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REVIEW

BMP signaling pathway and spinal cord development

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Abstract **The development of spinal cord is a precisely and sequentially regulated process, which is controlled by signaling pathways and transcription factors in each stage. Overwhelming data have shown the essential roles of BMP signaling in different stages of this developmental process. It is also clear that the proper functions of BMP signaling require its cross-talk with several other signaling pathways including Notch, Wnt and retinoic acid (RA) pathways. Here, we highlight the recent advancement in understanding the roles of BMP signaling during neurogenesis, neural tube patterning, axon development and glial differentiation in the spinal cord, and emphasize its integrations with other pathways during these processes.**

Keywords BMP, spinal cord, neurogenesis, patterning, glia

Introduction

Precise spatiotemporal regulation of neural development is crucial for generating the complicated central nervous system (CNS) (Shen et al., 2006; Guillemot, 2007). In spinal cord development, neural progenitor cells (NPCs) are seemingly homogeneous at early neurodevelopmental stage (Alvarez-Buylla et al., 2001; Götz and Huttner, 2005; McConnell, 1995). As neurogenesis proceeds, part of NPCs progressively initiate the expression of proneural genes and homeodomain transcription factors (HD factors) to acquire different neuronal identities and to form neuronal pattern along the dorsal-ventral neural tube (Jessell, 2000). Subsequently, these cells differentiate into various nascent neurons and the newborn neurons undergo the dendrite and axon development for further maturation (Bertrand et al., 2002). After a neurogenic period to generate neurons, part of the remaining NPCs differentiate into different types of glial cells including astrocytes and oligodendrocytes (Bertrand et al., 2002). To rigorously control these neurodevelopmental processes, various signaling pathways such as bone morphogenetic protein (BMP), Wnt, retinoic acid (RA), sonic hedgehog (Shh) and Notch pathways are required, and their regulation networks are also important (Ciani and Salinas, 2005; Kasai et al., 2005; Liu and Niswander, 2005; Louvi and Artavanis-Tsakonas, 2006; Maden, 2007; Ruiz i Altaba et al., 2002). In this review, we discuss roles of the BMP signaling and its cross-talk with other pathways in spinal cord development including neurogenesis, neural tube patterning, axon development and glial differentiation.

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BMP signaling pathway

BMPs which contain at least eight different BMP proteins are members of the transforming growth factor-β (TGFβ) superfamily (Feng and Derynck, 2005). BMPs form a homomeric or heteromeric complex binding to BMP receptors (BMPRs) (Liu and Niswander, 2005). After binding with different BMP ligands, BMPRs are phosphorylated, resulting in phosphorylation of different members of the receptor-regulated Smad (R-Smad) proteins (Smad1, Smad5 and Smad8 for BMP pathway) (Derynck and Zhang, 2003; Shi and Massagué, 2003). Phosphorylated R-Smads interact with a common Smad (Smad4) to form a complex and then translocate to the nucleus. This R-Smad-Smad4 complex together with transcriptional co-activators, such as p300, binds to DNA chromosome to regulate downstream gene expression (Derynck and Zhang, 2003; Shi and Massagué, 2003). BMP signaling plays important roles in cell differentiation, tissue morphogenesis and tumorigenesis (Feng and Derynck,

2005). To achieve its precise regulations in different physiological conditions and cell contexts, the activity of BMP signaling should be modulated. And the BMP pathway can be regulated at different levels. Extracellular antagonists, such as Noggin, Chordin, Gremlin and Follistatin, interfere the interaction of the ligand with the receptor (Liu and Niswander, 2005). In the cytoplasm, the inhibitory Smads, including Smad6 and Smad7, suppress BMP signaling by repressing R-Smad phosphorylation, disturbing interactions between R-Smads and Smad4 or directly promoting R-Smad degradation through recruiting Smurfs (Feng and Derynck, 2005; Massagué et al., 2005; Guo and Wang, 2009). In the nucleus, phosphatase such as PPM1A, SCPs and PDP, can promote dephosphorylation of R-Smads; and the co-repressors, C-terminal binding proteins (CtBPs), can be recruited by Smad6 to bind with SBE (Smad Binding Element) thereby inhibiting BMP signaling (Lin et al., 2003; Lönn et al., 2009; Wrighton et al., 2009). Moreover, BMP signaling activity can be modulated by other signaling pathways as discussed below.

BMP signaling and neurogenesis

At early stage of the neurognesis, NPCs in the developing spinal cord undergo self-renew to expand their populations (McConnell, 1995; Alvarez-Buylla et al., 2001; Götz and Huttner, 2005). As neurogenesis proceeds, some of the NPCs initiate to express proneural genes such as Ngns, Mash1 and Math1 (Lillien, 1998; Bertrand et al., 2002; Hirabayashi et al., 2004). Then, these proneural genes drive NPCs to differentiate into neuronal progenitor cells (Britz et al., 2006). The neuronal progenitor cells exit cell cycle and differentiate into various neurons including motor neurons in the ventral part of spinal cords and sensory neurons in the dorsal part of spinal cords (Jessell, 2000; Temple, 2001).

BMP signaling pathway plays important roles in neurogenesis. BMP proteins are generated at roof plate and secreted along dorsal to ventral spinal cord to form a gradient activity of BMP signaling (Helms and Johnson, 2003). Before neurogenesis, BMP signaling activation is essential for neural tube closure by interacting with the apicobasal polarity pathway (Eom et al., 2011). During neurogenesis, overexpression of constitutively activated *BMPR1A* (*caBMPR1A*) promoted NPC proliferation in the mouse spinal cord (Panchision et al., 2001). Activation of the BMP signaling also increases NPC number and decreases neuronal differentiation in chick spinal cords (Liu et al., 2004). Thus, BMP signaling pathway promotes NPC proliferation and prevents neuronal differentiation. However, it is not clear whether BMP signaling promotes NPC maintenance at early neurogenesis and/or blocks neuronal progenitor cell differentiation at mid-neurogenesis. Recent study found that Id proteins which were downstream targets of BMP pathway repressed the expression of proneural genes to sustains NPC maintenance during early neurogenesis (Bai et al., 2007), suggesting that BMP pathway is essential for NPC maintenance. Other studies showed that Id proteins interfered the interaction between E protein and proneural proteins by sequestering the E proteins to suppress the transcriptional activities of proneural proteins in neuronal progenitor cells (Yokota, 2001) and Ids could down-regulate p16 expression levels to inhibit Rb protein activity and then to prevent cell cycle exit (Ruzinova and Benezra, 2003). Thus, BMP signaling also play crucial roles in inhibiting neuronal differentiation at mid-neurogenesis. Together, BMP signaling pathway not only functions in regulation of NPC maintenance but also in preventing neuronal progenitor cell differentiation.

In addition to BMP signaling pathway, Notch pathway is also involved in neurogenesis. Notch pathway maintains NPC by up-regulating Hes1 protein levels (Louvi and Artavanis-Tsakonas, 2006). However, the Hes1 expression can not be maintained at a high level because of its negative feedback regulation (Hirata et al., 2002). Studies found that Id proteins could sustain Hes1 expression by releasing the negative autoregulation of Hes1 to maintain NPC pool (Bai et al., 2007). Therefore, a cross-talk that mediated by the downstream targets of the BMP pathway and the Notch pathway is necessary for NPC maintenance. In addition to BMP and Notch pathways, Wnt/β-catenin signaling is another pathway that plays a key role in NPC differentiation during neurogenesis. In β-catenin knockout mice, NPC proliferation was decreased and neuronal differentiation was increased (Zechner et al., 2003; Woodhead et al., 2006). Wnt1 or constitutively activated β-catenin overexpression promoted NPC proliferation and inhibited neuronal differentiation in the chick spinal cord (Megason and McMahon, 2002). The similar functions of BMP and Wnt signaling pathways suggest that these two pathways may have synergistic effects during neuronal differentiation. Indeed, studies found that the integration of BMP and Wnt signaling regulated neural proliferation and differentiation in the dorsal spinal cord (Chesnutt et al., 2004; Ille et al., 2007). However, it arises a question that how the BMP/Wnt signaling pathways are modulated when NPCs initiate to differentiation. The latest work showed that Smad6, a negative regulator of BMP signaling, promoted neuronal differentiation by inhibiting BMP pathway as well as repressing Wnt/β-catenin pathway (Xie et al., 2011). Thus, Smad6 mediates a novel cross-talk between BMP and Wnt pathways to promote neuronal differentiation. In addition, another paper found that RA pathway repressed BMP signaling to release the inhibition effects of BMP pathway on neuronal differentiation (Sheng et al., 2010), which provides an intersection between RA pathway and BMP signaling.

BMP signaling and spinal cord patterning

During neurogenesis, cells in the neural tube are specified to

acquire different neuronal identities contemporaneously. There are two main classes of cells comprising floor plate cells and ventral progenitor cells in ventral spinal cords (Helms and Johnson, 2003). Floor plate cells are organizer for patterning ventral neural tubes. Morphogens such as Shh from floor plate induce ventral progenitor cells to form five kinds of progenitor cells including p0, p1, p2, pMN and p3 (Briscoe et al., 2000). These progenitor cells express two classes of specific HD factors (Briscoe et al., 2000). The class I HD proteins (Pax7, Dbx1, Dbx2, Irx3 and Pax6) and Class II HD proteins (Nkx6.2, Nkx6.1, Oligo2, Nkx2.2 and Nkx2.9) form cross-repressive interactions between neighboring cells to refine and sharp the boundaries of these progenitor domains, and each of these progenitor cells gives rise to distinct classes of postmitotic neurons (Briscoe et al., 2000; Mizuguchi et al., 2001; Novitch et al., 2001; Vallstedt et al., 2001; Shirasaki and Pfaff, 2002). In dorsal spinal cords, there are three types of cells including roof plate cells, dorsal NPCs, and neural crest cells which delaminate and migrate into the periphery as neural tube close (Helms and Johnson, 2003). Morphogens from the roof plate instruct dorsal progenitor cells to subdivide into six progenitor populations called dP1-dP6. These progenitor cells are marked by different proneural genes such as Math1 for dP1, Ngn1/2 for dP2, Mash1 for dP3-dP5 and Ngn1/2 for dP6 during mouse embryonic day E10-E12.5 (Helms and Johnson, 2003). The progenitor cells further differentiate into six classes of early-born neurons termed dI1-dI6 which express specific HD factors (Table 1) (Helms and Johnson, 2003). These neurons migrate to deep or superficial dorsal horn to process somatosensory information.

BMP proteins are generated from roof plate and form gradient along dorsal to ventral spinal cords as described above. The importance of BMP signaling in dorsal spinal cord patterning is revealed *in vitro* and *in vivo* (Lee and Jessell, 1999). Double knockout of both BMP type 1 receptors, *BMPR1A* and *BMPR1B* in the mouse neural tube resulted in loss of the dorsal dI1 neurons, decrease of the dI2 neurons and dorsal shift of the dI3 and dI4 populations (Wine-Lee et al., 2004). Overexpression of activated *BMPR* promoted expression of dorsal regulators such as Pax7, Msx and Cath1 in chick neural tubes to instruct dorsal neuronal identities (Timmer et al., 2002). These results support the idea that BMP signaling plays a key role in specification of dorsal neuronal subtypes. In the dorsal part of neural tube, Wnt/β-catenin signaling which has the similar gradient to BMP signaling along dorsal-ventral axis of spinal cord is also involved in patterning. In Wnt1 and Wnt3a double mutant mouse embryos, the populations of dI1-dI3 interneurons were reduced and cells of dI4-dI5 were shifted to dorsal region (Muroyama et al., 2002). This phenotype is similar to the phenotype of *BMPR1* knockout mice. It has been suggested that BMP signaling was a dominant factor in dorsal neural tube patterning, while Wnt proteins acted as downstream targets of BMP signaling to maintain the populations of dorsal progenitor cells by stimulating their proliferation (Helms and Johnson, 2003; Chesnutt et al., 2004; Zechner et al., 2007). However, there is still no evidence to confirm whether Wnt/β-catenin signaling has a directly function in neural tube patterning. In addition to the cross-talk of dorsal signaling pathways, RA pathway in the intermediate region also plays crucial role in patterning by integrating with BMP pathway. Recent study showed that RA pathway could repress the BMP signaling to maintain proper specification of dorsal neural tubes (Sheng et al., 2010). In the ventral spinal cord, Shh proteins which are generated from floor plate and notochord are essential for establishing and maintaining ventral neuronal identities (Briscoe et al., 2000). Studies found that BMP and Shh signals had opponent and antagonistic functions to determinate dorsal-ventral patterning (Liem et al., 2000). However, the directly interaction between these two pathways is uncovered during dorsal-ventral neural tube patterning.

Considering different functions of the BMP signaling in spinal cord neurognesis and patterning, it is reasonable to address how the BMP signaling to carry out these different functions. Liu et al. found that BMP signaling activated different downstream targets to exert distinct functions (Liu et al., 2004). BMP signaling repressed neurogenesis by activating *Msx1* at early stages of neurogenesis, while BMP pathway specified dorsal interneurons by up-regulating *Msx3* at later stages (Liu et al., 2004). This study provides a paradigm that BMP pathway can regulate different functions by activating specific target genes at different stages during spinal cord development.

BMP pathway and axon development

After generation of neurons, a couple of events occur including migration, establishment of axon-dendrite polarity, axon growth, axon guidance and synapse formation (Polleux et al., 2007; Barnes and Polleux, 2009). These processes are important for further forming functional neuronal circuits and wiring the nervous system (Polleux et al., 2007; Barnes and Polleux, 2009). Recently, the functions of BMP signaling in axon development have been uncovered. Studies showed that BMP proteins significantly promoted axonal growth in the spinal cord (Zou et al., 2009). Another study showed that constitutive activation of *BMPR1B* caused commissural axon guidance defects in the chick spinal cord, whereas loss of *BMPR1B* in commissural neurons resulted in a perturbation of its axon trajectory in mouse spinal cord (Yamauchi et al., 2008). In addition, research in zebrafish revealed that BMP signaling was important for motor neuron axon architecture and stability because up-regulation of BMP signaling by loss of atlastin (atl1), which was found to be an inhibitor of BMP signaling, resulted in abnormal architecture of spinal motor axons (Fassier et al., 2010). Therefore, these studies suggest that proper BMP signaling activity is essential for axon development in different stages. The underline mechanisms

Table 1 Determination of spinal cord dorsal layers by homeodomain transcription factors

Dorsal layer	HD factors
dI1	Lhx2/9, BarH1, Brn3a
dI2	Lhx1/5, Brn3a, Foxd3
dI3	Isl1/2, Brn3a, Rnx
dI4	Lbx1, Lhx1/5, Pax2
dI5	Lbx1, Brn3a, Lmx1b, Rnx/Tlx1
dI6	Lbx1, Lhx1/5, Pax2

of BMP signaling in axon development should be addressed in the future.

BMP pathway and gliogenesis

During neural development, NPCs are multipotent and can give rise to neurons, astrocytes and oligodendrocytes. In general, NPCs first undergo a neurogenic period to generate neurons and then gliogenesis which produces glial cells (Bertrand et al., 2002). Compared to neurogenesis, the mechanisms that control gliogenesis are not well explored. It has been proposed that NPCs first differentiate into glial progenitor cells and subsequently differentiate into astrocytes and oligodendrocytes (Bertrand et al., 2002). The regulation networks of transcription factors are discovered progressively during gliogenesis (Zhou and Anderson, 2002; Zhou et al., 2001; Muroyama et al., 2005). Extrinsic signaling pathways that regulate glial development are also revealed. BMP signaling is one of the most important pathways involved in this process. The functions of BMP signaling in cortex glial development have been fully reported (Nakashima et al., 1999; Bonaguidi et al., 2005). In the spinal cord, the role of BMP signaling in regulation of glial development is also demonstrated. During astrocytogenesis, BMP signaling is a positive regulator in the developing spinal cord. BMP4 protein treatment or overexpression of *BMPR1B* significantly promoted the expression of astrocyte marker GFAP in the chick developing spinal cord (Agius et al., 2010). In contrast, blocking BMP signaling with Noggin protein decreased GFAP expression and inhibited astrocytogenesis (Agius et al., 2010). During the oligodendrocyte differentiation, BMP signaling is considered as a negative regulator. Studies found that BMP signaling not only inhibited the specification of oligodendrocytes by reducing the expression of Olig2 which was an important gene for oligodendrocyte development, but also repressed the maturation of oligodendrocytes through decreasing the expression levels of three key myelin proteins, proteolipid protein (PLP), myelin basic protein (MBP) and 2V-3V-cyclic nucleotide 3V-phosphodiesterase (CNP) (Mekki-Dauriac et al., 2002; See et al., 2004; Samanta and Kessler, 2004). Although the functions of BMP signaling during gliogenesis in the developing spinal cord have been explored, the detailed mechanisms and its relationships with other signaling pathways (such as LIF, Notch and Fgf pathways) that involved in glial development are unknown.

Conclusion and prospective

BMP signaling is essential for many aspects of spinal cord development which include neurogenesis, neural tube patterning, axon development and gliogenesis. Integrations of BMP signaling with other pathways such as Wnt, RA and Notch pathways are also crucial for most of the processes as described above. Although the pivotal roles of BMP signaling and its signaling networks in spinal cord development have been uncovered gradually, many questions are still unsolved. For example, what are the directly targets of the BMP signaling in different stages of spinal cord development? How do the NPCs in the spinal cord respond to different gradient of BMP signaling activities during neural tube patterning? How to modulate BMP signaling precisely according to temporal and spatial requirements during spinal cord development? In addition, to explore the functions of BMP signaling at later stages of the spinal cord development such as neuron migration, axon development, synapse development, neurotransmitter maturation or release and neuronal circuit formation will be challenges in the future.

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