Bone morphogenetic proteins mediate crosstalk between cancer cells and the tumour microenvironment at primary tumours and metastases (Review)

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Abstract. Bone morphogenetic proteins (BMP) are pluripotent molecules, co-ordinating cellular functions from early embryonic and postnatal development to tissue repair, regeneration and homeostasis. They are also involved in tumourigenesis, disease progression and the metastasis of various solid tumours. Emerging evidence has indicated that BMPs are able to promote disease progression and metastasis by orchestrating communication between cancer cells and the surrounding microenvironment. The interactions occur between BMPs and epidermal growth factor receptor, hepatocyte growth factor, fibroblast growth factor, vascular endothelial growth factor and extracellular matrix components. Overall, these interactions co-ordinate the cellular functions of tumour cells and other types of cell in the tumour to promote the growth of the primary tumour, local invasion, angiogenesis and metastasis, and the establishment and survival of cancer cells in the metastatic niche. Therefore, the present study aimed to provide an informative summary of the involvement of BMPs in the tumour microenvironment.

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1. Introduction

Bone morphogenetic proteins (BMPs) were originally termed by Urist (1) in 1965 as it induced bone formation ectopically. They are members of the transforming growth factor β (TGF β) superfamily (2). In humans, there have been >20 BMPs identified. They are pluripotent molecules that co-ordinate cellular differentiation, proliferation and apoptosis in early embryonic and postnatal development (3,4). They are essential in controlling tissue repair, regeneration and homeostasis (4-6).

BMPs serve important roles in tumourigenesis, disease progression and the metastasis of various solid tumours (7-10). BMP signalling has been found to be both oncogenic and tumour suppressing, depending on context. For example, studies have shown that BMPs are upregulated in certain tumours, particularly those originating from soft tissues such as osteosarcomas, chondrosarcoma, ameloblastoma and salivary tumours (11-14). They are actively involved in cancer development and metastasis (7-10). BMP-6 overexpression in prostate cancer is associated with osteoblastic bone metastasis (7). BMP-4 may promote the invasion and motility of breast cancer cells via upregulation of matrix metalloproteinase (MMP)1 and C-X-C chemokine receptor 4 (8). The above studies indicate an oncogenic effect of BMPs in certain solid tumours. In contrast, impairments in BMP signalling observed in colorectal cancers and polyposis syndromes suggest a tumour suppressor role in these situations (15). Our previous study reported that BMP-10 inhibits prostate cancer cell growth by promoting apoptosis via Smad-independent signalling, and that it can also reduce the invasiveness and motility of cancer cells (9). BMP-4 can also reduce the capacity of myeloid-derived suppressor cells to prevent metastasis of breast cancer cells (10). It appears that the same BMPs may have varied roles in different types of tumour, potentially due to the involvement of distinct downstream molecules.

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As pleiotropic growth factors, BMPs are actively involved in tumorigenesis, disease progression and metastasis, not only directly due to their own signalling pathway, but also via complex interactions with other growth factors and other signalling pathways (16-24). More importantly, BMP-mediated interactions between cancer cells and the local environment also occur during the development of both the primary tumour and metastasis, forming a large, intricate network that promotes the epithelial to mesenchymal transition (EMT) of tumours, remodelling of tumour-associated extracellular matrix (ECM), angiogenesis and bone metastasis.

2. Signal transduction of BMP

Both type I receptors [activin A receptor type I (ACVR)-like 1, ACVR1, BMP receptor (BMPR)1A, ACVR1B, TGF β receptor (TGF β R)1, BMPR1B and ACVR1C] and type II receptors (TGF β R2, TGF β R3, BMPR2, ACVR2A and ACVR2B) are indispensable for signal transduction of TGF β (25). The type I receptors are also respectively known as activin receptor-like kinase (ALK)1-7. Certain type I receptors (ALK1, ALK3 and ALK6) exhibit a higher binding affinity to BMPs (25). Smad-dependent signalling will be induced by the preformed hetero-oligomeric complexes (PFC) upon binding with BMP ligands (26,27). Alternatively, upon binding between BMP ligands and type I receptors, type II receptors are then recruited, leading to the formation of BMP-induced signalling complexes, which activate the Smad-independent pathway (26,27).

Smad-dependent pathway. As transcription factors, Smad proteins are vital for intracellular transduction of BMP signalling (25,27,28). There are three subgroups of Smad proteins: Smad 1, 2, 3, 5 and 8 are pathway-restricted Smads (R-Smads); Smad 4 is known as a common mediator Smad; and Smad 6 and 7 are inhibitory Smads (I-Smads) (27,28). After BMP homodimers or heterodimers bind to the PFC, the glycine-serine region of type I receptors is phosphorylated by the type II receptor, leading to the activation and translocation of R-Smads (Smad 1, 5 and 8) into the nucleus, and regulation of BMP-responsive genes such as Id1-3, Smad 6/7, type I collagen, JunB and Mix.2 (25). Smad 4 translocates the signal complex into the nucleus, and Smad 6 and 7 act as inhibitory factors for the signal transduction through the Smad-dependent pathway (Fig. 1) (25,29).

Smad-independent pathway. There is greater affinity between BMPs and type I receptors compared with type II receptors (25). Thus, BMP ligands are also able to bind to ALK3 or ALK6, and then recruit BMPR2 into a hetero-oligomeric complex; this activates the Smad-independent pathway (25-27). The X-linked inhibitor of apoptosis protein acts as an adaptor protein to relay signalling from the type I receptor to downstream TGF β -activated binding protein, leading to activation of TGF β -activated tyrosine kinase 1 (30-32). BMP-4 can induce apoptosis through this Smad-independent pathway, in which p38, a mitogen-activated protein kinase (MAPK) (26,33,34), Jun N-terminal kinases (JNKs), NF- κ B and Nemo-like kinase (35-37) are involved (Fig. 1).

Regulatory factors of BMP signalling. Regulation of BMP pathway activity can be mediated through several positive or negative modulators, which may be extracellular when ligands bind to receptors, intracellular when the signal is being relayed or intranuclear when modulating R-Smad-mediated regulation of BMP-responsive genes (25).

Extracellular regulatory factors. Secreted extracellular BMP antagonists, including Noggin, Gremlin, Chordin and twisted gastrulation-1, provide important regulation (25). These antagonists exert their regulatory role in two ways. BMP antagonists can prevent BMPs from the binding to receptors by binding directly to BMP ligands, thus preventing ligand-receptor interaction (Fig. 1) (25). Antagonists are often target genes of BMP signalling; thus, a negative regulatory feedback loop is formed to ensure signalling homeostasis (38). For example, it has been shown that BMP-2, 4 and 6 can induce Noggin expression in osteoblasts (39). By upregulating their antagonist expression, the BMPs are thus able to regulate their activity (39).

Other factors also regulate BMP signalling extracellularly, such as pseudoreceptors and co-receptors. For example, BMP and activin membrane-bound inhibitor (BAMBI) acts as a pseudoreceptor by competitively binding to the BMP ligands with its extracellular domain, which shares high homology with type I receptor; however, as it lacks intracellular domains, the signal is not transduced (40). Similar to the BMP antagonists, BAMBI can be induced by BMP-4 in mouse embryonic fibroblasts, leading to negative feedback regulation of BMP signalling (41).

In addition to these negative regulators, there are positive regulators for the BMP pathway, such as co-receptors, which enhance BMP signalling (25,42-44). Previous studies showed that repulsive guidance molecules (RGMs; including RGMA, RGMB and RGMC) are co-receptors for BMP-2 and BMP-4. RGMB, also known as Dragon, can bind directly to BMP-2 and BMP-4, enhancing signalling (42-44).

Intracellular regulatory factors. Among the intracellular regulatory factors, I-Smads can prevent R-Smads from the binding to the activated type I receptors, as well as blocking the recruitment of Smad 4 to the activated R-Smads (Fig. 1). For example, it has been reported that Smad 6 and 7 can weaken BMP signalling by preventing Smad 1 and 5 activation by the type I receptor, and that they can also prevent the interaction between Smad 1/5 and Smad 4 (45). In addition, BMP signalling can induce Smad 6/7 expression, enhancing the negative regulation of further BMP signalling (46,47). Secondly, as Smads exhibit low binding affinity to the Smad binding elements (SBEs) of target genes, other transcription factors are required for the regulation of BMP-responsive genes, such as Smad interacting protein-1 (48), activating transcription factor (ATF)2 (49), p53 (50), Runx (51) and Forkhead box H1 (FOXH1); FOXH1 can specifically help recruit activated Smad 2/4 to the promoters of target genes in TGF β signalling (52). Additionally, the interactions between certain transcriptional co-activators/repressors and the MH2 binding domain of Smad have been shown to regulate BMP. For example, P300 and CREB-binding protein interactions with Smads can increase the transcription of target genes by making the transcriptional machinery more accessible (53). However,

Figure 1. Smad-dependent and -independent signal transduction of BMPs. BMP signalling is mediated via oligomeric complexes of type I and type II receptors. With canonical Smad-dependent signalling, the BMP ligand binds a preformed oligomeric complex, resulting in the phosphorylation of the glycine-serine region of the type I receptor, and subsequent recruitment and phosphorylation of the pathway-restricted Smad 1/5/8 complex. With the common mediator Smad 4, Smad 1/5/8 is able to translocate to the nucleus and form regulatory complexes with co-factors/transcription factors that will ultimately affect transcription of target genes. This may include upregulation of regulatory elements within the signalling pathway such as the I-Smads (Smad 6 and 7), which provide homeostatic negative feedback regulation. Other negative regulators include secreted BMP antagonists, including Noggin, Chordin and Gremlin, which bind the BMP ligands and prevent receptor interaction, and BAMBI, which is a type I pseudoreceptor that can sequester BMP ligands. In addition, Smurf1/2 can directly induce Smad 1/5/8 ubiquitination and degradation. BMP ligands can also induce other cell signalling pathways via the non-canonical Smad independent signalling pathway. This occurs when the BMP ligand initially binds type I receptors and then recruits the type II receptor into the BISC. This initiates a cascade of adaptor proteins and linking molecules, such as XIAP, TAB and TAK1, with resultant activation of several distinct mitogen-activated protein kinase pathways. This figure was prepared using pathway builder tools from www.proteinlounge.com. BAMBI, BMP and activin membrane-bound inhibitor; BMP, bone morphogenic protein; BISC, BMP-induced signalling complex; I-Smad, inhibitory Smad; JNK, Jun N-terminal kinase; P, phosphorylation; Smurf, Smad ubiquitination regulatory factor; TAB, TGF β -activated binding protein; TAK1, TGF β -activated tyrosine kinase I; TGF β , transforming growth factor β ; XIAP, X-linked inhibitor of apoptosis protein.

transcriptional co-repressors, including Ski and Ski related novel gene, ecotropic viral integration site-1, TG interacting factor (TGIF)1 and TGIF2, prevent Smad 3/4 from binding to the SBE of BMP-responsive genes (54-57). Lastly, the BMP pathway can be influenced by Smad ubiquitination regulatory factor (Smurf)1/2, which induce degradation of Smads (Fig. 1) (58). The regulatory factors that co-ordinate BMP signal transduction have been summarised previously (59).

3. Interaction between BMP and other signalling pathways

BMP and its signalling pathways are not isolated in normal tissues and tumours, but are intricately linked to numerous other growth factors, such as the epidermal growth factor (EGF) receptor (EGFR) (16), receptor tyrosine kinase (RTK)/MAPK (17-19), PI3K/Akt (20-24,60), Wnt (61-65) and hepatocyte growth factor (HGF)/Met pathway (66,67);

together, they form a vast network that regulates various biological functions. There are multiple levels where cross-talk can occur: By regulating ligands, antagonists, receptors, or signalling components expression or activities; by direct interactions with Smads or other signalling components (68); and by incorporating into transcription complexes that alter target gene expression (69-71).

Interaction between BMP and EGFR signalling. EGFR is regarded as an oncogenic factor belonging to the ErbB RTK family, and is overexpressed in various types of cancer, such as colorectal cancer, non-small cell lung cancer, gastric cancer, esophagogastric cancer and pancreatic cancer (72). Intracellular signalling of EGFR is generally mediated through PI3K/Akt, Ras/MAPK and the phospholipase C/protein kinase C (PKC) signalling cascades (73), which are critical for cell proliferation, differentiation, motility and survival (74).

Figure 2. Crosstalk between RTKs and the BMP signalling pathway. BMP activates Smad-dependent pathways through the phosphorylation of R-Smads by its type I receptor, and regulates the translocation of R-Smad and common mediator Smad. The translocation of Smad can be inhibited by ERK signalling. BMP and RTKs also regulate cellular responses through Smad-independent pathways with the involvement of RTK/mitogen-activated protein kinase, RTK/Akt and RTK/Wnt signalling. This figure was prepared using graphical materials from Servier Medical Art (<http://servier.com>). BMP, bone morphogenic protein; EGFR, epidermal growth factor receptor; JNK, Jun N-terminal kinase; R-Smad, regulatory Smad; RTK, receptor tyrosine kinase; TF, transcription factor.

Studies have shown that EGF can directly influence the expression of BMPs. For example, BMP-6 in MCF-7 breast cancer cells can be induced by EGF/EGFR signalling (16). The function of the BMP pathway can also be indirectly regulated intracellularly by signalling molecules downstream of the EGFR, including the RTK/MAPK pathway and the PI3K/Akt pathway.

BMP and the RTK/MAPK pathway. RTK/MAPK signalling can regulate BMP function. Secretion of additional growth factors and cytokines which promote EMT and cell invasion can often result from the interaction between TGFβ and RTK/MAPK pathways (17-19,75,76). ERK has been shown to upregulate Smad 3 in epithelial and smooth muscle cells (77).

The linking region of Smad proteins plays a vital role in interactions between BMP signalling and RTK/MAPK pathways. For example, activation of oncogene Ras can restrict BMP-induced Smad 2/3 signalling, including translocation into the nucleus and binding to the target genes (78). RTK-induced activation of ERK or JNK can phosphorylate endogenous Smad 2/3 (75,76). Furthermore, Thr178, Ser203 and Ser207 within the linker region of Smad 3 can be phosphorylated by ERK, leading to suppression of nuclear translocation (79). However, in MCF10CA1h breast cancer cells, p38 MAPK-induced phosphorylation of the Ser203 and Ser207 residues of Smad 3 facilitate, rather than inhibit, BMP-induced growth inhibition (80). These results suggest

that varied phosphorylation of the Smad 2/3 linker region can lead to different results depending on the specific kinase, as well as the specificity of phosphorylation sites in intracellular events downstream of those activated receptors (81).

ERK1/2 can also prevent the nuclear translocation of Smad 1/5 via similar phosphorylation of their linker region (81). Furthermore, the oncogene Ras can reduce the stability of Smad 4 via the ERK pathway (82). Conversely, activation of JNK and p38 can target a tumour-associated mutant Smad 4, leading to degradation of the protein (83). There is suggested involvement of ERK, JNK and p38 in the regulation of Smad 7 transcription (84-86).

In addition to the above direct effects, MAPKs can also indirectly affect the activity of the BMP pathway by phosphorylating other nuclear transcription factors involved in the pathway within the nucleus, including Jun and activator protein-1 proteins such as Maf, Fos and ATF3 (87). For example, p38 MAPK can activate ATF1, ATF2 and ATF3, which bind Smads and participate in BMP-regulated activities (Fig. 2) (49,88-91).

BMP and the PI3K/Akt pathway. Various studies have shown that BMP signalling can regulate the PI3K/Akt pathway, affecting cell proliferation (20), invasion (21), migration (22), EMT (92,93) and differentiation (94). This regulation can be achieved via activation of Smad-independent pathways (23,24). Secondly, BMP signalling can regulate the

PI3K/Akt pathway by altering the transcriptional level or activity of PTEN. For example, Beck and Carethers (60) showed that long-term exposure to BMP-2 downregulated PTEN in Smad 4-null colon cancer cells through the Ras/ERK pathway. Previous studies showed BMP signalling could enhance PTEN activity (95,96). Conversely, in hematopoietic cells, BMP/Smad signalling can also suppress Akt activity via regulation of SH2 domain-containing 5' inositol phosphatase, which is a lipid phosphatase targeting phosphatidylinositol (3,4,5)-trisphosphate (Fig. 2) (97). Furthermore, PI3K/Akt activation could promote the nuclear translocation of β -catenin (98,99), increase transcription of EGFR and enhance EGFR signalling, forming a vicious circle comprising Akt, β -catenin and EGFR (Fig. 2).

BMP and the HGF/Met pathway. HGF is a regulator of cell motility, mitogenesis, morphogenesis and angiogenesis (100). HGF and its receptor c-Met are actively involved in tumour growth, invasion and metastasis (101). Targeting HGF/c-Met can inhibit the proliferation and invasion of cancer cells both *in vitro* and *in vivo* (101-106).

HGF is mainly produced by fibroblasts and stored in adipose cells (101). Both solid tumour cells and leukaemia cells have also been reported to produce HGF (107-110). For example, overexpression of HGF in prostate cancer has been associated with disease progression and androgen independence (111,112).

There have been studies reporting an interaction between the BMP and HGF signalling. For example, Ye *et al* (29,100) reported that BMP-7, BMPRII and BMPRII were upregulated in prostate cancer cells. Imai *et al* (66) also showed that HGF was able to regulate BMP receptors. A recent study showed that HGF promoted bone regeneration and the formation of new blood vasculature via upregulation of BMP-2 (67). However, the exact transcriptional regulatory mechanism remains unclear. Further investigation is required to determine how the interaction between BMP and HGF is involved in bone metastasis.

BMP and Wnt pathway. The Wnt signalling pathway is essential for cell proliferation, differentiation, migration, survival and other processes (68). Dysregulated Wnt signalling has been observed in colorectal cancer and leukaemia (113). The Wnt signalling pathway has been extensively studied and reviewed, and comprises canonical and non-canonical pathways, the latter of which include the planar cell polarity pathway and Wnt/calcium pathway (61).

In terms of the canonical pathway, upon binding with Wnt ligand, Frizzled receptors and the transmembrane protein low-density lipoprotein receptor-related protein 5/6 induce intracellular signalling and regulation of responsive genes through β -catenin (68). Outside of Wnt signalling, β -catenin is generally degraded by a protein complex which comprises adenomatous polyposis coli, Axin, casein kinase 1 α and glycogen synthase kinase 3 β (GSK-3 β) (61). Degradation of β -catenin is prevented when GSK-3 β and Axin are recruited via the Wnt signalling, leading to nuclear translocation and regulation of Wnt target genes (62-65). Crosstalk between the BMP pathway and the Wnt pathway can occur at multiple levels.

Reciprocal regulation of the expression of pathway ligands and antagonists. The Wnt signalling pathway can regulate the expression of BMPs, BMP co-receptors or their antagonists during embryonic development and in cancerous cells (81). Conversely, BMP-2 and BMP-4 are able to regulate the expression of certain Wnt proteins, such as Wnt-7c (89) and Wnt-8 (114).

Direct interaction between key components in the cytoplasm and nucleus. GSK-3 β can regulate the BMP pathway by phosphorylating the linker region of Smad (68,115-117). In the absence of upstream signalling, Smad 3 can be degraded by GSK-3 β when it is recruited into a protein complex comprising Axin and GSK-3 β (68,116). GSK-3 β can also target the BMP-activated R-Smads, Smad 1 or Smad 3, leading to their degradation and the inhibition of downstream signalling (68). However, the regulation of Smad by GSK-3 β can be prevented by Wnt signalling, leading to a stabilisation of Smad proteins (Fig. 3) (68).

Certain molecules in the BMP pathway are also involved in the regulation of Wnt signalling, such as Smurf1 (118) and Smurf2 (119). Smurf1 and Smurf2 are key molecules in the degradation of Axin, which may consequently disrupt the Wnt signalling. In addition, Smad 3 is also involved in the nuclear translocation of β -catenin (Fig. 3) (120).

Convergence at transcription complexes. In response to Wnt signalling and BMP signalling, activated transcriptional factors such as Smads, T cell factor/lymphoid enhancer-binding factor 1 and cofactors can co-ordinate the regulation of target genes, including gastrin X-twin, Msh homeobox (Msx)2 and T-box transcription factor 6 (Fig. 3) (69-71).

Other pathways. In addition to the above, there are also interactions between the BMP pathway and other pathways, including the Hedgehog (Hh) pathway (121-124), Notch pathway (125-128), Janus kinase/STAT pathway (129-133) and NF- κ B pathway (134-136). For example, Smads can co-ordinate Hh signalling through regulation of GLI (124). BMP and Notch orchestrate cell differentiation and proliferation by targeting common genes (125). BMP and NF- κ B act against each other in co-ordinating immune responses (133).

Overall, the BMP pathway is integrated into various signalling networks through these interactions, thus orchestrating cellular events in tumorigenesis and the progression of malignancies.

4. BMP and tumour-associated angiogenesis

Angiogenesis is essential for the tumour growth and haematological dissemination of cancer cells (137,138). There are two stages in the progression of neovascularisation, an activation phase and a late phase (25). ALK1 and downstream Smad signalling are involved in the activation phase, whilst ALK5 and Smad 2/3 promote maturation of the newly formed vasculature at the late phase (139). It has been shown that BMPs can affect angiogenesis via both direct and indirect routes.

Direct regulation of angiogenesis. BMP-2, 4, 6 and 7, and growth differentiation factor (GDF)-5 can directly

Figure 3. Interactions between BMPs and Wnt/β-catenin signalling. This figure was prepared using graphical materials from Servier Medical Art (<http://servier.com>). BMP, bone morphogenic protein; BMPR, BMP receptor; glycogen synthase kinase 3β; GSK-3β; LEF, lymphoid enhancer-binding factor 1; Smurf, Smad ubiquitination regulatory factor; TCF, T cell factor.

regulate the proliferation and migration of vascular endothelial cells (140-143). For instance, in a chorioallantoic membrane assay, GDF-5 promotes angiogenesis (140). BMP-2 exhibits pro-angiogenic effect in both *in vivo* tumour models (144) and *in vitro* functional assays of vascular endothelial cells (145). In addition to direct effects on vascular endothelial cells, BMP-2 can also promote the motility of vascular smooth muscle cells (146). BMP-4 and BMP-7 can also promote the migration of vascular smooth muscle cell (147,148). Of note, BMP-9/-10 elicit concentration-dependent biphasic effects on angiogenesis, specifically an inhibitory effect at high concentrations and a promotive effect at lower concentrations (Fig. 4) (149).

BMP receptors are important mediators of the pro-angiogenic BMP signal. For example, vascular endothelial cells exhibited higher expression of BMPRI and BMPRII in an *in vitro* tubule formation assay (150).

Studies have shown that distinct Smad pathways may play opposing roles in angiogenesis, and that the same Smad may also play different roles in angiogenesis for distinct types of tissues. For example, Smad 3 mediates an upregulation of vascular endothelial growth factor A (VEGFA), whereas Smad 2 is involved in the regulation of thrombospondin-1 in rat proximal tubular cells NRK52E (151). However, Smad 3-mediated repression of VEGF impaired angiogenesis induced by the gastric cancer cell line SNU484 (152).

As antagonists of BMPs, Noggin and Gremlin are also key regulators of tumour angiogenesis. Noggin can prevent BMP-7-induced angiogenesis (153); conversely, Gremlin can promote angiogenesis by directly targeting VEGF receptors (154).

Indirect regulation of angiogenesis. In addition to these direct effects, BMPs can also indirectly promote angiogenesis via upregulation of VEGF in other cells, such as cancer cells and stromal cells (138). For example, BMP-7 is actively involved in the bone metastasis of prostate cancer cells via regulation of VEGF (153), in addition to its direct regulation of VEGF receptor in vascular endothelial cells (155). BMP-2 promotes tumour-associated angiogenesis via upregulation of VEGF mediated by the p38 pathway in breast cancer (156). In contrast to most BMPs, BMP-9 elicits inhibition of the proliferation of vascular endothelial cells through ALK-1 (157). In addition, BMPs can indirectly induce VEGF (158), basic fibroblast growth factor and TGFβ1 in stromal cells (Fig. 4) (159).

5. BMPs and EMT

EMT is pivotal for the carcinogenesis and aggressive traits acquired by cancer cells during disease progression and metastasis (160,161). BMP-regulated EMT has been implicated in various studies regarding organ development (162,163) and cancer (164-167). *In vitro*, BMP-4 induces EMT-like properties in mammary epithelial cells, transforming them to express an invasive phenotype (165). BMP-2 can enhance the invasion and migration of breast cancer cells (168,169), and the effect may be mediated by the upregulation of ID-1 (170). However, there are other BMPs that play opposing role, such as BMP-7, which was not able to regulate the EMT in a murine mammary epithelial cell line, NMuMG (166). BMP-7 can prevent EMT in breast cancer cells by decreasing vimentin (171). BMP-6 can impair the metastatic capacity of breast cancer cells by

Figure 4. BMPs regulate tumour-associated angiogenesis via multiple mechanisms. This figure was prepared using graphic materials from Servier Medical Art (<http://servier.com>). BMP, bone morphogenic protein; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor.

repressing miR-21 and zinc finger E-box-binding homeobox 1 (ZEB1), which subsequently leads to upregulation of E-cadherin (167,172,173). Both Smad-dependent (174-176) and Smad-independent pathways (178,179) have been observed to be involved in BMP-regulated EMT. For example, BMP signalling could directly activate the transcription of Snail, Twist1 and Msx1/2 (174-176). Regarding the Smad-independent pathway, BMP-2 could induce EMT via the PI3K/Akt pathway (177,178). Furthermore, BMPs could influence tumour invasion by regulating MMPs, extracellular matrix components, cytokines, and immune or inflammatory cells in the tumour microenvironment (158). BMP-4-regulated MMP3 and interleukin-6 are involved in the fibroblast-stimulated invasion of breast cancer cells (179).

6. BMP-co-ordinated interaction between cancer cells and other cellular/non-cellular parts within the tumour

BMPs play an important role in co-ordinating the interactions between cancer cells and the surrounding environment in tumorigenesis and disease progression (158,180). For example, BMP released from tumour-associated stromal cells can induce EMT in cancer cells via the induction of ZEB1 (158). Meanwhile, BMP-2 and BMP-4 secreted by breast cancer cells can reciprocally act on stromal cells to synthesise more tenascin-W and MMPs, which can further enhance their invasiveness (158,180). However, BMP-6, BMP-10 and BMP-15 are able to inhibit the invasion and motility of cancer cells, while BMP-4 exhibits biphasic effects (158).

A number of cells located within tissues are embedded in the ECM, which comprises collagens, proteoglycans and adhesion proteins (181). The ECM is very versatile and undergoes remodelling during tumour development (181,182). Within the tumour stroma, both the cancer cells and cancer-associated

fibroblasts can remodel the ECM (182). Growth factors and cytokines will be released to the ECM, thus contributing to the tumour-supporting microenvironment (182), which is actively involved in disease progression and metastasis. Studies have shown that the remodelling of ECM can be regulated by BMP (183,184). For example, secretion of collagen type I and type III from hepatic stellate cells can be reduced by recombinant human BMP-7 via inhibition of TGF β 1 and its signalling (183). Another study showed that Type I and type III collagen synthesis was significantly up-regulated following BMP-2 treatment in human scleral fibroblasts (184).

The CCN family, including CCN1-6, are a family of matricellular proteins (185-187). CCN proteins are regulators of cell proliferation (188-190), adhesion (191), migration (192,193), survival (194), apoptosis (195), angiogenesis (196) and inflammation (197,198) in numerous types of cells, including vascular endothelial cells and other cells within the stroma.

CCN proteins can directly interact with BMPs; for example, binding of CCN2 to BMP-4 prevents its interaction with BMP receptors, thus inhibiting BMP-induced cell proliferation (199). In addition, there have been reported interactions between CCN3 and BMP-2 (200), CCN4 and BMP-2 (201), and CCN6 and BMP-4 (202). CCN proteins may act as both antagonists and agonists for BMP signalling, depending on the expression profile of related molecules (189,203,204). CCN2 promotes the proliferation of chondrocytes via ERK and JNK signalling pathways, and induces differentiation via p38 (189,203). BMP-2 can suppress the phosphorylation of ERK1/2, which impairs CCN2-promoted proliferation (204). Similarly, CCN2 can abolish BMP-2-promoted cell proliferation by inhibiting Smad-dependent and independent pathways (205).

In addition, studies have shown that certain non-coding RNAs play roles in the interaction between the tumour microenvironment and BMPs. For example, Xiao *et al* (206)

Figure 5. BMPs actively engage in a vicious cycle during the development of bone metastasis. Secretion of BMPs and other cytokines by cancer cells within the bone niche can influence the differentiation of mesenchymal stem cells into osteoclasts and/or osteoblasts, and also regulate the cellular behaviour of osteoclasts and osteoblasts. This results in bone deposition or osteolysis, and facilitates secretion of factors that then further support the establishment of tumour cells within the niche, thus propagating a vicious cycle in bone metastasis. This figure was prepared using graphic materials from Servier Medical Art (<http://servier.com>). BMP, bone morphogenic protein; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; PTHrP, parathyroid hormone-related protein; TGFβ, transforming growth factor β; VEGF, vascular endothelial growth factor.

Figure 6. BMPs in the tumour microenvironment. This figure was generated using ScienceSlides graphics from Visiscience (<https://www.visiscience.com/>). BMP, bone morphogenic protein; ECM, extracellular matrix; EMT, epithelial to mesenchymal transition.

Table I. Related clinical trials.

Target	Specific agent and effect	Agent(s) used in clinical trial	Tumour type	Clinical trial number and phase
CD105	TRC105, a novel antibody targeting CD105 with anti-angiogenic effects	TRC105 + Avastin [®] (bevacizumab)	Kidney cancer	NCT01727089 ^a /Phase 2B randomised
		TRC105	Prostate cancer	NCT01090765 ^a /Phase 1 & 2
		TRC105	Urothelial carcinoma	NCT01328574 ^a /Phase 2A
		TRC105 + Nexavar [®] (sorafenib)	Liver cancer	NCT01306058 ^a /Phase 1B/2A
		TRC105	Liver cancer	NCT01375569 ^a /Phase 2A
		TRC105 + Avastin	Glioblastoma	NCT01648348 ^a /Phase 1B/2B randomised
		TRC105 + Avastin	Glioblastoma	NCT01564914 ^a /Phase 2A
		TRC105 + Avastin	Choriocarcinoma	NCT02396511 ^a /Phase 2
		TRC105	Ovarian cancer	NCT01381861 ^a /Phase 2A
		TRC105 + Xeloda [®] (capecitabine)	Metastatic breast tumours	NCT01326481 ^a /Phase 1B
		TRC105 + Inlyta [®] (axitinib)	Advanced renal cell cancer	NCT01806064 ^b /Phase 1B/2B randomised
		TRC105 + Votrient [®] (pazopanib)	Advanced soft tissue sarcoma	NCT01975519 ^b /Phase 1B/2A
		TRC105 + Avastin	Advanced solid tumours	NCT01332721 ^a /Phase 1B
		TRC105 + paclitaxel/ carboplatin + bevacizumab	Non-small cell lung cancer	NCT03780010 ^b /Phase 1
		TRC105 + bevacizumab	Refractory gestational trophoblastic neoplasia	NCT02664961/Terminated
		TRC105 + sorafenib	HCC	NCT02560779 ^b
		TRC105 + pazopanib	Angiosarcoma	NCT02979899 ^b
		TRC105 + nivolumab	Metastatic non-small cell lung cancer	NCT03181308 ^b
		TRC105 + abiraterone + enzalutamide	Metastatic, castration-resistant prostate cancer	NCT03418324 ^b
		TRC105 + paclitaxel/ carboplatin + bevacizumab	Stage 4 non-squamous cell lung cancer	NCT02429843 ^b
		TRC105	Recurrent glioblastoma	NCT01778530/Terminated
		Bevacizumab + axitinib + pazopanib + capecitabine	Solid tumours	NCT02354612 ^c /Phase 1/2
		TRC105 + Femara [®] (letrozole) + Afinitor [®] (everolimus)	Breast cancer	NCT02520063 ^c /Phase 1/2
		TRC105	Advanced or metastatic solid tumours	NCT00582985 ^a /Phase 1
ALK1	Dalantercept, a fusion protein that binds to ALK1 ligands and inhibits ALK1 signalling	Dalantercept (also known as ACE-041)	Ovarian cancer and primary peritoneal carcinoma	NCT01720173 ^b /Phase 2
		Dalantercept + axitinib	Advanced renal cell carcinoma	NCT01727336 ^a /Phase 2
		Dalantercept + sorafenib	Advanced adult HCC	NCT02024087 ^a /Phase 1 and 2
		ACE-041	Advanced solid tumours, multiple myeloma	NCT00996957 ^a /Phase 1
		Dalantercept	Recurrent or persistent endometrial cancer	NCT01642082 ^a /Phase 2

Table I. Continued.

Target	Specific agent and effect	Agent(s) used in clinical trial	Tumour type	Clinical trial number and phase
		Dalantercept	Squamous cell carcinoma of the head and neck	NCT01458392 ^a /Phase 2
	PF-03446962, a novel monoclonal antibody targeting ALK1 with reported dose-dependent anti-angiogenic activity	PF-03446962 + regorafenib	Colorectal cancer	NCT02116894 ^a /Phase 1
		PF-03446962	Transitional cell carcinoma of bladder	NCT01620970/Unknown
		PF-03446962	HCC	NCT01911273/Terminated
		PF-03446962	Malignant pleural mesothelioma	NCT01486368 ^a /Phase 2
		PF-03446962	Neoplasms	NCT01337050 ^a /Phase 2
		PF-03446962	Advanced solid tumours	NCT00557856 ^a /Phase 2

^aCompleted; ^bongoing; ^crecruiting or enrolling. Table was updated from a previously published table (147). ALK1, activin receptor-like kinase 1; HCC, hepatocellular carcinoma.

reported that microRNA (miRNA/miR)-885-3p inhibits the *in vivo* growth of HT-29 colon cells by disrupting angiogenesis via targeting BMPRI1A, leading to a blockage of BMP signalling. Nishida *et al* (207) found that miR-17-92a and miR-106b-25 clusters were upregulated in colorectal cancer stromal tissues compared with normal stroma; putative targets of these miRNAs predicted by Target Scan were significantly downregulated in cancer stromal tissues, including TGF β R2, Smad 2 and BMP family genes.

7. BMP-related activities in bone metastasis

BMPs enriched in bone matrix are the most potent factors to induce the formation of new bone (58). Numerous studies have reported that BMPs are expressed to varying degrees in a range of benign and malignant bone tumours, such as osteoid osteoma (208), fibrous dysplasia (209), giant-cell tumours (210) and osteosarcoma (211). BMP expression was detected in both human osteosarcoma cell lines (212,213) and human osteosarcoma specimens (214,215). Furthermore, differential expression of BMPs was evident in different histopathological subtypes (215). For example, Yoshikawa *et al* (215) found that high-grade osteosarcoma with a malignant fibre histio-sarcoma-type pattern exhibited the strongest expression of BMP-2/4. Additionally Sulzbacher *et al* (216) reported that BMPs are expressed in osteosarcoma specimens, and their expression is related with osteosarcoma histopathological subtype; high expression of BMP-6 was detected in osteosarcomas with chondroblastic differentiation. Aside from this aberrant expression, little is known regarding the biological function of BMPs in bone tumour cells. Li *et al* (217) showed

that BMP-9 inhibited tumour growth and migration by blocking the PI3K/AKT signalling pathway in an osteosarcoma cell line.

In bone metastatic tumours, BMPs can be synthesised by both cancer cells and osteoblasts (218). There is increasing evidence showing that BMPs are implicated in bone metastases of prostate and breast cancer (156,219,220). BMPs are expressed in both primary prostate tumours and bone metastases with different phenotypic patterns. For example, BMP-7 and GDF-15 are reduced in or absent from primary prostate tumours, but overexpression of both molecules is evident in the bone metastases (219,220). In contrast, BMP-6 is consistently expressed at high levels in both primary tumours and bone metastases of prostate cancer (138). The expression profiles of BMP in primary tumours and bone metastases reflects an adaptive phenotype acquired by the cancer cells during disease progression based upon requirements at different metastatic locations. Elevated expression of BMP in cancer cells is more likely to result in osteoblastic bone lesion by enhancing bone formation (138). In addition to BMP ligands, the BMP antagonist Noggin has been associated with the osteolytic bone lesions of prostate cancer in a murine model (221). Moreover, loss of Noggin can also enhance osteoblastic activity in bone metastasis (222).

BMPs released from cancer cells can regulate osteoblastic or osteoclastic activities in bone lesions, leading to bone formation or resorption. BMPs secreted by osteoblasts/osteoclasts or released from disrupted bone can reciprocally induce EMT in cancer cells, promoting the development of bone lesions (218). These interactions form a vicious cycle during the development of bone metastasis (Fig. 5). However, the exact machinery

underlying the regulation of BMP signalling utilised by the cancer cells requires more intensive investigation.

In addition to direct stimulation, BMPs can also enhance the vicious cycle during bone metastasis via regulation of other factors. For example, osteoprotegerin can be upregulated by BMP-2 in PC-3 cells, acting as a pseudo-receptor for receptor activator of NF- κ B (RANK) ligand (RANKL) to prevent RANKL/RANK-induced osteoclastogenesis (223). BMP-7 can enhance osteoblastic activity via upregulation of VEGF in cancer cells (59). As angiogenic factors, BMPs can also facilitate the formation of bone metastasis by promoting tumour-associated angiogenesis.

8. Therapeutic potential and perspectives

The role played by BMP signalling in cancer progression, metastasis and angiogenesis has raised interest in developing targeted therapies. ALK1 appears to be the most attractive target for preventing tumour-associated new vasculature. PF-03446962, a monoclonal antibody against ALK1 from Pfizer, has exhibited dose-dependent anti-angiogenic effects (224). ALK1-Fc, known as Dalantercept or ACE-041, which exhibits high binding affinity to BMP-9 and BMP-10, has demonstrated an inhibitory effect on angiogenesis and thus tumour growth (225). These anti-angiogenic therapies are currently being evaluated for their therapeutic potential in the treatment of advanced cancers and metastases in different clinical trials (Table I). In addition to ALK1, CD105, a co-receptor for BMP-9, has been targeted with a monoclonal antibody, TRC105, to prevent angiogenesis (226). In a recent analysis of BMP and BMP receptors in gastric cancer in our lab (227), it was shown that elevated expression levels of BMP receptors in GC were highly associated with tumour-associated angiogenesis and lymphangiogenesis, which facilitate the tumour growth, expansion and spread. However, BMP signalling is only part of the orchestrated signalling required for the formation of new vasculature in tumours, with interactions with other pro-angiogenic factors and pathways, such as HGF, VEGF and fibroblast growth factor, also involved (138). More targeted and specific therapeutic approaches to meet the requirements of each individual patient are expected when improved understanding of the exact underlying mechanisms has been obtained. Therefore, the side effects, adverse effects, and imbalances between BMPs and BMP antagonists should be comprehensively considered when they are evaluated as targets to prevent bone metastasis. Additionally, antibodies or small inhibitors targeting the BMP pathway may affect human bone formation during development and tissue repair. Relevant side effects should be considered in future clinical studies.

In contrast to the development of anti-angiogenic therapies, BMPs have been evaluated for their direct anti-cancer potential with caution. This is mainly as a result of their biphasic effects in both primary tumours and secondary tumours. Most BMPs elicit inhibition of proliferation while also acting as potent inducers of EMT through Smad signalling (2). In bone metastases, imbalanced BMP signalling may facilitate either osteoblastic or osteolytic lesions. None of these will likely result in a favourable outcome in patients with solid tumours (158). More intensive research is required to elucidate the precise role played by BMP signalling in more specific windows of malignancy.

BMPs play a role in tumorigenesis and disease progression, not only from the activation of BMP signalling pathways (25-28), but also from BMP-mediated crosstalk between tumour cells and local environments comprising vascular endothelial cells (140-143), fibroblasts, ECM (183,184), osteoclasts and osteoblasts (137,217,219). BMPs can directly induce angiogenesis by acting on vascular endothelial cells (140-141), and also indirectly promote the synthesis and secretion of pro-angiogenic factors in both cancer cells and stromal cells (138,153). BMP-2 and BMP-4 secreted by breast cancer cells can facilitate their invasiveness via upregulation of tenascin-W and MMPs in adjacent fibroblasts (158,180). BMPs can also alter the ECM by promoting the secretion of ECM components, generating a tumour-supporting tumour microenvironment (183,184). BMPs also play an important part in the vicious cycle of forming metastatic bone lesions (59,218,223,228). Emerging evidence shows that the BMP signalling is also involved in the regulation of immunity. For example, BMP signalling can regulate the activation and differentiation of T cells (229,230). BMP-2 could robustly activate macrophages through Smad 1/5/8 signalling pathway. However, potential roles of BMPs in immunotherapies targeted against malignancies remain to be fully investigated.

Collectively, BMP, tumour cells and the tumour microenvironment constitute a large, intricate network that regulates tumour proliferation, EMT, invasion, angiogenesis, development of metastasis and immune regulation (Fig. 6).

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Authors' contributions

ZS, SC, CZ, CL and LY prepared the figures and drafted the manuscript. ZS, CZ and LY revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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