Abstract: Bone morphogenetic proteins (BMPs) are multifunctional cytokines that belong to the transforming growth factor-β family. BMPs were originally identified based on their unique activity, inducing heterotopic bone formation in skeletal muscle. This unique BMP activity is transduced by specific type I and type II transmembrane kinase receptors. Among the downstream pathways activated by these receptors, the Smad1/5/8 transcription factors appear to play critical roles in BMP activity. Smad1/5/8 transcription factors are phosphorylated at the C-terminal SVS motif by BMP type I receptors and then induce the transcription of early BMP-responsive genes by binding to conserved sequences in their enhancer regions. The linker regions of Smad1/5/8 contain multiple kinase phosphorylation sites, and phosphorylation and dephosphorylation of these sites regulate the transcriptional activity of Smad proteins. Gain-of-function mutations in one BMP type I receptor have been identified in patients with fibrodysplasia ossificans progressiva, a rare genetic disorder that is characterized by progressive heterotopic bone formation in the skeletal muscle. The mutant receptors activate the Smad signaling pathway even in the absence of BMPs, therefore novel inhibitors for the BMP receptor – Smad axis are being developed to prevent heterotopic bone formation in skeletal muscle. Taken together, the data in the literature show that the BMP type I receptor – Smad signaling axis is the critical pathway for the unique activity of BMPs and is a potential therapeutic target for pathological conditions caused by inappropriate BMP activity.

Keywords: bone morphogenetic protein; dephosphorylation; phosphorylation; receptor; Smad.

Bone morphogenetic proteins and their role in bone formation

The discovery of bone morphogenetic protein

Bone morphogenetic protein (BMP) was originally discovered as a protein with heterotopic bone-inducing activity in the bone matrix (Urist, 1965; Reddi and Huggins, 1972). Marshall R. Urist (1965) observed the induction of new cartilage and bone with bone marrow in skeletal muscle after the implantation of bone matrix demineralized by treatment with hydrochloric acid. The demineralized bone matrix factor with this unique activity was named BMP because it was destroyed by digestion with trypsin (Urist and Strates, 1971). These findings also indicated that skeletal muscle and other soft tissues contain progenitor cells that are capable of differentiating into chondrocytes and osteoblasts after the implantation of bone matrix demineralized by treatment with hydrochloric acid. The intracellular signal transduction downstream of BMP may play an important role in physiological and pathological bone formation (Miyazawa et al., 2002; Katagiri, 2010).
demineralized bovine bone matrix and successfully cloned four independent BMP cDNAs (BMP-1 through BMP-4; BMP-4 was originally called BMP-2b). The BMPs, except BMP-1, have strong homology with transforming growth factor-β1 (TGF-β1) and have been shown to be novel members of the TGF-β family (Wozney et al., 1988). Based on cDNA homology, more than 10 BMPs and related growth differentiation factors have also been identified in vertebrates (Figure 1) (Katagiri et al., 2008; Mueller and Nickel, 2012).

The members of the TGF-β family function as dimers (Sampath et al., 1990). Although bone matrix contains several types of BMPs, each recombinant BMP homodimer induces heterotopic cartilage, tendon and/or bone formation in vivo, suggesting that the original ‘BMP’ activity found in demineralized bone matrix represented the combined activity of heterogeneous BMPs (Rider and Mulloy, 2010). Furthermore, the overlapping expression of some BMP mRNAs during embryogenesis suggests a possibility of BMP heterodimer formation during skeletal development. BMP-2/BMP-6 and BMP-2/BMP-7 heterodimers show higher specific activity in vitro and in vivo than their respective homodimers (Israel et al., 1996; Valera et al., 2010; Buijs et al., 2012). BMP-1, a metalloproteinase, also induced heterotopic cartilage formation in vivo, though the molecular mechanisms underlying this activity remain unclear (Wozney et al., 1988). Dpp and 60A, BMP-2/4 and BMP-5/6/7 homologs in Drosophila, respectively, were capable of inducing heterotopic bone formation in rodents, even though flies do not have bone tissue (Sampath et al., 1993; Shimmi et al., 2005). A common intracellular signaling system activated by BMPs and homologs in vertebrates and flies may have different functions that are species- and cell type-dependent. Indeed, the TGF-β family members have multiple roles in proliferation, differentiation and apoptosis during embryonic development and in tissue maintenance and regeneration after birth (Giacomini et al., 2007; Wordinger and Clark, 2007; Katagiri et al., 2008; Miyazono et al., 2010; Cai et al., 2012; Otsuka et al., 2012). For example, BMP-9 has been shown to regulate blood glucose levels; a single subcutaneous injection of BMP-9 reduced the blood glucose levels in diabetic mice to near-normal levels (Chen et al., 2003). Moreover, some BMPs have been identified and/or purified from serum (Borovecki et al., 2004; Kodaira et al., 2006; Vukicevic and Grgurevic, 2009; Grgurevic et al., 2011). These findings suggest that BMPs act not only at the local but also the systemic level (Simic et al., 2006; Nemeth, 2008). The mechanisms that regulate the expression and activation of BMPs should be investigated further.

### An in vitro model reflecting the unique activity of bone morphogenetic proteins

Heterotopic bone induction, one of the defining activities of BMPs, can be reproduced in vitro, at least in part, in C2C12 myoblasts derived from the thigh muscles of C3H mice (Blau et al., 1983). Similar to primary myoblasts, C2C12 cells proliferate as mononuclear cells and express MyoD, a master gene of skeletal muscle differentiation, but do not express muscle-contracting proteins, such as myosin heavy chain and troponin T. Terminal myogenic differentiation is induced upon entering G0. The treatment of C2C12 cells with osteogenic BMPs inhibits myogenic differentiation and induces an osteoblast differentiation phenotype, including high alkaline phosphatase activity and osteocalcin secretion (Katagiri et al., 1994). Similar effects were observed in primary myoblasts treated with BMPs (Katagiri et al., 1994). Although many types of hormones and cytokines inhibit the myogenesis of myoblasts in vitro, these molecules never induce osteoblastic differentiation in C2C12 cells (Katagiri et al., 2008). Furthermore, although TGF-β1 is known as a potent inhibitor of myogenesis, it does not induce osteoblastic differentiation in C2C12 cells in vitro or heterotopic bone formation in vivo (Sampath et al., 1987; Katagiri et al., 1994). Thus, an experimental model using C2C12 myoblasts may be a useful system for studying the unique intracellular signal transduction of BMPs in vitro. Indeed, Osterix, which is

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**Figure 1** Osteogenic and non-osteogenic members of the TGF-β family.

Among the members of the TGF-β family examined their osteogenic activities, most BMPs are capable of inducing heterotopic bone formation when applied to skeletal muscle as recombinant proteins. In contrast, TGF-β proteins, activins, inhibins and BMP-3 do not have this activity.

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**The TGF-β family**

<table>
<thead>
<tr>
<th>BMP-2</th>
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<tr>
<td>BMP-5</td>
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<tr>
<td>BMP-7/OP-1</td>
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<td>GDF-7/BMP-12</td>
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<td>BMP-9</td>
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</tbody>
</table>

**Osteogenic activity**

Yes

No
an essential transcription factor for osteoblast differentiation in embryogenesis, has been identified in C2C12 cells stimulated with BMP-2 (Nakashima et al., 2002).

**Bone morphogenetic protein signal transduction**

**Bone morphogenetic protein receptors**

The members of the TGF-β family bind to transmembrane serine/threonine kinase receptors (Figure 2) (Rosen, 2006; Sieber et al., 2009; Miyazono et al., 2010; Mueller and Nickel, 2012). Although their structures are conserved overall, these proteins are classified into two subgroups, type I and type II receptors, based on the presence (type I) or absence (type II) of the GS domain, a glycine- and serine-rich sequence between the transmembrane and kinase domains (Figure 2) (Wrana et al., 1994). Osteogenic BMPs bind to four forms of type I receptors [ALK1, ALK2, BMPR-IA (also called ALK3) and BMPR-IB (also called ALK6)] and three forms of type II receptors (ActR-II, ActR-IIB and BMPR-II) (Figure 2) (Rosen, 2006; Miyazono et al., 2010; Mueller and Nickel, 2012). The BMP type I and II receptors exhibit >35% amino acid similarity with one another (Figure 2). The non-osteogenic members of the TGF-β family, such as TGF-β1 and activin, bind to the type I receptors ALK4 (also called ActR-IB), ALK5 (also called TβR-I) and ALK7, suggesting that the type I receptors and their downstream effectors determine the biological activity in response to these molecules (as discussed below).

A ligand dimer binds to a tetramer of two type I and two type II receptors (Greenwald et al., 2003; Keller et al., 2004; Ehrlich et al., 2012). The kinase of the type II receptor is constitutively active independent of ligand binding and phosphorylates the GS domain of the type I receptor (Figure 3). The receptor complex activates downstream signaling components including Smads, p38 mitogen-activated protein (MAP) kinase and phosphoinositide 3 kinase (Figure 3) (Hassel et al., 2003; Nohe et al., 2004). FKBP12, a binding partner of the immunosuppressant FK506, has been shown to suppress type I receptors by binding to unphosphorylated GS domains, and the phosphorylation of the GS domain by type II receptors releasing FKBP12 (Figure 3) (Nishinakamura et al., 1997; Huse et al., 1999, 2001).

It has been reported that BMP-3 does not induce heterotopic bone formation in vivo and that BMP-3 knockout mice showed higher bone mineral density than wild-type mice (Daluisi et al., 2001; Gamer et al., 2009). BMP-3 bound to ActR-IIB with high affinity, suggesting that it may...
competitively inhibit other osteogenic BMPs (Kokabu et al., 2012a). BAMBI is a natural BMP receptor that lacks the kinase domain but still retains its ligand-binding domain and thereby blocks BMP activity in a dominant-negative fashion (Onichtchouk et al., 1999; Xavier et al., 2010). In addition, the substitution of a conserved asparagine residue in the GS domain has been shown to generate constitutively active type I receptor kinases, i.e., kinases that are active in the absence of ligand binding (Wieser et al., 1995; Akiyama et al., 1997; Aoki et al., 2001). These findings suggest that type II receptor-activated type I receptor kinases are critical for intracellular signal transduction.

**Bone morphogenetic protein-dependent Smad-signaling**

**Smad1/5/8s are substrates of bone morphogenetic protein type I receptors**

Among the proteins that are phosphorylated by BMP type I receptor kinases, Smad1/5/8s appear to be critical substrates for the most unique activity of BMPs (Figure 3) (Kretzschmar et al., 1997; Hassel et al., 2003). Smads are the mammalian counterparts of Sma and Mad in Caenorhabditis elegans and Drosophila, respectively, that transduce the intracellular signaling downstream of the TGF-β family of ligands (Derynck et al., 1996). Smad1, Smad5 and Smad8 have a sequence homology of more than 78% (Figure 4). In contrast to the osteogenic BMPs, the non-osteogenic members of the TGF-β family induce the phosphorylation of Smad2 and Smad3 rather than Smad1, Smad5 and Smad8 (Massague et al., 2005; Wu and Hill, 2009; Zi et al., 2012).

The receptor-regulated Smads have conserved structures, including an N-terminal Mad homology 1 (MH1) domain and a C-terminal MH2 domain that are required for the DNA-binding activity of the protein and protein–protein interactions, respectively (Figure 4) (Shi and Massague, 2003). The MH1 and MH2 domains are connected by a linker region that has multiple phosphorylation sites and an E3 ubiquitin ligase recognition sequence, the PPAY motif (Figure 4) (Bruce and Sapkota, 2012). Mouse Smad8 lacks the PPAY motif and is shorter than Smad1 and Smad5 due to a deletion of the end of the linker region. Humans have both the short and long forms of Smad8. Smad1, Smad5 and Smad8 all have a conserved C-terminal SVS motif, which is the phosphorylation site for activated type I receptor kinases (Arnold et al., 2006).
Signaling pathways other than the Smad pathway are also induced by activated BMP type I receptors (Figure 3) (Hassel et al., 2003; Nohe et al., 2004). To manipulate the Smad pathway without affecting these other pathways, a constitutively activated form of Smad1 has been established. The receptor-phosphorylation of Smad1 in the C-terminal SVS motif introduces negative charges at the two serine residues. To mimic this condition, these serine residues in Smad1 have been replaced with aspartic acid, an acidic amino acid with an additional negative charge, termed Smad1(DVD) or Smad1(2SD), see Figure 5 (Qin et al., 2001; Nojima et al., 2010). Cells over-expressing Smad1(DVD), but not wild-type Smad1, exhibit various phenotypes in the absence of BMPs, such as positive recognition by an antibody specific to phosphorylated Smad1/5/8s, the activation of luciferase reporters driven by BMP-responsive elements (BREs) and osteoblastic differentiation in C2C12 myoblasts (Qin et al., 2001; Nojima et al., 2010). Moreover, an injection of Smad1(DVD) mRNA into Xenopus embryos induced ventralization, a typical BMP-mediated activity in this system (Nojima et al., 2010). In contrast to osteoblastic differentiation, the inhibition of myogenesis by BMP stimulation seemed to be dependent on nuclear Smad4, which might promote the expression of Id genes in cooperation with phosphorylated Smad1/5/8s (Nojima et al., 2010). These findings suggest that the type I receptor – Smad signaling axis plays a central role in the unique activity of BMPs.

**Target genes of bone morphogenetic protein-regulated Smads**

Phosphorylated Smad1/5/8s form complexes with Smad4 in the cytoplasm that then translocate to the nucleus to regulate the transcription of target genes, both positively and negatively. The Id1, Id2 and Id3 genes have been found to be induced within 1 hour after BMP treatment in various types of mammalian cells, suggesting that these genes have similar BREs in their regulatory regions (Katagiri et al., 1994; Hollnagel et al., 1999). The first BRE, a GC-rich short element that is recognized by Smad1 and Smad4 in electrophoresis mobility shift assays, was identified in the Id1 gene (Katagiri et al., 2002; Korchynskyi and ten Dijke, 2002; Lopez-Rovira et al., 2002). Additional conserved BREs were later identified in the Id2 and Id3 genes (Shin et al., 2012). Recently, the novel BMP-inducible transcript-1 was identified in a search for BREs using the sequence conserved among the promoter regions of the Id
genes (Shepherd et al., 2008; Nakahiro et al., 2010; Shin et al., 2012). The alignment of those BREs revealed a core sequence, GGCGCC, that is essential for the binding of Smad1 and Smad4 (Katagiri et al., 2002; Shin et al., 2012). An identical GGCGCC sequence was also found in human cells in a genome-wide chromatin immunoprecipitation sequence analysis using anti-phosphorylated Smad1/5/8 antibodies (Morikawa et al., 2011). Interestingly, the MDA-MB468 breast cancer cell line lacks the Smad4 locus, and Id1 mRNA was not expressed in response to BMP-2 in these cells (Katagiri et al., 2002). However, the over-expression of exogenous Smad4 in these cells restored the induction of Id1 mRNA by BMP-2, suggesting that Smad4 is an essential cofactor for BMP receptor-regulated Smads (Katagiri et al., 2002).

Roles of Smad post-translational modifications

Protein phosphatases for Smads

The phosphorylation of the SVS motif in Smads activates their transcriptional activity, therefore the dephosphorylation of this motif may have the opposite effect (Kokabu et al., 2012b). Some protein phosphatases that mediate this reaction have been identified (Figure 5) (Bruce and Sapkota, 2012). Protein phosphatase magnesium-dependent 1A (PPM1A) is one of the phosphatases that targets the phosphorylated SVS motif (Figure 5) (Duan et al., 2006; Lin et al., 2006), and the over-expression of PPM1A, but not an enzyme activity-deficient mutant, suppressed BMP activity, confirming that the phosphatase activity is essential for inhibition (Duan et al., 2006; Kokabu et al., 2010). However, PPM1A suppressed the activity of constitutively activated Smad1(DVD), even though the SVS motif of this protein cannot be dephosphorylated (Kokabu et al., 2010). Moreover, PPM1A decreased the protein levels of unphosphorylated and phosphorylated wild-type Smad1 and Smad1(DVD), suggesting that PPM1A may suppress Smad1 indirectly by dephosphorylating some additional substrate(s) (Kokabu et al., 2010).

Small C-terminal domain phosphatase 1 and 2 (SCP1 and SCP2) have also been shown to dephosphorylate the type I receptor-phosphorylated Smads (Knockaert et al., 2006; Sapkota et al., 2006). In addition to the C-terminus, SCP1 and -2 act on the Smad linker regions that are phosphorylated by mitogen activated protein (MAP) kinases to suppress the transcriptional activity of Smads (Figure 5) (Sapkota et al., 2006). The effects of the SCPs on Smads may therefore depend on a balance between phosphorylation and dephosphorylation at the linker region and the SVS motif. Interestingly, similar to PPM1A, SCP1 suppressed the constitutively active Smad1(DVD)-induced osteoblastic differentiation of C2C12 cells (Kokabu et al., 2011). In contrast to PPM1A, however, SCP1 did not change the protein levels of Smads and showed minimal effects on Id1 expression, suggesting that SCP1 may target the downstream effector(s) of the BMP–Smad axis rather than the Smads themselves, at least in this model (Kokabu et al., 2011). The phosphorylation of the linker region by Cyclin-dependent kinase 8/9 has been shown to enhance Smad activity (Alarcon et al., 2009), although phosphorylation by MAPK and glycogen synthase kinase 3 (GSK3) suppresses Smad activity (Figure 5). The linker region of Smads has multiple sites that may be phosphorylated by protein kinases, therefore the combination of position-specific phosphorylation and/or the timing of phosphorylation may regulate Smad functions both positively and negatively in cooperation with other post-transcriptional modifications.

Smad ubiquitination

Smad1 and Smad5 contain PPAY motifs in their linker regions that are recognized by E3 ubiquitin ligases such as Smurf1 (Zhu et al., 1999; Sangadala et al., 2007). Smurf1 polyubiquitinates Smads to induce their degradation via the proteasome pathway, and this proteasomal degradation has been associated with linker phosphorylation (Zhu et al., 1999). In some cases, Wnt signaling cooperatively stimulates BMP activity (Nakashima et al., 2005; Fukuda et al., 2010). GSK3, a critical kinase in Wnt signaling, further phosphorylates the linker regions of Smads that have already been phosphorylated by MAP kinases, and phosphorylation by both kinases is required for the proteasomal degradation induced by Smurf1 via polyubiquitination (Sapkota et al., 2007; Verheyen, 2007).

USP15 has been identified as an enzyme that stimulates Smad deubiquitination (Inui et al., 2011). The expression of a siRNA targeting USP15 in C2C12 cells reduces the alkaline phosphatase activity induced by BMP-2 (Inui et al., 2011). Monoubiquitination at the MH1 domain of Smad3 prevents its DNA binding, while USP15 stimulates its transcriptional activity by removing ubiquitin (Inui et al., 2011). Thus, ubiquitination negatively regulates Smad activity.
Deregulated bone morphogenetic protein signaling in fibrodysplasia ossificans progressiva

Point mutations in ALK2 cause fibrodysplasia ossificans progressiva

Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder that is characterized by progressive heterotopic bone formation in skeletal muscle tissue (Kitterman et al., 2005; Katagiri, 2010, 2012; Pignolo et al., 2011). Currently, there is no effective treatment for preventing heterotopic bone formation in FOP. BMP signaling has been suggested to be involved in FOP because the process of heterotopic bone formation is similar to that induced by BMP implantation in skeletal muscle (Kaplan et al., 1990).

A recurrent heterozygous mutation in the ACVR1 gene, which encodes the BMP type I receptor ALK2, was identified in familial and sporadic FOP patients (Shore et al., 2006). The mutation alters a single amino acid in the GS domain of ALK2 (Shore et al., 2006). Even in the absence of stimulation by BMPs, the mutant ALK2 found in FOP induces specific BMP signal transduction events, such as the phosphorylation of Smad1/5/8s and the activation of the Id1-luciferase reporter in C2C12 myoblasts (Fukuda et al., 2008, 2009). BMP stimulation of mutant ALK2-expressing cells further promoted these BMP activities, suggesting that the mutant ALK2 is mildly constitutively activated by the genetic mutation and hypersensitive to activation by type II receptors (Fukuda et al., 2009). A reduction in the affinity for FKBP12 at the GS domain was suggested to be involved in this activation (Shen et al., 2009). To date, 12 mutations have been identified in the GS or kinase domains of ALK2 in patients with typical and atypical FOP (Katagiri, 2012).

The role of the Smad pathway in fibrodysplasia ossificans progressiva

In FOP, muscle injury induces acute local heterotopic bone formation, suggesting that an inflammatory reaction synergistically activates the intracellular signaling of BMPs (Katagiri, 2010). Smad1 and Smad5 mRNA expression are transiently increased after muscle injury in mice (Fukuda et al., 2009). Co-transfection with mutant ALK2 and Smad1 or Smad5 induces osteoblastic differentiation in C2C12 cells, suggesting that the Smad-dependent pathway activated by mutant ALK2 plays a critical role in heterotopic bone formation in FOP (Fukuda et al., 2008, 2009; Ohte et al., 2011).

Based on these findings, the BMP receptor–Smad axis is being investigated as a potential target for treatments to prevent heterotopic bone formation in FOP. Some small chemical inhibitors have been generated for the BMP type I receptor kinases (Figure 6). Dorosomorphin is the first chemical inhibitor identified that is specific for the receptor-induced phosphorylation of Smad1/5/8s but not the MAP kinase pathway (Yu et al., 2008b). Dorosomorphin and its potent derivative, LDN-193189, block induction of the osteoblastic differentiation of C2C12 cells that is induced by the over-expression of the ALK2 mutant (Fukuda et al., 2009; Ohte et al., 2011; Lowery and Rosen, 2012). In addition, LDN-193189 has been shown to reduce heterotopic bone formation in a transgenic mouse model carrying a mutant ALK2 gene (Yu et al., 2008a). Using this model, all-trans retinoic acid (RA) and RARγ agonists have also been shown to inhibit heterotopic bone formation (Shimono et al., 2011). Both RA and RARγ agonists inhibited the BMP-induced Id1-luciferase reporter and reduced the protein levels of Smads, indicating that RA and RARγ inhibit BMP signaling via a different mechanism from that of dorosomorphin and LDN-193189 (Figure 6) (Shimono et al., 2011).

Recently, novel types of inhibitors for BMP signaling were reported in the development of treatments for FOP (Figure 6). NG-391 and NG-393, which are structurally-related compounds produced by a mold, were found in a screen for inhibitors of osteoblastic differentiation in C2C12 cells expressing the ALK2 mutant found in FOP (Figure 6) (Fukuda et al., 2011). From another screen using 1040 US Food and Drug Administration-approved drugs, fendiline hydrochloride and perhexiline maleate were found to inhibit the Id1-luciferase activity induced by the ALK2 mutant found in FOP (Yamamoto et al., 2012). Perhexiline reduced the phosphorylation levels of Smad1/5/8s in vitro and decreased the heterotopic bone volume induced by BMP implantation in vivo (Figure 6) (Yamamoto et al., 2012). Induced pluripotent stem cells provide a powerful system in which to study human diseases, particularly rare genetic disorders such as FOP. Recently, it was found that the generation of induced pluripotent stem cells from FOP skin fibroblasts was repressed due to the constitutive activation of ALK2 (Hamasaki et al., 2012). The treatment of the cells with an ALK2 inhibitor, LDN-193189, overcomes this repression, suggesting that phosphorylated Smad1/5/8s are involved in this repression (Hamasaki et al., 2012). RK-0071142 was also identified as a candidate drug for FOP using this system (Figure 6) (Hamasaki et al., 2012). Allele-specific RNA interference is a novel type of
inhibition that is specific for the \( ALK2 \) mutant (Lowery and Rosen, 2012). Although siRNAs targeting \( ALK2 \) carrying one of the FOP mutations also reduced the levels of wild-type \( ALK2 \) mRNA, the introduction of an additional mismatch in each siRNA conferred allele specificity for each mutant \( ALK2 \) (Figure 6) (Takahashi et al., 2012).

**Open questions regarding the bone morphogenetic protein signaling pathway**

Although BMPs have been identified as bone-inducing factors in the bone matrix, their functions are not limited to skeletal tissue and have expanded to various tissues. It is still unclear how BMPs show these variable activities in tissues through the same receptor–Smad signaling system. It is possible that novel, tissue-specific non-Smad pathways and/or novel coactivators and corepressors of Smads are involved in the functions. The identification of such novel signaling pathways or factors will help us to understand the regulatory mechanisms of BMP functions in various tissues. Moreover, it may also help us to establish novel treatments for diseases caused by the deregulation of BMP signaling.

**Conclusions**

BMPs are able to induce heterotopic bone formation in skeletal muscle tissue. Their intracellular signaling is transduced by the ligand-bound type I and type II receptor kinases; among the proteins phosphorylated in response to type I receptor activation, Smad1/5/8s are critical effectors of BMP activity. Thus, inhibitors of this signaling pathway are potential candidates for therapeutic drugs for diseases caused by the pathological activation of BMP signaling, such as FOP.

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Takenobu Katagiri started working on BMPs in 1987, when he was a graduate student of Kitasato University. He was also a research student of the School of Dentistry, Showa University. He was interested in heterotopic bone formation in skeletal muscle induced by BMPs and in the similar phenomena in patients with FOP. He obtained his PhD at Kitasato University in 1992 and moved to Showa University as a Research Assistant. In 2004, he moved to Division of Pathophysiology, Research Center for Genomic Medicine, Saitama Medical University as an Associate Professor. Currently, he is a Professor and Division Head of the same division and is a leader of Project of Clinical and Basic Research for FOP at Saitama Medical University. His research interests are molecular mechanisms of musculoskeletal tissue interaction.

Sho Tsukamoto started working on BMPs and Smads in 2009, when he was an undergraduate student, at Saitama Medical University under the supervision of Professor Take Katagiri. Currently, he is a graduate student of the same university. His research interests include molecular biology and biochemistry of BMP signal transduction.