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Review

The role of TGF- β superfamily signaling in neurological disorders

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Abstract

The TGF- β superfamily signaling is involved in a variety of biological processes during embryogenesis and in adult tissue homeostasis. Faulty regulation of the signaling pathway that transduces the TGF- β superfamily signals accordingly leads to a number of ailments, such as cancer and cardiovascular, metabolic, urinary, intestinal, skeletal, and immune diseases. In recent years, a number of studies have elucidated the essential roles of TGF- β s and BMPs during neuronal development in the maintenance of appropriate innervation and neuronal activity. The new advancement implicates significant roles of the aberrant TGF- β superfamily signaling in the pathogenesis of neurological disorders. In this review, we compile a number of reports implicating the deregulation of TGF- β /BMP signaling pathways in the pathogenesis of cognitive and neurodegenerative disorders in animal models and patients. We apologize in advance that the review falls short of providing details of the role of TGF- β /BMP signaling or mechanisms underlying the pathogenesis of neurological disorders. The goal of this article is to reveal a gap in our knowledge regarding the association between TGF- β /BMP signaling pathways and neuronal tissue homeostasis and development and facilitate the research with a potential to develop new therapies for neurological ailments by modulating the pathways.

Key words: cognitive disease, neurodegenerative disease, TGF- β , BMP, GDFs, neurons

Introduction

The transforming growth factor- β (TGF- β) superfamily of growth factors comprises approximately 20 evolutionarily conserved cytokines subdivided into several families, including TGF- β s, bone morphogenetic proteins (BMPs), activins, inhibins, nodals, and growth and differentiation factors (GDFs) (Table 1) [1]. They bind to two sets of ligand-specific receptors (Types I and II), which contain serine/threonine kinases. Receptor activation is transduced to the nucleus by Smad proteins, and this short cascade is known as the canonical pathway (Fig. 1) [2,3]. Smads 1, 5, and 8 are substrates of the Type I BMP receptor kinases, while Smads 2 and 3 respond to the Type I TGF- β receptor; together they are known as ‘receptor-specific’ R-Smads (Table 1). Type II receptors phosphorylate the Type I receptors, which then phosphorylate the R-Smads (Fig. 1).

The activated R-Smads bind Smad4 (Co-Smad), and then the complex translocates to the nucleus and activates (or inhibits) transcription by binding to DNA-binding transcription factors (Fig. 1). The Smad-dependent signal can be negatively regulated by inhibitory Smads (I-Smads), Smad6 and Smad7 (Table 1 and Fig. 1). It is also known that the TGF- β /BMP signal can be transduced through a variety of intracellular Smad-independent pathways, including LIM domain kinase 1 (LIMK1)-actin depolymerizing factor (ADF)-cofilin and mitogen activated protein kinase pathways (known as ‘non-canonical’) [4] (Fig. 1). In this review article, we try to discuss the roles of TGF- β signaling pathways in neuronal diseases and to reveal a gap in our knowledge regarding the association between TGF- β /BMP signaling pathways and neuronal tissue homeostasis and development.

Table 1. Molecules in the BMP, TGF- β , and activin signaling pathway in mammals and *Drosophila*

	Mammals	<i>Drosophila</i>
Ligands		
BMP	BMP2, BMP4 GDF5, GDF6, GDF7 BMP5, BMP6, BMP7, BMP8 GDF1, GDF2, GDF3 BMP9, BMP10 BMP3, GDF10 Nodal	Dpp Gbb Scw
TGF- β	TGF- β 1, TGF- β 2, TGF- β 3 Lefty1, Lefty2	Mav
Activin	ActivinA, ActivinB, ActivinC, ActivinE InhivinA, InhivinC, InhivinE	Act- β , Daw Myo
Type I receptors		
BMP	ACVRL1 (ALK1), ACVRI (ALK2) BMPRI1A (ALK3), BMPRI1B (ALK6)	Sax Tkv
TGF- β	T β RI (ALK5), ACVRL1 (ALK1)	BaboA, BaboB, BaboC
Activin	ACVR1B (ALK4), ACVR1C (ALK7)	BaboA, BaboB, BaboC
Type II receptors		
BMP	BMPRII ACVRIIA (ACTRIIA), ACVRIIB (ACTRIIB)	Wit Punt
TGF- β	T β RII	Punt
Activin	ACVRIIA (ACTRIIA), ACVRIIB (ACTRIIB)	Punt
R-Smads		
BMP	Smad1, Smad5, Smad8	Mad
TGF- β	Smad2, Smad3	Smox
Activin	Smad2, Smad3	Smox
Co-Smads		
BMP	Smad4	Medea
TGF- β	Smad4	Medea
Activin	Smad4	Medea
I-Smads		
BMP	Smad6, Smad7	Dad
TGF- β	Smad7	Dad
Activin	Smad7	Dad

TGF- β Superfamily in Neuronal Development and Function

The BMP signaling pathway instructs key developmental events during early development of the nervous system and cell fate specification [5,6] (Fig. 2). The activities of BMPs and downstream effectors are dynamically and carefully regulated to play key roles during gastrulation and dorso-ventral patterning within the neural tube, the embryonic precursor of the brain and the spinal cord as well as the adult brain homeostasis and functions [7]. For example, an important cell type in embryos is the neural crest, which originates from the dorsal most region of the neural tube [8]. Neural crest cells give rise to several cell types in the peripheral nervous system (PNS), including glial and Schwann cells [8]. An intermediate level of BMP signaling is required for neural crest cell generation and cell fate choice [7] (Fig. 2). BMPs also control patterning of the dorsal spinal cord [6,9,10], while it has been reported that molecules in the canonical BMP signaling pathway, such as ligands (GDF7 and BMP7), receptors (BMPRI1A/B), and signal transducers (Smad1/5/8) are essential for patterning of the ventral spinal code, dorsal spinal code neural axonal guidance, forebrain development, and cerebellar granule neuron development [6,9,10] (Fig. 2). In the central nervous system (CNS), BMPs, activins, TGF- β s, and GDFs contribute to the differentiation of neural stem cells and neural progenitor cells (NPCs) [5] (Fig. 2). For example, the BMP signaling promotes

astroglialogenesis, and simultaneously inhibits oligodendroglial and neuronal lineages by activating downstream signals [7] (Fig. 2). Oligodendrogenesis is inhibited by BMP signaling and promoted by noggin [5] (Fig. 2). It has been shown that BMP signaling inhibits myelination through the inhibition of oligodendrogenesis [11,12] (Fig. 2). On the contrary, TGF- β and activin signaling promote both oligodendrogenesis and myelination [5,13] (Fig. 2). Thus, the TGF- β superfamily orchestrates patterning and determination of cell fate in the CNS, as well as the PNS.

The BMP signaling pathway regulates neurite outgrowth, dendritic development, and axon growth in neurons via various Smad-dependent and -independent signaling pathways, such as those involving LIMK1-cofilin, repulsive guidance molecule (RGM), and neurogenin [5,14,15] (Fig. 1). BMP signaling also facilitates axonal transport and organization of the microtubule network in neurons [16] (Fig. 2). The BMP receptors undergo endocytosis and dynein-dependent retrograde transport along the axon [17], implying that the trafficking of BMP receptor complexes might affect the cytoskeletal dynamics and axonal development (Fig. 2). TGF- β 1–3 are found to increase the number and length of neurites [18] (Fig. 2).

The TGF- β superfamily also enhances synapse formation [19]. BMP7 and activin promote synapse development in hippocampal neurons [20] (Fig. 2). In addition, BMP signaling determines synaptic size [21], while astrocyte-derived TGF- β promotes synapse

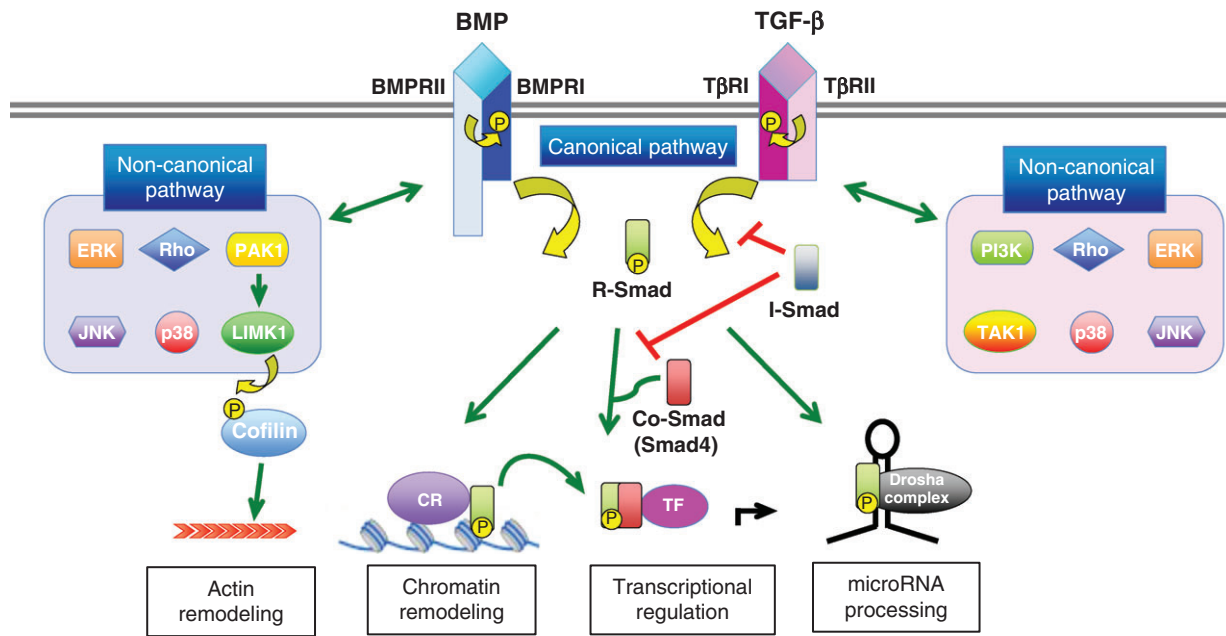


Figure 1. Signal transduction by TGF-βs and BMPs TGF-β and BMP ligands induce formation of heteromeric complex between specific Type II and Type I receptors. The Type II receptors transphosphorylate the Type I receptors and activate the Type I receptor kinases. The Type I receptor transmits the signal to the cell by phosphorylating receptor-regulated (R)-Smads, which form heteromeric complexes with Smad4 (common (Co)-Smad) and translocate in the nucleus where by interacting with other transcription factors regulate gene transcriptional responses, chromatin remodeling, and/or control of microRNA processing [‘canonical (or Smad-dependent) pathway’]. Inhibitory (I)-Smads; Smad6 and Smad7 inhibit activation of R-Smads. In addition, the activated Type I receptors can activate ‘non-canonical (or non-Smad) pathway’ via different effectors, such as extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK), p38, Rho, phosphoinositide 3-kinase (PI3K), transforming growth factor beta-activated kinase 1 (TAK1), p21 (RAC1) activated kinase 1 (PAK1), and LIM domain kinase 1 (LIMK1). CR and TF stand for chromatin remodeling protein and transcription factor, respectively.

formation (Fig. 2) [22]. The roles of the TGF-β superfamily pathways in synapse formation have been characterized in the development of neuromuscular junctions (NMJ) in *Drosophila* [23]. Glass bottom boat (Gbb), a *Drosophila* ortholog of BMP (Table 1) secreted from muscle cells, promotes pre-synaptic formation at the NMJ [23]. Gbb binds the Type II receptor wishful thinking (Wit) and the Type I receptor thickvein (Tkv) or Saxophone (Sax) (Table 1) and regulates synaptogenesis via Smad1/5/8 (Mothers against Dpp or Mad) (Table 1) and *Drosophila* ortholog of LIMK1 (Limk). Maverick (Mav), a *Drosophila* ortholog of TGF-β, is secreted by glia, binds to Punt, a Type II receptor (Table 1) expressed on the surface of muscle cells, and potentiates Gbb-dependent signaling, hence promoting synaptic growth at the NMJ [24]. The TGF-β signaling pathway also regulates synaptic plasticity and memory [22]. TGF-β2 enhances synaptic transmission in primary cultured hippocampus neurons [25]. Central nervous-specific knockout (KO) of TGF-β1 in mouse exhibits a reduction of dendritic spine density, impaired long-term potentiation (LTP), and facilitated long-term depression (LTD) in CA1, CA2, and CA3 synapses in the hippocampus [26]. *Bmpr1a* and *Bmpr1b* double KO mice show reduced synaptic transmission [21,27,28]. Activin increases the number of synaptic contacts and the length of dendritic spine necks [20], suggesting that activin improves synaptic plasticity and LTP by modifying synaptic morphology [29]. Based on a transgenic mouse expressing a dominant negative mutant of the activin receptor Type 1B (Acvr1b) (also known as ALK4), it has been suggested that activin signals suppress inhibitory synaptic transmission [30,31]. In summary, multiple conserved members of the TGF-β superfamily of cytokines play key roles both in synaptogenesis and in plasticity of the nervous system. In the next paragraph, we list the instances in

which TGF-β superfamily pathways have been linked to the pathogenesis of different neurological disorders.

TGF-β/BMP Signaling in Developmental Disorders

Fragile X syndrome

Fragile X syndrome (FXS) (OMIM No. 300624) is the most common cause of inherited intellectual disability and the genetic cause of autism spectrum disorders (ASDs). Inactivating mutation of the *fragile X mental retardation 1 (FMR1)* gene, which locates at Xq27.3, a ‘fragile site’, or the expansion of CGG repeats (more than 200 repeats) in the 5’ UTR of *FMR1* causes FXS [32]. It is estimated that 1 in 4000 men and 1 in 8000 women are affected worldwide [32,33]. It is thought that the X chromosome with the fragile X site is more often inactivated compared with the nonaffected X chromosome [33]. FXS is diagnosed within the first 3 years of life by genetic testing. The FXS patients exhibit cognitive impairment, anxiety, hyperactivity, and autistic behavior as well as characteristic physical features, such as large and prominent ears, macroorchidism, and ovarian insufficiency [32,33]. Females with FXS tend to present less affected but wider range of phenotypic characteristics than males, depending on the inactivation ratio of the fragile X site [32]. The *FMR1* gene encodes fragile X mental retardation protein (FMRP), an RNA binding protein that, in a majority of cases, represses translation [34]. Several genome-wide analyses to identify FMRP target mRNAs have been performed [35,36]. Based on the identification of FMRP targets, various pharmacological or genetic strategies to reduce the expression or activity of FMRP targets and rescue the

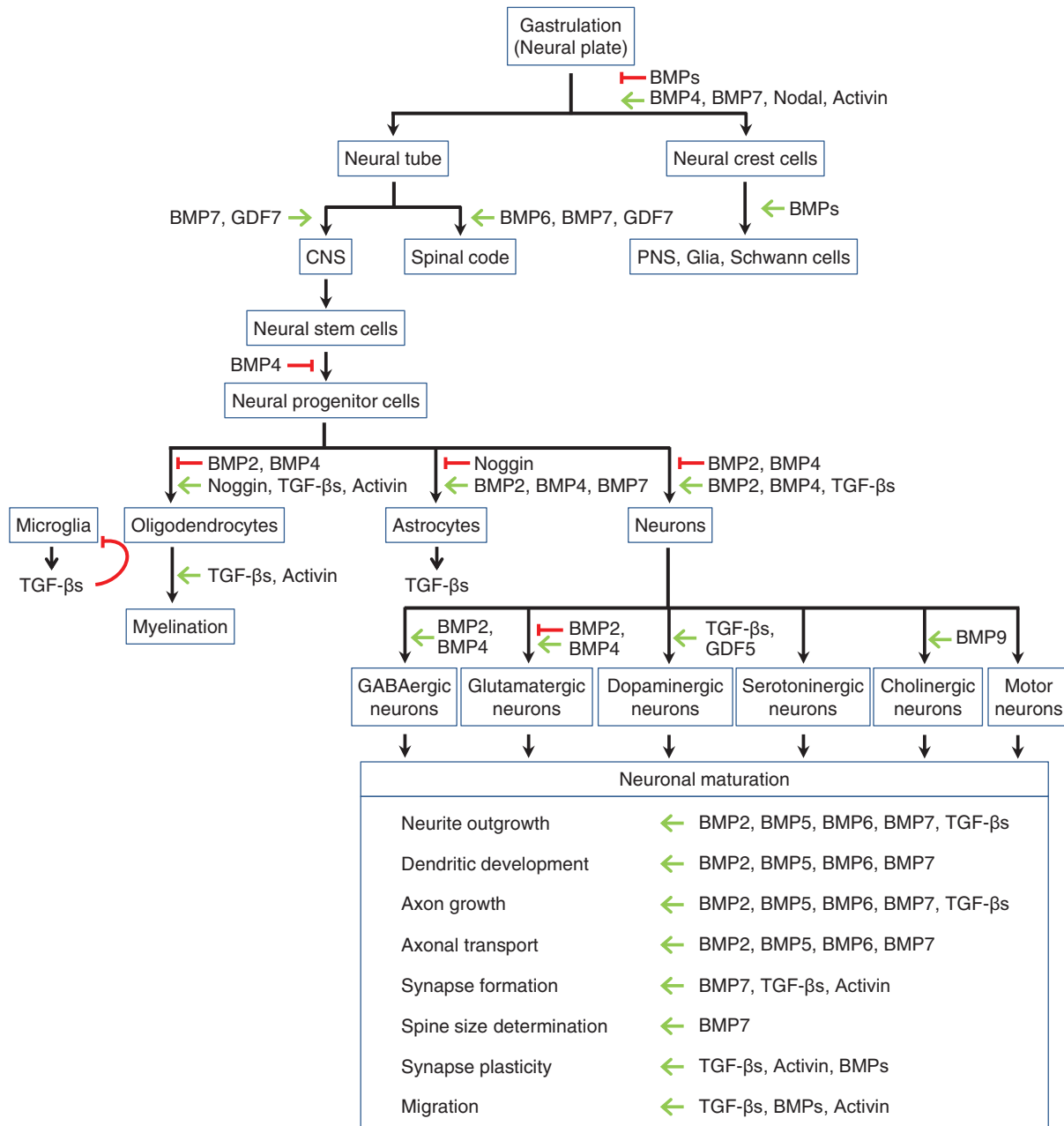


Figure 2. Roles of TGF- β s and BMPs in the neural development and function Signaling by the TGF- β family is required for proper neural development and function. Both inductive (green arrows) and inhibitory signals (red lines) of different ligands at various steps of neural differentiation are shown. CNS and PNS stand for central nervous system and peripheral nervous system, respectively.

pathogenesis have been employed in FXS model animals [34]. However, currently there is no effective therapy for FXS. Recently, the transcript of the *Type 2 BMP receptor (BMPR2)* gene has been identified as a novel target of FMRP [37] (Table 2). In FXS patients- and *Fmr1*-KO mice-derived brains and neurons, BMPR2 protein amount is increased [37], resulting in LIMK1 activation and increased phosphorylation of cofilin [37]. The BMP-LIMK1-cofilin pathway regulates dendritogenesis and axon growth in CNS neurons [14,38]. It has been also reported that overexpression of wild-type or a constitutively active mutation in LIMK1 causes increased growth cone formation, axonal outgrowth, abnormal dendritogenesis, and impaired neural migration in primary neurons and in

transgenic mice expressing a constitutively active *Limk1* [39,40]. Interestingly, both *Fmr1*-KO mice and human FXS patients exhibit an increase of the spine density and the number of immature spines [41–44]. Genetic or pharmacological inhibition of the Smad-independent BMP-BMPR2-LIMK1-cofilin pathway rescues the neuron morphological and behavioral abnormalities in *Fmr1*-KO mice [37,45]. Retrograde BMP signaling also plays an important role in synapse growth and stability via both Smad-dependent and -independent (LIMK1-cofilin-dependent) pathways at the *Drosophila* NMJ [46,47]. Like FXS patients and *Fmr1*-KO mice, *Drosophila Fmr1 (dFmr1)* mutants have an increased number of synaptic boutons and branches at the NMJ [48–50]. These morphological

Table 2. Deregulation of TGF- β signaling pathway associated with various neurological disorders

Disease	Affected pathway	Mechanism	Impact on pathogenesis	Reference
Fragile X syndrome	BMP signaling (U)	Decreased translational inhibition of BMPR2 by FMRP	Increased dendritogenesis and spine number	[37]
Williams syndrome	BMP signaling (D?)	Deletion of LIMK1	Abnormal synapse morphology and function	[51]
Angelman syndrome	BMP signaling (U)	Decreased BMPR1A degradation by UBE3A	Abnormal spine formation	[52]
Mowat-Wilson syndrome	BMP signaling (U or D)	Deregulation of SIP1	Defective neural crest formation	[53,54]
Troyer syndrome	BMP signaling (U)	Decreased endocytotic degradation of BMPR2 by SPARTIN	Increased synapse formation and neurodegeneration	[55,56]
SPG3A	BMP signaling (U)	Decreased endocytotic degradation of BMPR2 by ATL1	Abnormal microtubule dynamics and axon guidance?	[57–59]
SPG4	BMP signaling (U)	Decreased endocytotic degradation of BMPR2 by SPAST	Abnormal microtubule dynamics and axon guidance?	[57,60]
SPG6	BMP signaling (U)	Decreased endocytotic degradation of BMPR2 by NIPA1	Abnormal synapse formation, microtubule dynamics, and axon guidance	[16,57,60,61]
Alzheimer's disease	TGF- β signaling (U or D) BMP signaling (U)	Deregulation of TGF- β 1, Smad7, nuclear R-Smad/Co-Smad. Elevation of BMP4 and BMP6	A β accumulation, aberrant microglia activation, and increased neurodegeneration Inhibition of neurogenesis	[62–71] [72–75]
Parkinson's disease	TGF- β signaling (U or D) BMP signaling (D)	Deregulation of ligands and receptors Deregulation of ligands and receptors	Degeneration of DA neuron Inhibition of DA neuron differentiation and protection from neurodegeneration	[76–79] [80–87]
Huntington's disease	TGF- β signaling (U or D) BMP signaling (U)	Deregulation of neuronal and circulating TGF- β 1 N.D.	Increased neurodegeneration? Increased dendritic branching and synapse size	[88–92] [93]
Amyotrophic lateral sclerosis	TGF- β signaling (U or D) BMP signaling (U or D)	Deregulation of ligands and Smad2/3 protein stability Deregulation of receptor trafficking	Inhibition of neuroprotection and increased axon degeneration Impaired synapse growth	[94–98] [99–102]
Multiple sclerosis	TGF- β signaling (U) BMP signaling (U)	N.D. Deregulation of BMP2, BMP4, BMP5 and noggin	Inflammation? Inhibition of neuronal differentiation and myelination	[103–105] [106–112]

U, D, and N.D. stand for 'Up', 'Down' and 'not determined', respectively.

changes of the synapses at the NMJ are accompanied by an increase in the crawling velocity of larvae [37]. Genetic or pharmacological inhibition of the Wit-Limk pathway in larvae ameliorates the neuro-morphological and locomotive abnormalities in *dFmr1* mutants [37,45], suggesting that FMRP-dependent regulation of the BMPR2-LIMK1-cofilin axis is an evolutionarily conserved pathway important for synapse development, and that aberrant activation of this pathway is one of the underlying causes of the FXS pathogenesis.

Williams syndrome

Williams syndrome (WS) (OMIM No. 194050) is a developmental disorder characterized by mental retardation or learning difficulties, cardiovascular problems, particular facial features, and a typical personality that includes overfriendliness and anxiety [113]. The prevalence is 1 in 20,000, occurring sporadically within the general population [114]. Post-mortem layer V/VI cortical neurons in WS patients' brain and iPSC-derived neurons show longer dendrites and an increased number of spines and synapses [115]. WS is caused by a deletion of the chromosome 7p11.23 locus, which comprises ~25 protein coding genes, including *CYLN2*, *ELN*, *GTF2I*, *GTF2IRD1*,

FZD9, and *LIMK1* [116]. *LIMK1* is considered as one of the critical genes in the pathogenesis of WS [51] because *Limk1*-KO mice exhibit abnormalities in synapse morphology and function, enhanced hippocampus LTP, increased locomotor activities, and impaired leaning [117]. Furthermore, both *Limk1*-KO mice and humans with the WS genetic mutation present spine abnormalities and cognitive impairment [117–119]. Additionally, overexpression of a dominant negative form of *Limk1* causes aberrant axonal guidance and neuronal migration in the embryonic mouse brain [40]. As described in the FXS section above, aberrant activation of the BMPR2-LIMK1 pathway is implicated in FXS, while inhibition or inactivation of LIMK1 leads to WS [37] (Table 2). It is intriguing to speculate that restoring the BMP-BMPR2-LIMK1-cofilin activity might be able to ameliorate the pathogenesis of WS.

Angelman syndrome

Angelman syndrome (AS) (OMIM No. 105830) is a neurodevelopment disorder resulted mainly from deficient expression or function of the maternally inherited allele of *UBE3A* gene on the chromosome 15q11.2-q13 locus. The incidence of AS is between 1 in

15,000 and 1 in 20,000 [120]. The clinical features of AS are microcephaly, severe intellectual deficit, speech impairment, epilepsy, electroencephalogram abnormalities, ataxic movements, tongue protrusion, paroxysms of laughter, abnormal sleep patterns, and hyperactivity [121]. *UBE3A* encodes an E3 ubiquitin ligase which plays an important role in the neuronal ubiquitin-proteasome pathway and synaptic development [122–125]. Several proteins have been identified as targets of UBE3A, such as ECT2, p53, p27, HR23A, Arc, and ephexin-5 [121]. AS model mice show reduced synapse formation and experience-dependent synapse remodeling [124,126]. Mice with maternal mutation in *Ube3a* develop defects in context-dependent learning and LTP [127]. The neurons from the *Ube3a* maternal-deficient mice exhibit shorter spines and reduced dendritic spine density [125]. *dUbe3a*-null mutants show a reduced dendritic branching and growth of the terminal dendritic processes of sensory neurons, as well as a decreased number of satellite boutons at the NMJ in *Drosophila* [52,128]. Along with morphological abnormalities, deficits in locomotor behavior, circadian rhythms, and long-term memory are also observed in the *dUbe3a* mutants [128]. Recently, *Tkv*, *Drosophila* ortholog of BMPR1A (Table 1), has been identified as a *dUbe3a* target [52]. The increased activation of the Smad pathway and bouton formation in *Ube3a* mutants are rescued by *Tkv* mutation, suggesting that aberrant activation of the BMP signaling pathway is responsible for the synaptic abnormalities in AS [52]. BMPR1A (ALK3) was also identified as a target of UBE3A in human [52] (Table 2). *UBE3A* knockdown (KD) results in increased BMPR1A protein followed by activation of the Smad pathway, indicating that the BMP-BMPR1A signaling axis is critical for the pathogenesis of AS. Moreover, a point mutation in *UBE3A* has also been identified in patients with autism spectrum disorders (ASD) [129,130], suggesting that the UBE3A-BMPR1A-BMP signaling pathway might be associated with the pathogenesis of a broad range of neurodevelopmental disorders, including ASD.

Mowat-Wilson syndrome

Mowat-Wilson syndrome (MWS) (OMIM No. 235730) is a mental retardation multiple congenital anomaly syndrome characterized by typical facies, severe mental retardation, epilepsy, and variable congenital malformations, including Hirschsprung disease (HSCR), genital anomalies, congenital heart disease (CHD), and agenesis of the corpus callosum (ACC) [131]. MWS is a very rare disease first described in 1998 [132], and the prevalence is between 1 in 50,000–70,000 [133]. Heterozygous mutation in the *Smad-interacting protein-1* (*SIP1* also known as *ZEB2* or *ZFHX1B*) gene causes MWS [131]. *SIP1* represses Smad signaling in response to activation by BMPs and leads to the induction of neural fate [134–136] (Table 2). The BMP-Smad pathway is crucial for the generation of neural crest cells [137,138], which gives rise to a variety of cell populations in the PNS and contributes to the formation of forebrain and midbrain [139]. In zebrafish, KD of two *Sip1* ortholog results in a loss of vagal/postotic neural crest cell derivatives [53]. In *Sip1*-KO mouse embryos, depletion of neural crest cells and inhibition in the neural crest of *Msh homeobox 1* (*Msx1*), a BMP target gene, can be observed, suggesting that functional BMP signaling is impaired in these mice [54]. *Sip1* also acts as an essential modulator of CNS myelination by inducing Smad7, an antagonist of the BMP-Smad pathway, specifically in oligodendrocytes, of which it promotes the differentiation [12]. However, the molecular mechanisms by which the *SIP1* mutation affects BMP signaling in MWS patients

and how SIP1-BMP signaling leads to the MWS pathogenesis remain unclear.

Hereditary spastic paraplegia

Hereditary spastic paraplegia (HSP), also known as familial spastic paraplegia, is a group of neurodegenerative disorders that leads to spastic weakness of the lower extremities [140]. HSP is classified into two groups, ‘pure HSP’ and ‘complex HSP’, according to whether the HSP occurs alone or is accompanied by additional neurological syndromes, such as cognitive impairment, dementia, epilepsy, and polyneuropathy, respectively [141]. HSP is rare and its prevalence is estimated from 1.27 to 9.6 per 100,000 [140]. Mutations in more than 40 distinct loci and 21 spastic paraplegia (SPG) genes have been associated with HSP. SPG genes encode proteins that are involved in the maintenance of corticospinal tract neurons [142] including *Spartin* (*SPG20*), *Atlastin-1* (*SPG3A*), *Spastin* (*SPG4*), and *non-imprinted in Prader-Willi/AS1* (*NIPA1*, also known as *SPG6*), some of which are inhibitory to BMP signaling [55,57]. The characteristics of different classes of HSP and their associated genes, such as Troyer syndrome (*SPG20*), *SPG3A*, *SPG4*, and *SPG6*, are discussed below.

Troyer syndrome (SPG20)

Troyer syndrome (OMIM No. 275,900) is a child-onset autosomal recessive complex HSP caused by mutation in *SPART*, which encodes Spartin [143]. Troyer syndrome is characterized by a progressive spastic partial paralysis of the lower limbs, motor speech disorder, and pseudobulbar palsy (inability to control facial movements), distal muscular atrophy, motor and cognitive delay, short stature, and subtle skeletal abnormalities, with both developmental and degenerative features [144]. Only 21 patients in the USA [143,144], 6 in Oman [145], and 3 in the Philippines [9] have been reported. Spartin is known to have multiple functions, including cytokinesis, endosomal trafficking and degradation of the epidermal growth factor receptor (EGFR), lipid/cholesterol metabolism, and mitochondrial function [147–152]. Interestingly, Spartin inhibits the BMP signaling pathway [55,56]. *Spartin*-KO mice develop progressive impairments in motor function similar to Troyer syndrome [153]. The cerebral cortical neurons from *Spartin*-KO mice exhibit increased branching, density of dendrites, and elongated axon length in cerebral cortical neurons [153]. In the *Drosophila* NMJ, Spartin localizes presynaptically [56]. *Spartin* homozygous mutants in *Drosophila* show an increase of the BMP signaling, overgrowth of synapses, and progressive neurodegeneration [56]. Mutation in *Wit* or the BMP inhibitor *Daughters against dpp* (*Dad*) (Table 1), an ortholog of *Smad6*, rescues the synapse number and neurodegeneration phenotype, suggesting that Spartin negatively controls BMP signaling by promoting endocytic degradation of Wit [56]. Therefore, these observations suggest that abnormal activation of BMP signaling is linked to the pathogenesis of Troyer syndrome (Table 2).

Spastic paraplegia-3A (SPG3A)

Mutations in the *Atlastin-1* (*ATL1*) gene are the most common cause of pure and complex HSP with early onset at around 4 years old [141]. The *ATL1* is a GTPase of the dynamin superfamily implicated in facilitating membrane interactions, fission, and fusion [154,155]. The mutants exhibit reduced GTPase activity and a prominently disrupted morphology of the endoplasmic reticulum (ER) network [156]. Knockdown of *ATL1* increases (while overexpression represses) BMP signaling in zebrafish [157]. *ATL1* colocalizes with the Type I BMP receptor [157] and associates with

BMPR2 [57]. HSP-related mutations in *ATL1* interfere with BMPR2 trafficking to the cell surface and attenuate BMP signaling [57]. On the contrary, null mutations of *Drosophila dATL1* [58] and of *ATL1* in mammalian cells [59] show augmented BMP activities, indicating that *ATL1* may also modulate trafficking, and similarly inhibit BMP signaling in mammals by interfering with microtubule dynamics and axon guidance [58,59] (Table 2).

Spastic paraplegia-4 (SPG4)

Mutations in the *Spastin* (*SPAST*) gene are commonly found in autosomal dominant pure and complex HSP. SPG4 patients show sensory disturbances, sphincter dysfunction, tremor, cognitive impairment, dementia, and ataxia. SPG4 is age-dependent, and the onset peak is 10 and 30 years old [141]. *SPAST* interacts with microtubules and promotes microtubule disassembly, which is essential for axon growth, branching, and neuronal plasticity [158]. Mutations in *SPAST* cause abnormal microtubule disassembly [159]. The *dSpastin* mutant *Drosophila* shows disorganized microtubules and disrupted proximal-distal transmission gradient along axon branches, which causes increased BMP signaling at the NMJ [57,60] (Table 2).

Spastic paraplegia-6 (SPG6)

SPG6 is a teenage-onset form of pure HSP, with some patients with complex HSP showing memory deficit and epilepsy [141]. All *NIPA1* mutations in SPG6 are missense mutations that affect trafficking of proteins and trapping in the ER [160]. Patients lacking one copy of the *NIPA1* gene seldom develop clinical HSP, thus it is unlikely that SPG6 is caused by haploinsufficiency of *NIPA1*, but rather by a 'toxic gain of function'. *NIPA1* binds *ATL1* and promotes efficient cell surface trafficking of *ATL1* [160]. *NIPA1* also directly binds *BMPR2* [55]. *NIPA1* mutants, which are prone to ER trapping, reduce endocytosis, lysosomal degradation, and recycling of *BMPR2*, and thus augment the amount of *BMPR2* on the cell surface [55] (Table 2). Transgenic rats expressing a *NIPA1* mutant in neurons show an increase of *BMPR2* in the spinal cord [61]. Interestingly, a null mutation of *Spichthyin* (*Spict*), a *Drosophila* ortholog of *NIPA1*, causes a distal axonal abnormality with synaptic overgrowth at the NMJ, due to the attenuation of *Wit* endocytosis [16]. *Spict* preferentially localizes in early endosomes and presynaptically regulates not only synaptic bouton formation at the NMJ but also microtubule maintenance and axonal transport, by inhibiting BMP signaling [16].

Taken together, abnormal *BMPR2* endocytosis and trafficking, followed by atypical activation of BMP signaling, is closely linked to the pathology of several subtypes of HSP.

TGF- β /BMP Signaling in Neurodegenerative Disorders

The TGF- β family plays an extensive role in the survival of neurons [161,162]. Levels of the ligands and the receptors of TGF- β family are regulated following neural injury and repair for proper function of CNS [163–165]. Hippocampal astrocytes from old rats secrete higher amounts of TGF- β s compared with postnatal or young rats [166]. The level of *BMP4* also increases in an age-dependent manner in both human and mouse hippocampus [167], suggesting that the changes of activities of the TGF- β family of signaling affect the homeostasis of aging brains by altering the function and the niches of neurons. Thus, it is not surprising that the TGF- β family is

implicated in the pathogenesis of age-related diseases, such as Alzheimer's and Parkinson's disease, as described below.

Alzheimer's disease

Alzheimer's disease (AD) (OMIM No. 104300) is an age-related, progressive neurodegenerative disease characterized by progressive cognitive impairment and pathological abnormalities, such as loss of neurons, amyloid plaque, and hyperphosphorylated tau in intracellular neurofibrillary tangles in the brain [168]. In addition to the neurodegenerative hallmarks, synaptic plasticity and neuronal integrity are also impaired in AD brains [169]. AD affects approximately 29.8 million people and is a major health concern worldwide [170]. Although pathological mutations in the amyloid precursor protein (APP), presenilin-1, and presenilin-2 are found in familial AD, more than 95% of AD patients do not carry these gene mutations [171]. The molecular mechanisms of pathogenesis of AD remain largely unclear.

It is likely that growth factors, such as TGF- β s and BMPs, are involved in the pathogenesis of AD [172] (Table 2). The phosphorylation of *Smad2/3* is decreased in the AD brain, indicative of impaired TGF- β signaling [62]. Nuclear *Smad2*, *Smad3*, and *Smad4* are also decreased in the temporal cortex of AD patients [63]. TGF- β receptor Type 2 (*T β R2*) expression is decreased in neurons in AD patients [64]. It has been proposed that impaired TGF- β signaling in neurons contributes to β amyloid ($A\beta$) accumulation, microglia activation [65], and neurodegeneration [64]. Accordingly, exogenous TGF- β 1 induces activation of microglia and clearance of $A\beta$ and protects against $A\beta$ -induced synapse loss, neurodegeneration, and apoptosis [66–69]. However, conflicting results have been also reported. In the brain of a mouse model of familial AD, there is an increase of TGF- β 1 and *Smad7*, an antagonist of TGF- β signal, which are thought to mediate neural apoptosis [70] (Table 2). Additionally, TGF- β 1 also affects the microglia and ameliorates neuroinflammation in AD [71]. Because TGF- β 1 seems to act as both survival and apoptotic factor depending on the context, the exact role of TGF- β 1 in AD is still unclear.

The BMP signaling pathway is also involved in AD-related neurodegeneration. In the hippocampus of AD patients, *BMP6*, but not *BMP2* or *BMP7*, is augmented [72]. $A\beta$ exposure induces *BMP6*, which then inhibits proliferation of NPCs [72]. Increase of *BMP4* is also observed in AD mouse brains [73]. These observations suggest that augmented *BMP6* is involved in AD-related altered neurogenesis. *BMP4* is increased and *noggin*, an antagonist of BMPs, is decreased in the dentate gyrus of the AD mouse model and the *apolipoprotein E* (*ApoE*)-KO mice [74,75]. Several observations suggest the implication of TGF- β /BMP signaling in the development and progression of AD. To further understand the molecular mechanism of the pathogenesis of AD and to develop therapeutics for AD, a more precise role of TGF- β /BMP signaling in AD brains should be clarified in the future.

Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after AD, affecting 6.2 million people globally [170]. The clinical symptoms of PD include tremor at rest, rigidity, bradykinesia, postural abnormalities and a freezing phenomenon [173]. The pathological findings in PD include a loss of nigrostriatal dopaminergic (DA) neurons with a subsequent loss of the neurotransmitter dopamine in the corpus striatum, an area of the brain which is critical for the control of movement [174]. One of the

pathological hallmarks of PD is the presence of intracellular protein aggregates called Lewy bodies [174]. Approximately 5% of PD patients carry a familial form of PD and several causal genes have been identified, including *leucine rich repeat kinase 2* (LRRK2), *Parkinson associated deglycase* (PARK7), *PTEN-induced putative kinase 1* (PINK1), *parkin RBR E3 ubiquitin protein ligase* (PRKN), and *synuclein alpha* (SNCA), but the genetic cause of 95% of PD is unknown [175].

It has been reported that the TGF- β superfamily signaling pathway controls DA neuron development and survival [76] (Table 2). Genetic studies suggest an association of single nucleotide polymorphisms (SNPs) in the *TGFB2* gene with PD [77]. *Tgfb2*^{+/-}; *Tgfb3*^{-/-} and *Tgfb2*^{-/-}; *Tgfb3*^{+/-} mice show a significant reduction of DA neurons at E14.5 [76]. *Tgfb2*^{+/-}, *Tgfb3*^{-/-}, and *Smad3*^{-/-} mice show postnatal or age-dependent loss of DA neurons [76]. Adult *Tgfb2*^{+/-} mice show more significant loss of striatal dopamine compared with young mice [176]. These data suggest that TGF- β s play more critical role in adult brain function and homeostasis. Neuron-specific expression of a kinase-inactive mutant T β R2 in mice displays age-dependent neurodegeneration in the nigrostriatal system [78]. TGF- β activation by overexpressing constitutively active T β R1 aborts degeneration of DA neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mouse model [78]. In the cerebrospinal fluid of PD patients, the amount of TGF- β 1 and TGF- β 2 is increased [79].

BMP signaling is also involved in DA neuron differentiation and protection from neurodegeneration [80–84]. Catecholaminergic neuron-specific knock-in of a dominant negative form of BMPR2 (a truncation mutant) results in a decrease of tyrosine hydroxylase (TH), which catalyzes the formation of L-dihydroxyphenylalanine (L-DOPA), the rate-limiting step in the biosynthesis of DA, and a number of neurons in substantia nigra compacta [80]. Pretreatment with BMP7 reduces neurodegeneration in 6-hydroxydopamine (6-OHDA)-induced PD [81]. BMP7 heterozygous KO (*Bmp7*^{+/-}) rats exhibit an increased sensitivity of adult DA neurons to methamphetamine [84]. BMP7 induces DA neuron differentiation from mesencephalic precursor cells *in vitro* [82]. BMP2 induces neurite outgrowth through Smad activation via BMPR1B in SH-SY5Y cells, which are capable of differentiating to DA neurons [83].

Finally, *glial-derived neurotrophic factor* (GDNF) heterozygous KO (*Gdnf*^{+/-}) mice show an accelerated decline of DA neurons during aging [85]. Based on these observations, GDNF was used in clinical trials for PD [86]. GDF5 and GDF15 also play important roles in DA neuron development and survival [76]. Transplantation of GDF5-expressing CHO cells into the striatum exhibits neuroprotective and neurorestorative effects on DA neurons in a 6-OHDA-induced PD rat [87]. Thus, impairment of TGF- β superfamily signaling is closely associated with the pathogenesis of PD.

Huntington's disease

Huntington's disease (HD) (OMIM No. 143100) is the most common inherited neurodegenerative disorder caused by the expansion of a polyglutamine (polyQ) stretch within the coding sequence of Huntingtin (HTT) [177]. HD is characterized by motor, cognitive, and emotional defects [178]. The incidence is 0.38 per 100,000 persons per year [179]. The expansion of a polyQ repeat causes HTT protein aggregation [180]. There is conflicting evidence on how aggregated HTT causes the neurotoxicity [181], but, in general, the polyQ repeat mediates neurotoxicity through impaired vesicle trafficking and axonal transport, altered proteasomal degradation,

mitochondrial dysfunction, and transcriptional deregulation [182]. Recently it has been found that an accumulation of pathogenic HTT protein in nerve terminals interferes with endosomal recycling and leads to buildup of early endosomal signaling compartments, such as BMP signaling molecules in *Drosophila* [93]. The augmented BMP signaling molecules trigger a robust overgrowth of synaptic boutons at NMJ [93] (Table 2). Disruption of BMP signaling rescues abnormal synapse formation and neurotoxicity of the pathogenic HTT, suggesting that the aberrant activation of BMP signaling is involved in the neuronal dysfunction in HD [93]. Indeed, extensive dendritic branching with increased number and size of spines are observed in striatal spiny neurons in HD patients [183].

Deregulation of TGF- β signaling appears to be involved in the pathogenesis of HD [88–92]. The amount of circulating TGF- β 1 in asymptomatic HD patients is decreased [88], while it is increased in symptomatic HD patients [88] (Table 2). The amount of TGF- β 1 in cortical neurons is also reduced in post-mortem brain samples from both asymptomatic and symptomatic HD patients as well as HD model mice [89]. Transcriptome analysis using iPSCs and neural stem cells (NSCs) from HD patients reveals that TGF- β signaling molecules are increased in HD [90]. An increase of the TGF- β signaling pathway is also observed in striatal cell lines expressing HTT mutant and iPSC-derived neural progenitor cells (NPCs) [92]. Smad7, an antagonist of TGF- β signaling, is significantly decreased in these cells, further supporting the increase of TGF- β signaling in HD neurons. It is possible that the boost in TGF- β signaling might be a compensatory response to neurodegeneration [92], or that it predisposes the NSCs toward quiescence during the neurodegeneration process [91]. It has also been reported that Smad3 binds to the promoter region of the *HTT* gene and activates transcription [92]. Further studies are required to clarify molecular link between the TGF- β family signaling to the pathogenesis of HD.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) (OMIM No. 105400) is a progressive neurodegenerative disease which affects the upper and lower motor neurons [184]. ALS is characterized by muscle stiffness, twitching, weakness, and atrophy throughout the body [184]. ALS affects about 2 in 100,000 individuals [184]. Mutations in >25 genes, including *superoxide dismutase 1* (*SOD1*), *alsin Rho guanine nucleotide exchange factor* (*ALS2*), *fused in sarcoma* (*FUS*), *TAR DNA-binding protein 43* (*TDP43*, also known as *TARDBP*), and *chromosome 9 open reading frame 72* (*C9orf72*), have been identified in association with ALS, but for 90%–95% of the patients with ALS, the causal genes are unknown [185]. Irregular TGF- β signaling has been implicated in ALS pathogenesis [94–97] (Table 2). TGF- β 1 is elevated in astrocytes in the spinal cord of *Sod1* mutant mice and sporadic ALS patients [94]. TGF- β 1–3 are also augmented in the muscle of ALS patients and *Sod1* mutant mice [95]. More TGF- β 1 is also detected in the serum and plasma of ALS patients [96]. Nuclear phospho-Smad2/3 (P-Smad2/3), readout of the TGF- β activity, is increased in neurons and glial cells in the spinal cord of *Sod1* mutant mice as well as both familial and sporadic ALS patients [97]. Administration of TGF- β inhibitor ameliorates ALS progression in *Sod1* mutant mice [94]. These reports suggest that astrocyte-derived TGF- β s inhibit neuroprotective responses, promote motor neuron axon degeneration, and contribute to ALS.

TDP43 is one of the ALS-related genes [186,187]. Pathological TDP43 can lead to deregulation of the TGF- β and BMP signaling pathways in ALS [98,99]. Mutant TDP43 protein found in ALS is

prone to aggregate [188]. Interestingly, in some sporadic ALS patients, wild-type TDP43 protein is also aggregated [189,190]. The intracytoplasmic inclusion bodies containing TDP43 are associated with frontotemporal dementia and cognitive impairment in ALS [191,192]. It has also been reported that Smurf2, an E3 ubiquitin ligase that promotes ubiquitin-dependent degradation of Smad2/3 proteins, and phosphorylated Smad2/3 proteins are colocalized with TDP43 and ubiquitin within neuronal intracytoplasmic inclusions in the spinal cord and medulla oblongata of sporadic ALS patients, suggesting that the TGF- β signaling pathway is decreased in neuron [98] (Table 2). In *Drosophila* model of ALS, BMP signaling pathway genes (*Smox*, *SkpA*, and *Sax*) (Table 1) are elevated in CNS of *dTDP43* mutant *Drosophila* according to the genome-wide transcriptome analysis [99]. Aberrant expression of TDP43 in *Drosophila* motor neurons mediates defective endosomal trafficking of Tkv and reduced synaptic BMP signal, leading to the impaired synaptic growth at NMJ accompanied by the abnormal larval crawling [100]. These reports suggest that deregulation of TDP43 can cause the neurological impairment in ALS pathogenesis through the impairment of the TGF- β /BMP signaling.

Mutations in the *Vesicle-associated membrane protein-associated protein B* (*VAPB*) gene are found in patients with familial ALS [193]. *VAPB* protein is reduced in the spinal cord of sporadic ALS patients [194]. *VAPB* is a Type II integral membrane protein that mainly localizes at the ER and implicated in a variety of cellular processes, including ER stress response and the unfolded protein response (UPR). A *Drosophila* expressing the mutant form of *dVAP33A*, a *Drosophila* ortholog of *VAPB*, shows reduced phospho-Mad both at NMJ and in CNS, indicative of reduced BMP signaling [101]. While it is unclear how *dVAP33A* modulates the BMP signaling, it is proposed that *VAPB* mutant might be involved in the abnormal UPR [102].

It is essential to elucidate the molecular mechanisms by which the deregulation of TGF- β signaling/BMP signaling pathway promoting ALS pathogenesis in order to develop a treatment for ALS.

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease with demyelination in CNS neurons [195] which affects over 2.3 million people [170]. Typically, MS patients are diagnosed in young adulthood with a higher incidence in women [195]. Clinical symptoms include blurred vision, muscle weakness and spasms as well as motor problems [195]. There are two major clinical courses of MS: (i) relapsing-remitting MS and (ii) progressive MS [195]. Despite these subtypes, all patients with MS have progressive and irreversible neurological disabilities [195]. Genome-wide association studies demonstrate that SNPs in the *major histocompatibility complex (MHC) class II and DR beta 1* (*HLA-DRB1*) are highly associated with MS [196,197], suggesting that chronic neuroinflammation and failure of the myelin-producing cells, followed by neurodegeneration, are involved in the pathogenesis of MS [198]. Myelin is critical for the propagation of nervous impulses and axonal maintenance and is synthesized as the plasma membrane of the oligodendrocytes in the CNS [199]. During neural development, myelin and oligodendrocytes are generated from oligodendrocyte progenitors under the control of various growth factors [200]. MS plaques are characterized by the presence of immune cell infiltration, demyelination, death of mature oligodendrocytes, axonal damage and neurodegeneration [195,201]. NPCs and oligodendrocyte precursor cells (OPCs) are present in the MS lesions [202–204], suggesting that

the failure of maturation of NPCs and OPCs is involved in MS pathogenesis.

The BMP signaling pathway is involved in NPC differentiation into astrocytes with concurrent suppression of oligodendroglial differentiation in adult brains, thus, deregulation of BMP signaling can contribute to demyelination in MS [106] (Table 2). Both BMPs and BMP antagonist noggin are potentially involved in MS pathology through the functions in neuronal differentiation, myelination, and immune system regulation [107]. It is thought that noggin, which is in a niche of NPCs, is associated with neurogenesis [205,206]. NPCs treated with or overexpressing noggin can differentiate into astrocytes, oligodendrocytes, and mature neurons [205,206]. Noggin is highly expressed in T cells, and the amount is reduced in MS patients [108], suggesting that the reduced production of noggin by T cells might contribute to demyelination in MS. It has also been reported that BMP4 is increased in the caudal cerebellar peduncle of rats in ethidium bromide-induced demyelinated lesions [109]. BMP4 and BMP5 are expressed at the lesions in post-mortem brain tissues from MS patients, and BMP5 expression is augmented in MS patients compared to healthy controls [110] (Table 2). T cell-derived BMP2, BMP4, and BMP5 are increased in peripheral blood mononuclear cells from MS patients [111]. The BMP signaling regulates myelination and demyelination through oligodendrogenesis [11,12]. Additionally, abnormal trafficking of BMP signaling molecules may also contribute to MS pathology [112]. Recent genome-wide association studies demonstrate that SNPs at the 16p13 locus containing *C-type lectin domain family 16, member A* (*CLEC16A*) increase the risk of MS as well as other autoimmune diseases [196,197,207,208]. *CLEC16A* protein in the white matter and peripheral blood mononuclear cells is increased in MS patients [209]. It has been suggested that *CLEC16A* promotes late endosomal maturation to disrupt the HLA-II antigen presentation pathway in MS [209]. In *Drosophila*, a mutation in *Em*, an ortholog of *CLEC16A*, causes abnormal synaptic growth and defective protein trafficking [112]. *Em* is an endosomal membrane protein that interacts with the class C Vps-HOPS complex to promote endosomal maturation [112]. The *Em* mutant fails to form mature late endosomes and lysosomes. In the *Em* mutant, Tkv, phospho-Mad, and synaptic bouton number are all increased, but they can all be reversed by overexpression of human *CLEC16A* [112]. These results suggest that *Em* and *CLEC16A* inhibit BMP signaling through endolysosomal trafficking and degradation of the signaling components [112]. Compared with the BMP pathway, studies linking the TGF- β pathway to MS are limited. TGF- β is augmented in peripheral blood and cerebrospinal fluid of MS patients [103]. The amount of TGF- β and the activity of the disease are linearly correlated [104,105], suggesting that the amount of circulating TGF- β can be used as a biomarker for MS. MS is yet another example of neurodegenerative disorder associated with the deregulation of both TGF- β and BMP signaling pathways.

Anxiety, Depression, and Dementia

Anxiety, depression, and dementia are common neurological disorders that are also linked to the deregulation of TGF- β signaling [2–218]. Forebrain-specific *Bmpr2*-KO mice exhibit reduced anxiety-related behavior [2]. Forebrain-specific *activin* transgenic mice also show decreased anxiety-related behavior [211]. Major depressive disorder patients show a reduction in TGF- β in the serum or a polymorphism in the *TGF- β* gene [212–214]. Antidepressant treatment increases TGF- β [215]. These reports suggest that TGF- β superfamily

signaling pathways modulate psychiatric disorders. Blocking BMP signaling by either transgenic or pharmacological methods significantly enhances hippocampus-dependent learning memory behaviors [216], suggesting that BMP signaling is involved in learning and memory processes. *Charged multivesicular body protein 2B (CHMP2B)* mutations are related with frontotemporal dementia [217]. Overexpression of Rab8, a negative regulator of TGF- β signaling, rescued synapse overgrowth phenotype in *Chmp2b* mutant *Drosophila* [218], implying that an overactive TGF- β signaling pathway is involved in frontotemporal dementia pathogenesis.

Conclusion

The TGF- β family of growth factors plays essential roles during embryonic development and in the regulation of tissue homeostasis. Here we summarized studies describing the association of deregulation of TGF- β signaling with neuronal development and neurological disorders. Abundant evidence in both invertebrates and vertebrates indicates that the TGF- β pathways play important roles in the maintenance of neuron and spine homeostasis. Causal links between deregulation of TGF- β signaling pathway and human disorders such as cancer and cardiovascular or bone diseases have been well documented, and a number of therapeutic molecules have been generated. Compared to other human diseases, the current knowledge of how TGF- β pathways lead to various neurological abnormalities is limited. Many studies are rather descriptive than mechanistic. We hope that this article will provide a basis for future research aimed at providing more mechanistic insights into neurological abnormalities stemming from deregulation of TGF- β signaling, which are essential for the future development of targeted therapies.

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