have important roles following CNS injury, although these processes have yet to be fully understood.

Neurodegenerative Diseases

The TGF-β family plays an extensive role in neurodegenerative diseases, injury and cancer. We will briefly discuss their roles in Alzheimer's and Parkinson's diseases, and amyotrophic lateral sclerosis pathologies (for further review, see Krieglstein 2013).

Alzheimer's disease is a neurodegenerative disease characterized by the formation of senile plaques and neurofibrillary tangles in the cortex and limbic areas. Senile plaques are deposits of amyloid-β (Aβ) peptides generated by abnormally cleaved amyloid precursor protein (APP). TGF-β1 contributes to Aβ precursor expression and Aβ deposition (van der Wal et al. 1993; Wyss-Coray et al. 1997; Burton et al. 2002); however, TGF-β1 attenuates microglia clustering to Aβ aggregates, and TGF-β1 expression in astrocytes causes a reduction in overall plaque burden (Wyss-Coray et al. 2001; Huang et al. 2010). Interestingly, TGF-β1 is enriched in plasma lipoprotein samples of apoliprotein E3 (apoE3), but occurs at a lower concentration in lipoproteins containing apoE4, a genetic risk factor for late-onset Alzheimer's disease (Tesseur et al. 2009; Bertram et al. 2010). Impairment in TGF-β/Smad signaling and decreased neuronal expression of TβRII are both characteristics of disease pathology, providing further evidence for a role for TGF-β in Alzheimer's disease (Tesseur et al. 2006; Ueberham et al. 2006; Wang et al. 2010).

Utilizing the anti-inflammatory effects of TGF-β as a treatment has been suggested as a possible therapy for Parkinson's disease, a disease in which midbrain DNs degenerate. TGF-β2 and TGF-β3 are expressed in adult nigral DNs, and TGF-β1 and TGF-β2 expression is increased in biopsies of Parkinson's disease patients (Unsicker et al. 1991; Nagatsu et al. 2000). Treatment of DN cultures with TGF-β1, TGF-β2, or TGF-β3 enhances cell survival following exposure to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an experimental model of Parkinson's disease in vivo (Krieglstein et al. 1995a; Roussa et al. 2009). TGF-β cooperates with GDNF, a potential therapeutic agent for Parkinson's disease, to promote DN survival (Krieglstein et al. 1998). Importantly, in the MPTP mouse model, GDNF-dependent neuroprotective effects are based on interaction with TGF-β (Schober et al. 2007).

Amyotrophic lateral sclerosis (ALS) is a fatal disease characterized by paralysis caused by loss of motor neurons. A familial form of this disorder is the result of a mutation in superoxide dismutase 1 (SOD1). Because TGF-β is a notable motoneuron survival factor (Martinou et al. 1990; McLennan and Koishi 2002), it is an ideal candidate for therapy. When mice with a mutated *Sod1* gene are given intraperitoneal injections of TGF-β2, they show rapid improvement in motor functions, but this improvement lasts for only a few weeks (Day et al. 2005). Thus, despite substantial evidence suggesting that TGF-β signaling exerts an anti-inflammatory and protective effect on the damaged nervous system, no convincing application has been shown.

CONCLUSION

The role of TGF-β family members has been well characterized in the early stages of neural development in several organisms including mice. Spatiotemporal signals mediate effects of TGF-β family members, allowing them to exert a wide range of functions from early stages of neurulation to later stages of development involving processes such as cellular specification, synaptogenesis, and axon guidance. The mechanisms involved later in development are less clear because of the need for multiple TGF-β family gene mutations to overcome their redundant functions. Overall, we conclude that members of the TGF-β family have important roles in virtually every stage of neural development. Continued study in the injured and diseased nervous system will have important clinical implications and could identify novel therapeutic targets.

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