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The Dynamic Role of Bone Morphogenetic Proteins in Neural Stem Cell Fate and Maturation

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Abstract

The bone morphogenetic proteins (BMPs) are a group of powerful morphogens that are critical for development of the nervous system. The effects of BMP signaling on neural stem cells are myriad and dynamic, changing with each stage of development. During early development inhibition of BMP signaling differentiates neuroectoderm from ectoderm, and BMP signaling helps to specify neural crest. Thus modulation of BMP signaling underlies formation of both the central and peripheral nervous systems. BMPs secreted from dorsal structures then form a gradient which helps pattern the dorsal–ventral axis of the developing spinal cord and brain. During forebrain development BMPs sequentially induce neurogenesis and then astrogliogenesis and participate in neurite outgrowth from immature neurons. BMP signaling also plays a critical role in maintaining adult neural stem cell niches in the subventricular zone (SVZ) and subgranular zone (SGZ). BMPs are able to exert such diverse effects through closely regulated temporospatial expression and interaction with other signaling pathways.

Keywords

BMP; neural stem cells; patterning; neurogenesis; gliogenesis

Introduction

Neural stem cells are multipotent progenitors that can differentiate into neurons, astrocytes, and oligodendrocytes in the central nervous system (CNS). Neural crest progenitor cells generate neurons or Schwann cells in the peripheral nervous system (PNS). Bone morphogenetic proteins (BMPs) are a class of morphogens that are critical for establishing tissue structure throughout the body. Though they were first discovered for their osteoinductive properties, it is now evident that BMP signaling is a pivotal regulator of stem cells in both the CNS and PNS. BMP signaling exhibits a dynamic range of functions and plays a role in neural stem cell fate and maturation at virtually every stage of neural development. BMP signaling is tightly regulated both temporally and spatially, and the effects of BMP signaling are modulated by other spatially and temporally specific signals. This four dimensional specificity enables BMPs to have wide ranging and often opposing effects during distinct stages of development. Here, we elaborate the changing role of BMP signaling in neural stem cell fate and maturation.

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Mechanisms of BMP Signaling

BMP Ligands and Their Receptors

BMPs are members of the transforming growth factor beta (TGFβ) superfamily of signaling ligands. Over 30 different BMPs have been identified across various species, and they can be divided into numerous subgroups based on structural similarities (Table 1). One subgroup composed of BMP2 and BMP4 in vertebrates and decapentaplegic (Dpp) in drosophila plays a particularly major role throughout CNS development (Mehler et al, 1997). Other members, such as BMP6, BMP7, and BMP9, are also critical during certain developmental events. BMPs are initially synthesized as large precursor proteins which dimerize and are then proteolytically cleaved at a consensus Arg-X-X-Arg site (Wozney et al., 1988; Rosen et al., 1989; Israel et al., 1992, 1996). The resulting carboxy-terminal mature dimers, which are generally held together by an intermolecular disulfide bond, are then secreted from the cell (Daopin et al., 1992; Schlunegger and Grutter, 1992; Griffith et al., 1996).

Mature BMP dimers exert their effects by binding to BMP receptors (BMPRs) on neighboring cells (paracrine) or on the cell that secreted the signal (autocrine). BMPRs are tetrameric complexes composed of pairs of Type I and Type II serine/threonine kinase receptor subunits (Fig. 1) (Wrana et al., 1992; Massague, 1998). BMP ligands bind with high affinity when both receptor subunits are preassembled in the membrane, but they may also bind one subunit and then recruit the other subunit to the complex. Each BMP family member has a unique affinity for different combinations of receptor subunits. For example, BMP2 and BMP4 preferentially bind to two kinds of Type I receptors (BMPRIa/Alk3 and BMPRIb/Alk6) and one kind of Type II receptor (BMPRII). Type II receptors are constitutively active kinases which, upon ligand binding, transphosphorylate and activate Type I receptors. Type I receptors in turn phosphorylate intracellular targets that mediate their downstream effects (Fig. 1).

Expression patterns of the three BMPRs (BMPRIa, BMPRIb, and BMPRII) do not always overlap and fluctuate with development. Though structurally similar, BMPRIa and BMPRIb have different expression patterns in the mammalian nervous system. After gastrulation BMPRIa is expressed in neural tube proliferative zones. In contrast, BMPRIb expression is not detectable until embryonic day 9 and is restricted to the dorsal aspect of the neural tube (Dewulf et al., 1995). BMPRII expression in the developing embryo is primarily restricted to proliferative regions in the CNS (Zhang et al., 1998). All three receptors are also expressed in the adult, with BMPRIa more abundant and broadly distributed than BMPRIb and BMPRII. BMPRIa is expressed heterogeneously in gray matter structures, while strong BMPRIb expression is localized to the anterior olfactory nucleus. BMPRII is found in all regions of the hippocampus as well as in the cerebellar Purkinje layer (Zhang et al., 1998).

Differences in BMPR expression patterns reflect their individual functions. BMPRIa signaling both maintains precursor cell proliferation and induces BMPRIb expression. Predominant BMPRIb signaling induces mitotic arrest through either differentiation or apoptosis (Panchision et al., 2001). Functional differences between the two Type I receptors have also been demonstrated in mice with conditional Olig1-lineage BMPRIa ablation. In these mice, disproportionate numbers of cortical oligodendrocytes and interneurons are formed, indicating that BMPRIb signaling cannot compensate for loss of BMPRIa signaling (Brederlau et al., 2004; Samanta et al., 2007). However, in other aspects of development, such as limb patterning and cerebellar formation, the roles of BMPRIa and BMPRIb are not as distinct, indicating that BMPR subunit function is flexible and cell-type specific (Yi et al., 2000; Ahn et al., 2001; Qin et al., 2006).

BMP Signaling Pathways

In *C. elegans* the downstream signaling molecule Sma is phosphoyrlated by BMP-orthologs, and in Drosophila Mothers against dpp (Mad) is similarly activated (Sekelsky et al., 1995; Savage et al., 1996). Vertebrate members of this protein family, named Smad (fusion of Sma and Mad), constitute the canonical intracellular pathway of BMP signaling (Fig. 1). Receptor-regulated Smads (R-Smads) −1/5/8 are directly phosphorylated and activated by BMPRIa and BMPRIb at their C-terminus (Wrana, 2000). These in turn bind with co-Smad4, and the resulting heteromeric complex translocates into the nucleus (Hoodless et al., 1996; Heldin et al., 1997; Nishimura et al., 1998; Kawai et al., 2000). Once in the nucleus, the complex interacts with transcription factors as well as co-activators/repressors to modulate gene expression.

There are also a number of non-canonical pathways for BMP signaling, adding complexity to its downstream mechanisms. X-chromosome-linked inhibitor of apoptosis (XIAP) mediates signaling between BMP receptors and TAB1, an activator of TAK1, which is a member of the MAP kinase kinase kinase family (Shibuya et al., 1996, 1998; Shirakabe et al., 1997; Yamaguchi et al., 1999; Takaesu et al., 2000; Nohe et al., 2003; Matluk et al., 2010). During early development the XIAP-TAB1-TAK1 pathway is proposed to mediate BMP signaling's switch from a proliferation to an apoptosis signal through neurotrophin receptor interacting MAGE (NRAGE)-mediated activation of p38 (Kendall et al., 2005). Another non-canonical mediator of BMP signaling is the LIM-domain-containing protein kinase 1 (LIMK1). LIMK1 associates with the carboxy tail of BMPRII and is important for actin stabilization and neurite outgrowth (Foletta et al., 2003; Lee-Hoeflich et al., 2004; Eaton and Davis, 2005; Matsuura et al., 2007; Hocking et al., 2009).

Inhibition of BMP Signaling

While BMP signaling is crucial for many events in development, its inhibition is equally necessary for others. As a result, there are a number of extracellular and intracellular mechanisms that block the influence of BMP signaling. Extracellular signaling is inhibited by competitive binding of BMPR ligands with more than 20 different antagonists, including noggin, chordin, dan, cerebrus, twisted gastrulation, follistatin, and others (Fig. 1) (Holley et al., 1996; Piccolo et al., 1996; Zimmerman et al., 1996; Fainsod et al., 1997); for a review of BMP inhibitors see (Rider and Mulloy, 2010). These proteins seem to have evolved independently of one another as there is little primary sequence similarity amongst them. Moreover, these inhibitors have different binding affinities for various BMP ligands, and some inhibit other signaling pathways as well. For example, follistatin binds a number of BMP family members, but binds Activan A with the highest affinity. Cerebrus binds BMP2, BMP4, and BMP7, but it also binds members of the Wnt family. Similarly, twisted gastrulation acts as a competitive antagonist of BMP signaling but also may act as an agonist by enhancing cleavage of BMP-chordin complexes. At each stage of development a unique cocktail of inhibitors works to specifically target the impact of BMPs.

BMP signaling can also be inhibited intracellularly by blocking downstream signaling pathways. Inhibitory Smads (I-Smads) −6 and −7 directly compete with R-Smads for binding Type I receptors, preventing R-Smad phosphorylation (Fig. 1). I-Smads can also bind with Co-Smads to prevent nuclear translocation of phosphorylated R-Smads (Itoh et al., 2001). Some BMPs, such as BMP7, can induce expression of Smad-6 and −7, suggesting that BMPs can self-regulate through a negative feedback loop. Smad ubiquitin regulatory factors (Smurfs) target R-Smads for ubiquitin mediated degradation (Lo and Massague, 1999; Zhu et al., 1999). BAMBI (BMP and Activin membrane-bound inhibitor) is a Xenopus pseudoreceptor (mammalian homologue, Nma) that contains an extracellular domain similar to the Type I receptors, but lacks the catalytic intracellular domain

(Onichtchouk et al., 1999; Grotewold et al., 2001). This allows single BAMBI subunits to bind Type I receptor subunits, creating an unstable dimer that prevents formation of active BMP receptor complexes.

BMPs in Early CNS Development and Patterning

BMP signaling is a potent regulator of CNS development and patterning. Initially BMP signaling promotes the formation of non-neural ectoderm and inhibition of BMP signaling is required to establish primitive neural tissue (neuroectoderm). Thereafter BMP gradients are essential for patterning the dorsal–ventral axis. Thus, BMP signaling in early embryonic stem cells plays a major role in sculpting the CNS.

BMP Inhibition Induces Neuroectoderm

The level of BMP signaling determines the fate of embryonic ectodermal stem cells as either epidermal or neuroectodermal [Fig. 2(A,B)]. In Xenopus embryos, neural tissue formation is normally restricted to the dorsal side of the embryo. However, when dorsal tissue was transplanted on the ventral side of the embryo, neural tissue formed at the expense of epidermal tissue (Spemann and Mangold, 1924). This dorsal tissue contains a collection of cells called the Spemann organizer which express BMP antagonists noggin, chordin, and follistatin (Smith and Harland, 1992; Smith et al., 1993). Ectopic expression of noggin on the ventral side of Xenopus embryos demonstrates that inhibition of BMPs induces neural fate (Lamb et al., 1993). In addition, blocking BMP signaling through overexpression of dominant-negative Type I receptors or dominant-negative forms of BMP4 and BMP7 promotes neurulation (Hemmati-Brivanlou and Melton, 1994; Hawley et al., 1995; Wilson and Hemmati-Brivanlou, 1995). Alternatively, depletion of BMP antagonists inhibits neuroectoderm formation (Oelgeschlager et al., 2003; Kuroda et al., 2004; Khokha et al., 2005). The role of BMP signaling in neurulation is highly conserved among species including both vertebrates and non-vertebrates; for example, the drosophila BMP antagonist Short gastrulation (SOG) mimics the effects of chordin in vertebrates and vice versa (Holley et al., 1995; Schmidt et al., 1995). These findings demonstrate that neuroectoderm is the default fate of naïve ectoderm and that active BMP signaling is required to form non-neural tissue.

Neural induction in the embryo cannot progress simply in the presence of BMP antagonists, but instead requires coordination with multiple other signals including fibroblast growth factor (FGF) and insulinlike growth factor (IGF). FGF signaling downregulates BMP4 and BMP7 expression and is required for neural fate acquisition (Ishimura et al., 2000; Wilson et al., 2000). In addition, FGF and IGF signaling pathways negatively regulate Smad phosphorylation to inhibit downstream BMP signaling (Pera et al., 2001, 2003). Normally, BMPRI phosphorylates Smad on its C-terminus leading to nuclear localization. However, in the presence of FGF or IGF, MAPK phosphorylates Smad on its linker region, preventing translocation to the nucleus. These molecular insights explain why BMP signaling seems to oppose the effects of FGF, IGF, and other growth factors that activate tyrosine kinase receptors (Liu and Niswander, 2005).

Neural Crest Formation

After closure of the neural tube, a column of multipotent stem/progenitor cells—the neural crest—forms along the dorsal aspect of the neural tube at the border of ectoderm and neuroectoderm. These cells give rise to the sympathetic, peripheral sensory, and enteric nervous systems, as well as a variety of other cells such as melanocytes and facial osteocytes. When explant cultures from early neural tissue are exposed to BMP4 or BMP7 they give rise to neural crest, suggesting that BMP signaling plays a role in neural crest

induction (Liem et al., 1995). Given the location of the neural crest between high levels of BMP in the ectoderm and low levels of BMP signaling in neuroectoderm, a hypothesis has emerged that an intermediate level of BMP signaling is necessary for proper induction of neural crest [Fig. 2(C)] (Huang and Saint-Jeannet, 2004). Evidence supporting this idea comes from Xenopus studies where exacerbated BMP4 expression leads to reduction of neural crest markers, whereas overexpression of BMP antagonists expands neural crest (Mayor et al., 1995; Marchant et al., 1998). Similarly, zebrafish mutations in BMP signaling members, such as snailhouse (BMP7), swirl (BMPRIIb), and somitobun (Smad5), lead to reduced neural crest formation (Kishimoto et al., 1997; Nguyen et al., 1998, 2000; Hild et al., 1999; Dick et al., 2000; Schmid et al., 2000). However, the level of BMP signaling alone cannot account for neural crest induction, and other signaling pathways including WNT, FGF, and Notch are also crucial for neural crest formation (Coffman et al., 1993; Kengaku and Okamoto, 1993; Saint-Jeannet et al., 1997; LaBonne and Bronner-Fraser, 1998); for review see Sauka-Spengler and Bronner-Fraser (2008). This suggests a multistep process in which BMP signaling sensitizes cells to assume a neural crest identity, while other signaling pathways maintain this identity (Liu and Niswander, 2005).

A Gradient of BMPs Establishes Spinal Cord Patterning

Gradients of BMP signaling also play a central role in development of the spinal cord, which arises from the neural tube. BMPs are secreted from the ectoderm and the dorsal most aspect of the neural tube known as the roof plate. BMP2, BMP4, BMP7 as well as activin and GDF7 are expressed by the ectoderm and neural tube roof plate and form a dorsal–ventral concentration gradient of BMP signaling [Fig. 2(C)] (Basler et al., 1993; Liem et al., 1995; Lee et al., 1998). When this gradient of BMPs is perturbed, the balance of dorsal to ventral neurons becomes skewed. For example, loss of BMP secreting structures results in loss of the dorsal most population of sensory interneurons (marked by LIM homeodomain transcription factors 2a and 2b), which arise from Math1+ precursor cells (Lee et al., 2000; Millonig et al., 2000). Similarly, deletion of both BMPRIa and Ib from the dorsal spinal cord leads to a complete loss of the dorsal most dI1 interneurons with a concurrent dorsal expansion of more ventral dI3 and dI4 interneurons (Wine-Lee et al., 2004). Inhibition of BMP signaling through mis-expression of noggin or knockdown of Smad4 also causes loss of dI1 interneurons and expansion of dI2-4 interneurons (Chesnutt et al., 2004). In contrast, overexpression of BMPRIa and Ib in chick or mouse embryos leads to an expansion of dorsal and intermediate interneurons at the expense of ventral interneurons (Panchision et al., 2001; Timmer et al., 2002). It is increasingly evident that differentiation of some specific spinal cord interneuron subtypes is directly dependent on the BMP signaling gradient. Lim1+ intermediate interneurons are increased in various zebrafish BMP mutants such as swr, sbn, and snh. Strikingly, a further decrease of BMP signaling through overexpression of chordin in the swr mutants results in a decrease of Lim1+ cells, suggesting that cell type specification is dependent upon specific ranges of BMP signaling (Nguyen et al., 2000). Moreover, NGN1+ interneurons are lost in embryos that have either high levels or no expression of BMPs, while a ventral expansion of NGN1+ cells is seen with low levels of BMPs (Lee et al., 2000; Timmer et al., 2002).

Sonic Hedgehog (Shh) secreted from the floor plate and notochord directly opposes the dorsalizing effects of BMP signaling and promotes ventral patterning of the spinal cord [Fig. 2(C)] (Chiang et al., 1996). However, active inhibition of BMP signaling is also required for proper ventralization. BMP inhibitors, such as noggin and follastin, are expressed in the notochord, and knockout of noggin results in loss of ventral interneurons and progenitors, such as those expressing Nkx2.2 (McMahon et al., 1998; Liem et al., 2000). In addition, expression of Smad7 in intermediate spinal cord confines BMP signaling to dorsal spinal cord (Hazen et al., 2011). Interestingly, BMP signaling rapidly induces noggin expression,

establishing an effective feedback loop that limits the effects of BMP signaling (Akizu et al., 2010). As a whole these studies suggest that discrete levels of BMP signaling are required for spinal cord dorsalization and for proper patterning.

Once spinal cord neurons have differentiated, BMP signaling influences their axonal projections. Commissural neuron axons grow ventrally, away from the roof plate, due to the repulsive effects of BMP7 and GDF7 (Augsburger et al., 1999; Butler and Dodd, 2003). Roof plate explants affect axon orientation of cultured neurons through the actions of BMPs secreted from the roof plate. Furthermore, BMPRIb, but not BMPRIa, mediates the effects of BMPs on axonal projections in the spinal cord (Yamauchi et al., 2008).

BMPs also regulate spinal cord proliferation. When noggin is over-expressed in the neural tube, proliferation is decreased, implying that BMP signaling promotes proliferation (Chesnutt et al., 2004). BMP-induced proliferation is mediated, in part, by Wnt signaling, another group of morphogens important for embryonic patterning (Zechner et al., 2003). Deletion of BMPRIa and Ib in double-knockout mice reduces Wnt1 and Wnt3a expression, suggesting that BMPs induce Wnts (Wine-Lee et al., 2004). Moreover, Wnt signaling has been shown to induce BMP signaling by increasing the levels of phosphorylated Smad1/5/8 (Ille et al., 2007). These studies propose that Wnt signaling mediates BMP-induced proliferation through a positive feedback loop and illustrate how the effects of BMPs can change through interaction with other signaling pathways.

BMP Signaling Patterns the Forebrain and Cerebellum

As in the spinal cord, BMPs secreted from the dorsal midline pattern brain structures such as forebrain and cerebellum. BMPs are secreted from two signaling centers in the dorsal midline of the telencephalon, the roofplate and cortical hem. These BMPs promote dor-somedial identity and local apoptosis (Furuta et al., 1997). Forebrain explants exposed to BMP4 down-regulate anterior forebrain markers, whereas deletion of BMP antagonists causes loss of anterior brain structures (Anderson et al., 2002). BMPRIa knockout in telencephalon results only in loss of the most dor-salmedial derivative, choroid plexus, whose progenitors remained proliferative and cannot differentiate (Hebert et al., 2002). In contrast, double-knockout of BMPRIa and Ib in dorsal telencephalon causes holoprosencephaly and complete loss of all dorsal midline cell types (Fernandes et al., 2007). However, when BMP signaling is conditionally knocked out only after neural tube closure, holoprosencephaly does not occur, but there are serious defects in dentate gyrus formation (Caronia et al., 2010).

Cerebellar granule neurons originate in the rhombic lip, part of the rhombencephalon, located adjacent to the dorsal midline. BMPs secreted from the dorsal midline initiate the differentiation of granule neurons by inducing expression of granule neuron markers, such as the basic helix-loop-helix (bHLH) transcription factor Math1 (Alder et al., 1999). Multiple BMPs work in concert to promote granule neuron differentiation through distinct mechanisms. BMP2 suppresses the proliferative effect of Shh signaling through phosphorylation of Smad5 and initiates differentiation by causing exit from cell cycle (Rios et al., 2004). BMP4 stimulates granule neuron differentiation by increasing Smad1 expression and translocating it to the nucleus (Angley et al., 2003). BMP6 promotes granule neuron survival through non-canonical activation of the MEK/ERK/CREB pathway (Barneda-Zahonero et al., 2009). Furthermore, double-knockout of BMPRIa and Ib results in severe cerebellum patterning defects and almost complete loss of granule neurons, despite correct specification of Purkinje cells (Qin et al., 2006). Single knockout of BMPRIa or Ib displays no defects, demonstrating the functional redundancy of Type I BMPRs in cerebellar development.

BMPs in Forebrain Cell Fate Specification

Neural fate specification involves both acquisition and maintenance of a particular phenotype and suppression of all other phenotypes. This manifests as a cell type-specific transcriptional profile in which some gene expression is stimulated, while other gene expression is repressed. For example, to commit to the neuronal lineage progenitors must express pro-neuronal genes and inhibit expression of astrocyte-and oligodendrocyte-specific genes. Remarkably, BMP signaling is critical for progenitor fate specification in both neurogenesis and later in astrogliogenesis through dynamic transcriptional regulation.

Neurogenesis

During neural fate specification, BMP signaling initially promotes neurogenesis by pushing progenitors toward a neuronal fate and suppressing the oligodendroglial fate (Li et al., 1998; Mabie et al., 1999; Mehler et al., 2000; Moon et al., 2009). BMP signaling induces expression of the neuron-specific class II beta-tubulin (Tuj1) through activation of the extracellular-signal-related kinase (ERK) pathway (Moon et al., 2009). This mechanism of neuronal induction is similar to that of other pro-neurogenic growth factors, such as platelet-derived growth factor (PDGF) (Menard et al., 2002; Moon et al., 2009). BMP signaling's role in neuronal fate specification can be dissociated from its suppression of oligodendroglial differentiation, suggesting separate mechanisms which will be discussed later (Mabie et al., 1999). Notably, BMP signaling switches from a pro-neuronal to pro-astroglial cue towards the end of neurogenesis, before the transition to gliogenesis (Mabie et al., 1999; Mehler et al., 2000). Levels of expression of the pro-neuronal bHLH transcription factor neurogenin (Ngn1) help to regulate the changing role of BMP signaling in cell fate determination. Ngn1 expression is tightly linked to the time course of neurogenesis; it is highly expressed during the peak of neurogenesis and gradually decreases with the transition to gliogenesis (Ma et al., 1996). During the peak of neurogenesis high levels of Ngn1 expression are thought to contribute to the pro-neuronal effects of BMPs. As neurogenesis proceeds, Ngn1 then works to suppress BMP-mediated astrocyte differentiation by sequestering downstream transcriptional regulators away from glial gene promoters, such as the glial fibrillary acid protein (GFAP) promoter (Sun et al., 2001). As Ngn1 expression diminishes during with the transition to gliogenesis, the pro-astroglial effects of BMP signaling are unmasked. Together these data suggest that the temporally restricted expression of Ngn1 regulates, at least in part, the transition of BMP signaling from being pro-neuronal to being pro-astroglial.

Neuronal Subtype Specification

Different BMP family members are highly expressed in embryonic signaling centers and are critical for the specification of certain CNS cell types. For example, BMP9 is transiently expressed in the embryonic septum during a critical period for basal forebrain cholinergic neuron (BFCN) development. Treatment of septal cultures with BMP9 induces the BFCN phenotype and transcriptome, suggesting that BMP9 may be sufficient for the generation of BFCNs (Lopez-Coviella et al., 2000, 2005). Recent work done with human embryonic stem cells confirms that BMP9 induces expression of two transcription factors, Lhx6 and Gbx1, which are necessary and sufficient to generate basal forebrain cholinergic neurons (Bissonnette et al., 2011). BMP signaling in the cortex also determines the fate of GABAergic interneuron precursors, promoting differentiation of parvalbumin-positive interneurons and blocking differentiation of calbindin- and somatostatin-positive interneurons (Samanta et al., 2007; Mukhopadhyay et al., 2009).

Neurite Outgrowth

After neurogenesis has been completed, BMP signaling regulates neurite outgrowth and dendritogenesis in post-mitotic neurons 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). BMP-mediated dendritogenesis is transduced non-canonically through BMPRII and requires local cytoskeleton rearrangement by LIMK1. Activated LIMK1 regulates actin dynamics by phosphorylating and inactivating actin depolymerizing proteins like actin-depolymerizing factor (ADF) and cofilin (Foletta et al., 2003). Interestingly, ADF/cofilin-mediated actin dynamics regulate AMPAR trafficking during synaptic plasticity in cultured hippocampal neurons (Gu et al., 2010). The Drosophila homologue to BMPRII, wishful thinking, also regulates actin dynamics and synaptic stability through LIMK, suggesting that this mechanism of dendritogenesis is evolutionarily conserved (Eaton and Davis, 2005). In addition to regulating actin dynamics, signaling through BMPRII stabilizes dendritic microtubules through another kinase, c-Jun N-terminal kinase (JNK) (Podkowa et al., 2010). Together, these studies demonstrate that non-canonical signaling through BMPRII regulates cytoskeletal rearrangements and ultimately dendritogenesis in post-mitotic neurons.

Astrogliogenesis

During the late embryonic and postnatal periods BMP signaling promotes astroglial differentiation (Gross et al., 1996; Mehler et al., 2000). Similarly, members of the ciliary neurotrophic factor-leukemia inhibitory factor (CNTF-LIF) cytokine family are also potent astrocytic differentiation factors that operate through activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway (Bonni et al., 1997). LIF-STAT3 and BMP-Smad signaling cascades synergize to promote astrocytic differentiation by activating the GFAP promoter through a STAT3-p300/CBP-Smad1 complex (Nakashima et al., 1999). p300 and CBP (CREB-binding protein) are co-activating proteins that interact with multiple transcription factors to enhance expression of their target genes. However, BMP-mediated astroglial fate commitment may also occur by non-canonical mechanisms. Under high density conditions BMP4 treatment has been reported to activate STAT proteins through the serine-threonine kinase FKBP12/rapamycin-associated protein (FRAP), mammalian target of rapamycin (mTOR) (Rajan et al., 2003). FKBP12 is sequestered to the BMPRIa receptor and, upon BMP4 binding, is released to activate FRAP. FRAP in turn catalyzes phosphorylation of STAT, which ultimately promotes astrocytic gene expression. This suggests that BMP-and LIF-mediated astroglial fate commitment can occur through distinct mechanisms and may explain in part why LIF and BMP signaling generate different types of astrocytes. LIF signaling promotes the generation of GFAP+ progenitor cells, while BMP signaling promotes the generation of mature GFAP+ astrocytes which lack stem/progenitor cell properties (Bonaguidi et al., 2005).

In addition to promoting an astrocytic identity, BMP signaling also activates downstream signals that inhibit oligodendroglial and neuronal lineage commitment (Gross et al., 1996, Mehler et al., 2000). BMPs induce expression of the Hes (homologue of hairy and enhancer of split) and Id (inhibitor of differentiation) gene families, which negatively regulate bHLH transcription factors. Oligodendrogenesis is promoted by the bHLH transcription factors Olig1 and Olig2 (Ross et al., 2003). BMP-induced expression of Id2 and Id4 in neural progenitors prevents oligodendrocyte lineage commitment by binding Olig1 and Olig2 and sequestering them away from their targets (Samanta and Kessler, 2004). bHLH transcription factors such as Mash1 (mammalian achaete-scute homologue), neurogenin, and NeuroD promote neurogenesis and are negatively regulated by Hes-1, Hes-5 and the Id family of proteins (Bertrand et al., 2002; Ross et al., 2003). Exposure to BMP2 upregulates the expression of Id1, Id3, and Hes-5 in neural progenitors, which inhibits neuronal

differentiation and promotes astroglial commitment (Nakashima et al., 2001). As mentioned earlier, fate specification requires both acquisition and maintenance of a particular phenotype. BMP-induced expression of the Ids and Hes-5 is transient and likely contributes to the acquisition but not the maintenance of the astrocytic fate (Nakashima et al., 2001; Kohyama et al., 2010). Thus, BMPs rely on the transcriptional repressor RE1 silencer of transcription/neuron-restrictive silencer factor (REST/NRSF) for continual suppression of neuronal gene expression. Canonical BMP signaling upregulates and sustains expression of REST/NRSF, which blocks neuronal gene expression throughout the life of the astrocyte (Kohyama et al., 2010).

BMP Signaling in Adult Neurogenesis

Though the mammalian brain continues to develop postnatally, by adulthood most regions of the brain no longer maintain a dividing progenitor population. The subventricular zone (SVZ) of the forebrain and the subgranular zone (SGZ) of the hippocampus are the only two regions that contain stem cell niches and continue to generate new neurons in adulthood. Both regions contain stem cells that self-renew and can give rise to all neural lineages (Altman and Das, 1965; Morshead et al., 1994; Palmer et al., 1997; Bonaguidi et al., 2008; Walker et al., 2008). As might be expected, similar signaling systems are important during developmental and adult neurogenesis, including BMP signaling.

Subventricular Zone Neurogenesis

The SVZ is located along the lateral ventricles and is made up of various cell types. Ependymal cells line the ventricle to provide a barrier between ventricular cerebrospinal fluid and the niche, and there are suggestions that ependymal cells themselves have stem cell properties (Johansson et al., 1999). Adjacent to the ependymal cells is the subependymal layer which consists of radial glial-like stem cells (Type B), transient amplifying progenitors (TAPs) (Type C), and neuroblasts (Type A) (Ihrie and Alvarez-Buylla, 2011). Neurogenesis starts when radial glial-like stem cells divide to give rise to TAPs which rapidly divide and become neuroblasts [Fig. 3(A)]. BMP2, 4, and 7 are expressed in radial glial-like stem cells and TAPs, but not in ependymal cells or neuroblasts (Lim et al., 2000; Peretto et al., 2002); noggin is expressed in ependymal cells (Lim et al., 2000; Peretto et al., 2002). BMP signaling in the SVZ promotes astroglial lineage commitment and inhibits the differentiation of neurons and oligodendrocytes (Lim et al., 2000; Colak et al., 2008). In contrast, noggin suppresses astroglial lineage commitment (Chmielnicki et al., 2004). Interestingly, BMP signaling also seems to promote the survival of dividing neuroblasts which have already committed to the neuronal lineage (Lim et al., 2000; Colak et al., 2008). Brain-derived neurotrophic factor (BDNF) is also an important regulator of adult neurogenesis in the SVZ (Ahmed et al., 1995; Kirschenbaum and Goldman, 1995), and overexpression of BDNF in SVZ induces addition of neurons to the olfactory bulb and striatum (Benraiss et al., 2001). Notably, co-overexpression of noggin along with BDNF results in a marked and sustained increase in recruitment of new medium spiny neurons to the striatum, which is usually non-neurogenic (Chmielnicki et al., 2004; Benraiss et al., 2011). Long-term overexpression of BDNF/noggin in SVZ is sufficient to maintain ongoing addition of medium spiny neurons to striatum and delays motor impairment and increases survival of a mouse model of Huntington's disease (Cho et al., 2007; Benraiss et al., 2011). These behavioral effects require the synergy of BDNF and noggin and their positive effects on neurogenesis. As during development, it is likely that BMP signaling in adult SVZ has differential effects at various stages of the lineage and interacts with other signaling pathways.

Subgranular Zone Neurogenesis

In the hippocampus, the SGZ is the innermost layer of the dentate gyrus, adjacent to the hilus. The SGZ contains no ependymal cells, but still contains radial glial-like stem cells which give rise to TAPs that divide to form neuroblasts [Fig. 3(B)]. Neuroblasts migrate radially into the granule cell layer and mature into dentate granule cells. Postnatally BMPs, their receptors, and noggin are expressed in the dentate gyrus (Charytoniuk et al., 2000; Fan et al., 2003a; Mikawa et al., 2006; Sato et al., 2010; Mikawa and Sato, 2011), however, it is not exactly known which cell types express the receptors and secreted factors.

The existence of bona fide stem cells in the SGZ has been a contentious topic in the field of neurogenesis (Bonaguidi et al., 2011; Encinas et al., 2011; Kempermann, 2011). Cultured SGZ stem cells require the addition of either noggin or depolarizing levels of KCl to propagate *in vitro*, however, these treatments have no effect on SVZ stem cells (Bonaguidi et al., 2008, Walker et al., 2008). The fact that noggin specifically unveils the self-renewal capacity of SGZ neural stem cells suggests that BMP signaling is a critical factor in regulating adult hippocampal neurogenesis. *In vivo* noggin treatment increases neurogenesis and neuronal commitment (Gobeske et al., 2009, Mira et al., 2010), while exacerbated BMP signaling in the dentate gyrus decreases neurogenesis (Fan et al., 2003b) and promotes astroglial lineage commitment (Brederlau et al., 2004; Bonaguidi et al., 2005). One study proposes that long-term noggin treatment depletes the stem cell pool, suggesting that stem cells in the SGZ have a limited capacity to self-renew (Mira et al., 2010). However, other studies find that the proneurogenic effects of noggin are enduring and renewable (Bonaguidi et al., 2008, Gobeske et al., 2009; Guo et al., 2011). Though there is dissonance regarding the exact role of BMP signaling in the SGZ, it is clear that the antagonistic balance between noggin and BMPs is critical to the regulation of adult hippocampal neurogenesis.

Adult SGZ neurogenesis is influenced by various factors such as exercise, environmental enrichment, and aging. Not surprisingly, BMP signaling may be involved in modulating neurogenesis under these conditions. Neurogenesis is required for the formation of hippocampus-dependent memory (Saxe et al., 2006; Deng et al., 2009; Marin-Burgin and Schinder, 2011). Because BMP signaling limits neurogenesis, it could be hypothesized that BMP signaling also limits the formation of new memories. In fact, increased BMP signaling results in cognitive impairments on hippocampus-dependent tasks whereas decreased BMP signaling improves cognition (Fan et al., 2003b; Gobeske et al., 2009). Running is known to enhance SGZ neurogenesis and proliferation (van Praag et al., 1999) and has been associated with increased levels of noggin coincident with decreased levels of BMP4 protein in the hippocampus (Gobeske et al., 2009). Additionally, overexpression of BMP4 seems to block the neurogenic effect of running (Gobeske et al., 2009). SGZ neurogenesis declines with age (Kuhn et al., 1996; Knoth et al., 2010) and in mouse models of Alzheimer's disease (AD) (Rodriguez and Verkhratsky, 2011). Both decreased neurogenesis and an increase in BMP4 or BMP6 levels have been associated with mouse models of AD (Li et al., 2008; Crews et al., 2010). Additionally, infusion of noggin rescues the decrease in neurogenesis associated with models of AD (Tang et al., 2009). Together these studies suggest that changes in adult neurogenesis caused by environmental factors are modulated by BMP signaling.

Conclusion

BMP signaling affects neural stem cell fate and maturation at almost every stage of CNS development, from neurulation through adult life (Fig. 4). Spatiotemporal signals mediate its effects, enabling BMP signaling to exert a wide range of functions. In addition to its role in development, recent studies implicate BMP signaling in the cognitive decline associated with normal aging and neurodegenerative diseases. Continued study of the role of BMP

signaling in neural stem cells will have important clinical implications and could lead to novel therapeutic targets.

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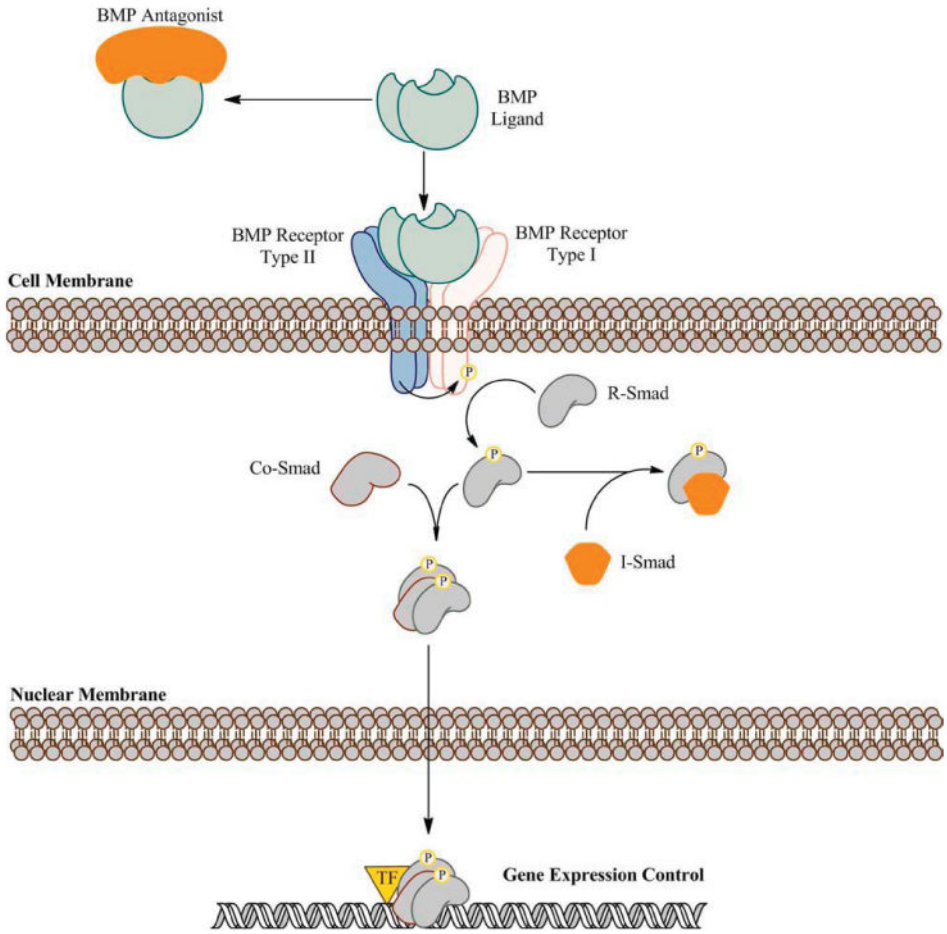

Figure 1.
Canonical BMP signaling. BMP signaling is transduced by a series of phosphorylation events. When BMP ligands bind their receptors, BMP Type II receptors transphosphorylate Type I receptors, which in turn phosphorylate R-Smads. Activated R-Smads bind with Co-Smads and translocate into the nucleus. In the nucleus, the R-Smad-Co-Smad complexes interact with transcription factors (TF) and other coregulatory proteins to control gene expression. BMP signaling can be inhibited extracellularly by antagonists, such as Noggin, which competitively bind BMP ligands. Intracellulary, inhibitory Smads (I-Smads) bind to activated R-Smads and prevent their binding with Co-Smads. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

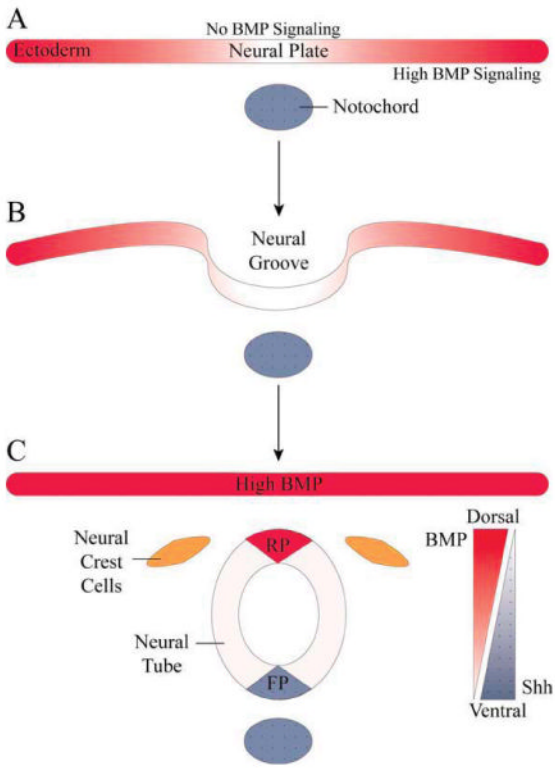

Figure 2.

BMP signaling during neurulation. A: A gradient of BMP signaling is established in ectoderm by BMP inhibitors. Neural plate formation is induced where BMP signaling is absent. B: The neural plate folds to create the neural groove and finally pinches off from the overlying ectoderm, forming the neural tube. C: The ectoderm and neural tube roof plate (RP) continue to secrete BMP ligands, which directly oppose ventrally secreted Shh from the notochord and floor plate (FP). The dual morphogen gradient of BMP and Shh establishes the dorsal–ventral axis and specifies neuron populations along this axis. Intermediate levels of BMPs induce neural crest cells. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

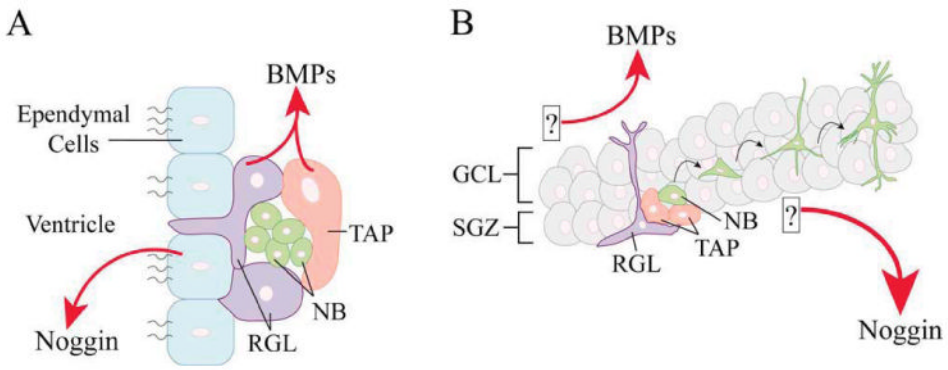

Figure 3.

BMP signaling in adult neurogenic niches. Adult brains contain two neurogenic niches, the SVZ and the SGZ. A: In the SVZ, radial glial-like (RGL) stem cells divide to give rise to transient amplifying cells (TAP) which rapidly divide to become neuroblasts (NB). These immature neurons travel through the rostral migratory stream to the olfactory bulb where they become interneurons. RGL stem cells and TAPs secrete BMP ligands, whereas ependymal cells secrete Noggin. BMP signaling in the SVZ promotes astroglial lineage commitment and promotes survival of neuronally committed neuroblasts. B: In the hippocampal SGZ of the dentate gyrus, RGL stem cells divide to give rise to TAPs, which in turn produce NBs, similar to the SVZ. NBs migrate radially into the granule cell layer (GCL) where they become mature dentate granule cells. Unlike in the SVZ, the sources of BMP ligands and Noggin have not yet been clearly identified in the SGZ. While noggin is required to maintain the proliferating, self-renewing population of stem cells, BMP signaling seems to block neurogenesis, indicating that a balance of BMP signaling regulates neurogenesis in the SGZ niche. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

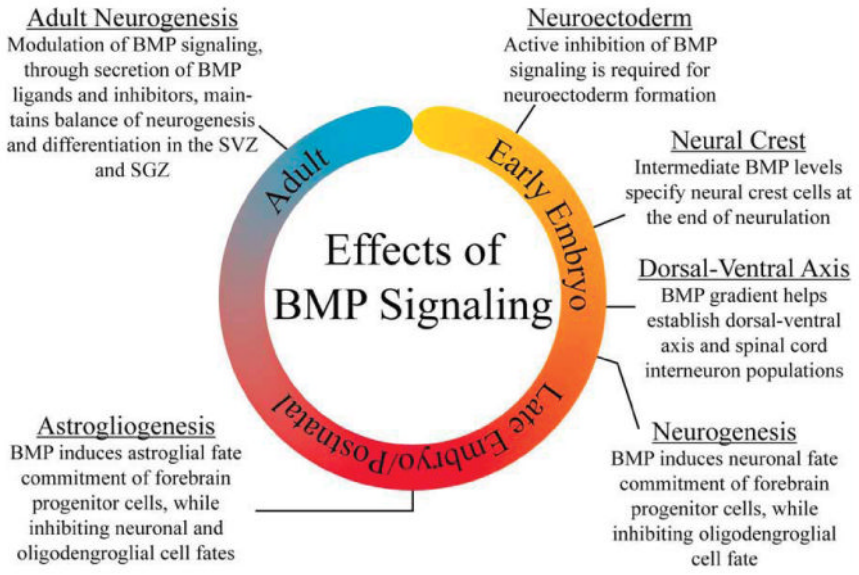

Figure 4.

The changing roles of BMP signaling. BMP signaling is involved in numerous aspects of neural stem cell development. Initially, inhibition of BMP signaling is required for neuroectoderm induction. A gradient of BMP signaling establishes the dorsal–ventral axis and specifies neural crest cells and distinct interneuron subgroups within the spinal cord. During forebrain development, BMP signaling promotes neuronal lineage commitment while inhibiting oligodendrocyte formation. In late embryogenesis and postnatally, BMP signaling changes to promote astroglial commitment while repressing commitment to the other two neural lineages. In adulthood, a balance of BMP signaling is critical for maintenance and differentiation of neural stem cell populations in the SVZ and SGZ. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

BMP Ligands Implicated in CNS Development and Maintenance

BMP Ligand	Selected References
BMP2	Mujtaba et al., 1998; Mabie et al., 1999; Sailer et al., 2005
BMP3b (GDF10)	Takao et al., 1996; Soderstrom and Ebendal, 1999
BMP4	Gross et al., 1996; Rajan and McKay, 1998; Pierani et al., 1999; Lillien and Raphael, 2000
BMP5	Vogel-Hopker and Rohrer, 2002; Holzschuh et al., 2005; Tilleman et al., 2010
BMP6	Schluesener and Meyermann, 1994; Gratacos et al., 2002; Crews et al., 2010
BMP7 (OP1)	Perides et al., 1992; Zhu et al., 1999; de Rivero Vaccari et al., 2009
BMP9 (GDF9)	Lopez-Coviella et al., 2005, 2006; Bissonnette et al., 2011
BMP11 (GDF11)	Wu et al., 2003; Kim et al., 2005; Shi and Liu, 2011
BMP12 (GDF7)	Lee et al,. 1998; Alder et al., 1999; Currle et al., 2005
BMP13 (GDF6)	Chang and Hemmati-Brivanlou, 1999; Hanel and Hensey, 2006; den Hollander et al., 2010
BMP14 (GDF5)	Krieglstein et al., 1995; O'Keeffe et al., 2004; Gajavelli et al., 2004