The Dual Role of Bone Morphogenetic Proteins in Cancer

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Bone morphogenetic proteins (BMPs) are a diverse class of molecules with over 20 growth factor proteins that belong to the transforming growth factor-β (TGF-β) family and are highly associated with bone formation and disease development. Aberrant expression of various BMPs has been reported in several cancer tissues. Biological function studies have elicited the dual role of BMPs in both cancer development and suppression. Furthermore, a variety of BMP antagonists, ligands, and receptors have been shown to reduce or enhance tumorigenesis and metastasis. Knockout mouse models of BMP signaling components have also revealed that the suppression of BMP signaling impairs cancer metastasis. Herein, we highlight the basic clinical background and involvement of BMPs in modulating cancer progression and their dynamic interactions (e.g., with microRNAs) in the tumor microenvironment in addition to their mutations and roles in chemoprevention. We also suggest that BMPs should be considered a powerful putative therapeutic target in tumorigenesis and bone metastasis.

Bone morphogenetic proteins (BMPs), originally disclosed as an osteogenic factor in 1965,1 are considered a unique extracellular multifunctional signaling cytokine and represent part of the transforming growth factor-β (TGF-β) superfamily.2 The identification of BMPs has increasingly attracted much attention due to their functions not only in embryonic and postnatal development but also in tumor development and dissemination.3 These roles of BMPs are also highly correlated to various aspects of carcinogenesis, such as angiogenesis, epithelial-mesenchymal transition (EMT), and cancer stem cells. There are several reviews demonstrating the backbone of the BMP signaling pathways.4,5 In summary, BMP ligands bind to their receptors, including type I and type II, to form a heterotetrameric complex, which then activates the phosphorylation, recruitment, translocation, and gene expression of small mothers against decapentaplegics (SMADs) in cells.6 These interactions between BMPs and their antagonists or receptors significantly support the identification of the aggressiveness of primary tumors and establish a mechanism for cancer cell metastasis.

Additionally, various tumor microenvironment factors that strongly affect tumorigenesis interact with BMPs, such as microRNAs (miRNAs), mutations, or drug treatment. miRNAs, small molecules of approximately 18–25 nucleotides in length, can modulate gene expression through translational repression, and their critical roles in cancer progression and osteogenesis were recently manifested.7-8 The molecular mechanisms involved in the negative regulation of BMP activity by miRNAs are also evident. The purpose of this review is to provide a comprehensive understanding of BMPs in modulating cancer progression and their dynamic interactions with tumor microenvironment factors.

Biological Actions of BMPs and Their Involvement in Cancer Antagonists, Ligands, and Receptors

BMP action is closely associated with certain classes of molecules that were recently characterized as BMP antagonists. These BMP antagonists may be broadly divided into three classes: ligand antagonists, which directly bind to BMPs; BMP pro-regions, which complex back with mature BMPs; and receptor antagonists, which prevent BMPs from occupying receptors, thus prohibiting BMPs from binding to their cognate receptors.9,10 Similar to their targets, they possess a signal peptide for secretion and putative N-linked glycosylation sites.9 Although BMP antagonists often exert biological functions as inhibitors of BMP action, in some cases, they function as activators of BMPs during distinct phases of development. Among the various BMP antagonists (Table 1; Figure 1),11-15 Noggin, which was originally isolated from the aquatic frog genus Xenopus16 and is encoded by the NOG gene, has received much attention due to its biological functions in cancer. Sharov et al.17 indicated that Noggin stimulates skin tumorigenesis via Wnt and sonic hedgehog (Shh) signaling pathways in K14-Noggin mice. Noggin was also identified as a specific breast cancer bone metastasis-supporting gene that enhances the metastatic ability of breast cancer cell lines, therefore promoting the tumor-initiating ability of 1833 and SKBR3 cells.18 Similar to Noggin, Gremlin 1 is also a BMP antagonist. Gremlin 1 knockdown suppresses cancer stem cell (CSC) proliferation and tumor development in CSC models.17 This function of Gremlin 1 is believed to be highly associated with stimulating cell cycle progression in CSCs via p21.17 Additionally, Gremlin 1 was investigated as the gene most consistently expressed at a higher level in basal cell carcinoma (BCC) tumor stromal cells compared to those from non-tumor skin.18 Sneddon et al.18 also reported that Gremlin 1 can stimulate tumor cell proliferation. In contrast, overexpression of Noggin leads to decreased tumor size and reduced bone loss.
comparing to control animals in prostate cancer (PC) cells implanted with tibias. Busch et al. reported that Noggin suppresses an EMT-like transition of melanoma cells and inhibits invasive growth of murine B16-F1 cells in the optic cup of the chick embryo. Similarly, Cyr-Depauw et al. found that inducible reduction of ShcA expression impairs mammary tumor development, and this stable reduction in the ShcA level enhances Chordin-like 1 (Chrdl1) in vivo. They also suggested that Chrdl1 blocks breast cancer cell migration and

| Components Involved | Cancer Cell/Model | Related Targets/Pathways | Roles | References |
|---------------------|------------------|--------------------------|-------|------------|
| **Antagonists**     |                  |                          |       |            |
| Noggin              | K14-Noggin mice  | Wnt, Shh                 | reduces tumor size and decreases bone loss compared to untreated control animals | 19 |
|                     | tumor cells      | –                        | promotes skin tumorigenesis | 15 |
|                     | blood vessels    | BMP4                     | suppresses BMP4 induction of vascular endothelial growth factor receptor (VEGFR)-2 | 87 |
|                     | tumor cells      | –                        | Noggin silencing suppresses the growth of PC-3/F/Luc cells in bone xenografts | 88 |
|                     | tumor cells      | BMP7                     | ectopic Noggin expression rescues tumorigenicity of Adenoviral (Ad)/BMP7-infected melanoma cells | 89 |
|                     | B16-F1 cells/chick embryo | BMP2          | suppresses the invasive growth of murine B16-F1 melanoma cells | 20 |
| Follistatin         | Inhibin-deficient mice | –                       | acts as a modulator of gonadal tumor progression and the activin-stimulated wasting syndrome | 90 |
| Gremlin 1           | basal cell carcinoma tumors | BMP4          | most consistently expressed at a higher level in BCC tumor stromal cells compared to non-tumor skin | 18 |
|                     | tumor cells      | BMP2, p21                | promotes proliferation and tumor growth by non-stem glioma cells | 17 |
| Drm/Gremlin         | chick embryo CAM implants | BMP4          | interacts directly with target endothelial cells | 91 |
| DMH1                | primary mammary tumor | SMAD1/5/8, inhibitor of DNA-binding (ID)1, Ecad | alters tumor-associated fibroblasts | 92 |
| **Receptors**       |                  |                          |       |            |
| BMPR2               | tumor cells      | SMAD1/5/8, pRb, Cyclin B | BMPRII expression is associated with clinicopathological features of chondrosarcomas | 93 |
|                     | MMTV.PyVmT mice  | cytokines, growth factors | BMPRII suppression inhibits chondrosarcoma tumor growth | 94 |
| BMPRIA and BMPPIB   | BMPRIA BMPPIB double-mutant mice | SMAD1/5 | ovarian tumor development was observed in BMPRIA BMPPIB dknockout (dko) mice but not in BMPRIA cKO or BMPPIB cKO mice | 95 |
| BMPRIA              | Muc5ac           | BMP signaling via BMPRIA inhibits tumorigenesis at gastric junctional zones | 28 |
| BMPRIA              | K19-C2mE mice    | PGE2                     | BMP suppression and prostaglandin E2 (PGE2) induction lead to gastric hamartoma development independent of the Wnt/β-catenin pathway | 96 |
| BMPRIB              | invasive ductal carcinoma (IDC) patients | –                       | low expression of BMPRIB shows poor prognosis of breast cancer and is sensitive to taxane-anticycline chemotherapy | 97 |
| BMPRIB              | breast tissue samples | –                       | reduced expression of BMPRIB increases the proliferation of breast cancer cells | 98 |
| BMPRIB              | estrogen receptor (ER)-stratified breast tumors | miR-125b | BMPRIB transcript is a direct target of miR-125b, which differentially modulates the C/T allele variants of rs1434536 | 99 |
| BMPRIA              | KO mice          | EMT-like changes         | BMPRIA acts as a tumor promoter in human breast cancer | 27 |

Table 1. BMP Components in Various Cancers

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invasion by regulating BMP-stimulated matrix metalloproteinases (MMP)2 and MMP9 enzymatic activity.21

Furthermore, BMPs are considered multifunctional cytokines belonging to the TGF-β superfamily. Like other members of the TGF-β superfamily, BMPs can bind and form heteromeric complexes with two types of serine/threonine kinase receptors (type I and type II) on the cell surface, both of which are required for signal transduction.22–24 Therefore, they modulate tumor growth, differentiation, or apoptosis in a variety of cancers (Tables 1 and 2; Figure 2).25,26 Pickup et al.27 recently found that deletion of the BMP receptor type IA (BMPR1A) impairs mammary tumor formation and metastasis in conditional knockout mice, suggesting that BMPR1A acts as a tumor promoter in human breast cancer. However, Bleuming et al.28 demonstrated that the squamous columnar and gastrointestinal junctional zones in mice are epithelial areas that enhance oncogenesis; nevertheless, these areas are inhibited by the BMPR1A signaling pathway.

**BMPs: Tumor Suppressors or Oncogenes?**

At present, there is a greater understanding of the critical functions of BMPs in cancer. BMP4 was reported to stimulate breast cancer cell invasion and promote bone remodeling.29 Clinically, Paez-Pereda et al.30 described the role of BMP4 in tumorigenesis with the stimulation of tumor formation. In contrast, emerging studies have suggested that BMPs exhibit tumor-suppressive functions in cancer development. Ye et al.31 suggested that BMP10 suppressed the growth and aggressiveness of PC cells by inducing apoptosis via a SMAD-independent pathway, which was correlated to the modulation of extracellular signal-regulated kinase (ERK)1/2 and X-linked inhibitor of apoptosis protein (XIAP). Cao et al.32 also reported that BMP4 suppresses breast cancer metastasis by inhibiting myeloid-derived suppressor cell activity in mice. They also suggested that BMP4 decreases granulocyte-colony stimulating factor (G-CSF) secretion via the suppression of nuclear factor-kB (NF-kB) activity.32 Taken together, the wealth of conflicting studies indicated that the same ligand may work differently depending on the cancer type, and it seems that multiple members in the BMP family should not be tested as simply equals.33 Furthermore, the same BMP ligand within the same cancer type is likely to work differently, depending on the study. Therefore, conclusions based on simply one cell line may be too straightforward, so diverse cancer cell lines or different types of tumors should be used; the suitable consensus is that multiple BMPs and their involvement might act as both tumor promoters and oncogenes in cancer development (Figure 3).34–39 Although there is no definitive correlation between BMPs and the development of tumorigenesis, a large number of studies indicate a positive effect of BMPs on cancer development. Therefore, BMPs should be paid careful attention for cancer patient treatment.

**Aberrance of BMPs and Their Implications in Cancer**

There is increasing evidence that BMP proteins and BMP signaling components are novel biomarkers with significant therapeutic implications for cancer treatment even though the expression of specific BMPs remains controversial. Among the various cancers summarized in Table 3, prostate and breast cancers have been commonly used to study BMP signaling due to the unique features of their metastasis to bone tissues. Horvath et al.40 suggested that BMP2 may act as a marker of poor prognosis due to its significant decrease in PC compared to benign prostate tissue. Furthermore, Morrissey et al.41 found that BMP7 protein is expressed at higher levels in PC bone
### Table 2. Bone Morphogenetic Protein Ligands in Various Cancers

| Tumor Type | Cell Type/Model | BMPs and Their Involvement | Related Targets or Pathways | Expression and Functions | References |
|------------|------------------|-----------------------------|----------------------------|--------------------------|------------|
| Lung cancer | A549/nude mice | BMP2 | ID-1, SMAD1/5 | highly overexpressed in human NSCLC compared to normal lung tissue or benign lung tumors | 100,101 |
| | | | Noggin, SMAD1/5/8, ERK-1/2 | enhances the angiogenic response in developing tumors | 102 |
| | 150 patients and 69 healthy volunteers | BMP2 | – | a significantly higher level of serum BMP-2 was observed relative to the control group | 103 |
| | A549/nude mice | BMP4 | p-ERK, VEGF, SMAD1 | BMP4-treated cells exhibit significantly smaller xenograft tumors compared to untreated cells | 104 |
| | lung tissues | BMP2 and BMP4 | miR-200, JAG2 | knockdown of BMP4 suppresses metastasis and tumorigenesis | 105 |
| | lung cancer patients | BMP2 and BMP4 | – | significantly higher in lung cancer samples than in adjacent normal lung tissues | 106 |
| | A549/nude mice | BMP3B | c-Myc | re-expressing of BMP3B caused tumors to grow significantly slower than those not expressing BMP3B | 107 |
| | lung cancer patients | BMP3b and BMP6 | mutation of K-ras codon 12 | BMP3b and BMP6 genes are common targets of epigenetic inactivation in NSCLC | 108 |
| | lung tissues | BMP7 | SMAD1 | higher BMP7 expression may be an indicator of bone metastasis | 109 |
| | A549/mouse | Spp24 | BMP2 | BMP7 expression is associated with lymph node involvement in patients with lung cancer | 110 |
| | MDA-MB-231/nude mice | BMP7 | – | stable overexpression of BMP7 suppresses de novo formation and progression of osteolytic bone metastases | 34 |
| | primary tumor specimens | BMP4 and BMP7 | – | BMP4 and BMP7 are the most frequently expressed and display the highest expression levels | 111-113 |
| Breast cancer | MDA-MB-231 cells and pre-adipocytes, adipocytes/Nude mice | BMP9 | signal transducer and activator of transcription (STAT)3, ERK-1/2, Akt | inhibits the growth and metastasis of breast cancer cells | 114 |
| | MDA-MB-231/mouse xenograft model | BMP4 | – | suppresses breast tumor growth and decreases leptin expression in pre-adipocytes/adipocytes | 115 |
| | BALB/c mice | BMP4 | NF-κB | causes a trend toward metastasis formation, especially in bone | 32 |
| | tumor patients | BMP12 | – | BMP12 expression is decreased in breast tumors and is associated with a poor prognosis | 117 |
| Adrenocortical carcinoma | tumors | BMP2 and BMP5 | Akt | expression of BMP2 and BMP5 is lower in ACC and adrenocortical tumor cell lines | 118 |

*Continued on next page*
| Tumor                          | Cell Type/Model       | BMPs and Their Involvement | Related Targets or Pathways | Expression and Functions                                                                 | References |
|-------------------------------|-----------------------|----------------------------|-----------------------------|------------------------------------------------------------------------------------------|------------|
| Medulloblastoma (MB)          | xenograft model       | BMP2                       | p38, apoptosis              | BMP2 mediates retinoid-stimulated apoptosis                                               | 82         |
| mice MB                       | Medulloblastoma (MB)  | BMP4                       | Atoh1, Shh                  | BMPs are potent inhibitors of MB                                                           | 119        |
| tissue MB                     | Medulloblastoma (MB)  | BMP7                       | Myc                         | BMP4 inhibits mouse MB proliferation in vivo                                             | 120        |
| primary tumors                |                       | BMP3                       |                             | BMP3 is downregulated in 50 of 56 primary tumors                                          | 121        |
| colorectal tumors             |                       | BMP4                       | PI3K/Akt                    | recombinant BMP4 induces apoptosis and differentiation of chemoresistant colorectal cancer stem cells (CRC-SCs) | 122        |
| HCT16/xenograft tumor model   |                       | BMP2                       |                             | activates the canonical and non-canonical BMP signaling pathways                          | 123        |
| mouse model of gastric        | BMP signaling         | PGE2                       |                             | forced expression of BMP2 stimulates a significantly induced level of apoptosis            | 125        |
| tumorigenesis                 |                       |                            |                             |                                                                                          | 124        |
| serum from patients           | BMP2                  | ERK-1/2, Akt, EMT           |                             | BMP suppression appears to contribute to gastric cancer development                        | 126        |
| cancer patients               |                       |                            |                             |                                                                                          | 127        |
| mice                          |                       | DNA damage                 |                             |                                                                                          | 128        |
| mice infected with            |                       |                            |                             |                                                                                          | 129        |
| Helicobacter spp.             |                       |                            |                             |                                                                                          | 130        |
| MDA-PCa-119b/tumor            |                       | BMP4                       | cytokines: Interleukin (IL)-8, GRO, C-C motif chemokine ligand (CCL)2                   | BMP4 mediates osteogenesis in the progression of PC in bone                               | 131        |
| Prostate cancer (PC)          | human PC tissue       | BMP7                       | SMAD1/4/5, E-cadherin, vimentin | acts as a potential inhibitor of PC bone metastasis in vivo                               | 132        |
| PC patients                   |                       | BMP7                       |                             | BMP7 induces reversible senescence in PC                                                 | 133        |
| cancer cases                  |                       | BMP6                       | ID-1, MMP activation        | associated with increased ID-1 protein level and a more invasive phenotype               | 134        |
| epithelial tumor cells        |                       | SMAD                       |                             | related to stromal features and shorter postsurgical overall survival in pancreatic ductal adenocarcinomas | 135        |
| Pancreatic cancer             | PANC-1 cells/ xenograft tumor model | BMP2 | Spp24 | BMP2 dramatically promotes tumor growth                                                | 136        |
|                              |                       |                            |                             | secreted phosphoprotein (Spp24) abolishes the effect of BMP-2 and induces tumor shrinkage when used alone | 137        |

(Continued on next page)
and soft tissue metastasis compared to primary PC. They also suggested that BMP7 signaling may be associated with clinical disease progression.41 Ye et al.42 previously reported that the upregulation of BMP7 in prostate tumors may be correlated with hepatocyte growth factor (HGF) or scatter factor (SF) (HGF/SF) in an in vivo murine tumor model. Ma et al.43 indicated that the expression of BMP2, BMPR1B, and BMPR2 is low in epithelial ovarian cancer tissue and suggested that these variations or loss of expression may elicit poor prognosis for ovarian cancer patients. Taken together, the aberrance of BMPs and their involvement in cancer have been implicated in various solid tumors and disease-specific bone metastasis.

**BMPs and Their Components with Mutations in Cancer**

Previous studies have shown that heterozygous mutations in BMPR2 were correlated to human familial and idiopathic pulmonary arterial hypertension, and decreased BMPR2 expression has been found in the lung tissues of all patients with pulmonary hypertension tested.44–46 Kraunz et al.47 found that the co-inactivation of BMP3b and BMP6 is highly associated with the mutation of k-ras (codon 12) in lung cancer, and these genes are common targets of epigenetic inactivation in non-small-cell lung cancer (NSCLC). Furthermore, BMP signaling may also be inactivated by a germline mutation of BMPR1A in the colon cancer predisposition syndrome, juvenile polyposis (JP).48,49 Recently, Voorneveld et al.50 provided evidence that p53 mutation can affect the activity of BMP signaling, thereby modulating Wnt signaling activity despite adenomatous polyposis coli (APC)/β-catenin mutations. Inactivation of activin signaling via mutations in activin type II (ACVR2) was also found in the majority of colon tumors with microsatellite instability.51,52 Therefore, the activity of BMPs and their involvement may be altered by changes in gene expression and mutations in cancer.

**Negative Modulation of BMPs by miRNAs**

miRNAs are short, non-coding RNAs of 18–25 nucleotides in length that play a significant role in numerous tumorigenic processes.7 Braig et al.15 determined the molecular mechanisms leading to the overexpression of BMP4 in melanoma cells compared to normal melanocytes and identified miR-196a as a BMP4-negative regulator that directly suppresses BMP4 in malignant melanoma. Similarly, by profiling miRNAs during BMP2-stimulated osteogenesis of C2L12 mesenchymal cells, Li et al.54 characterized two representative miRNAs and showed that miR-133 directly targets Runx2, an early BMP response gene essential for bone formation, and that miR-135 may also target SMAD5, a key transducer of the BMP2 osteogenic signal. Rai et al.55 employed unbiased genome-wide approaches in diffuse large B cell lymphoma and found that miR-155 directly targets the BMP-responsive transcriptional factor, SMAD5. miR-155 overexpression suppressed SMAD5 expression and disrupted its activity.56 In 100 hepatocellular carcinoma tissues, Li et al.56 found that miR-148a directly inhibited the expression level of activin A receptor type 1 (ACVR1), a key receptor in the BMP signaling pathway. They also determined that this miRNA is related to cancer development and metastasis via the ACVR1/BMP/Wnt...
In primary mouse keratinocytes following BMP4 treatment, Ahmed et al. identified miR-21, which is significantly suppressed by BMP4. They also found that miR-21 regulates two groups of BMP4 target genes, including tissue inhibitors of metalloproteinases (TIMP)1, TIMP3, and programmed cell death (PDCD)4. In primary keratinocytes and HaCaT cells, miR-21 can also prevent the inhibitory effects of BMP4 on cell migration and proliferation. Consistent with this observation, Qin et al. also showed that bone morphogenetic protein receptor II (BMPRII) is a direct target of miR-21 in PC3 and LnCap PC cells. Together, these studies indicate the existence of an additional level of complexity in the modulation of the BMP pathway.

**BMPs and Drug Resistance in Cancer**

Cancer cell chemoresistance is considered as a major impediment in medical oncology. Emerging studies indicated that drug resistance of cancer cells is able to be related to various factors such as epigenetics, miRNAs, and cytokines. Such a phenomenon has been indicated for the superfamily member TGF-β, which is suggested as an emerging player in drug resistance. BMPs and their components have also been implicated to various different drug resistance of cancer. Indeed, Wang et al. recently demonstrated that the resistance of lung squamous cell carcinoma patients with epidermal growth factor receptor (EGFR) mutations to EGFR tyrosine kinase inhibitors (EGFR-TKIs) was, in part, due to activation of the BMP-BMPR-SMAD1/5 signaling pathway. Subsequently, the combined treatment of these cancer cells together with inhibitors specific to BMPR may overcome the resistance to EGFR-TKIs. Xian et al. enrolled 938 patients with stage III or IV NSCLC and reported that patients with high-level expression of BMP4 had a significantly higher chance of being resistant to chemotherapy than those with low BMP4 expression. Du et al. reported that knockdown of BMP2 increased chemo-resistance of the MCF-7 breast cancer cell line. Similarly, Liu et al. also suggested that hypermethylation contributed to the regulation of BMP6 during the acquisition of drug resistance in breast cancer cells. BMP6 was recently indicated to induce castration resistance in breast cancer cells. However, employing the HH inhibitor, IPI-926, prevented the resistance to chemotherapy in breast cancer cells. Choi et al. also demonstrated that treatment with BMP2 in vivo leads to increased tumor growth and chemotherapy resistance. Octamer-binding transcription factor (Oct) and nestin, stem cell markers that promote cell survival, are highly associated with resistance to chemotherapeutic agents, suggesting that the failure of cancer treatment and BMP signaling is a growth stimulator in cancer cells expressing Oct4 or nestin. Lan- genfeld et al. employed DMH2, a small molecule BMP inhibitor, and found that DMH2 also significantly suppressed cell growth of nestin/GFP- or Oct4/GFP-expressing cells. Similarly, Coffman et al. found that human ovarian carcinoma-associated mesenchymal stem cells (CA-MSCs) promote chemotherapy resistance of ovarian cancer by stimulating the BMP4/Hedgehog (HH) signaling pathway. However, employing the HH inhibitor, IPI-926, prevented...
CA-MSC-mediated increases in chemotherapy resistance and tumor growth.72

Conversely, Persano et al.73 reported that BMP2-based treatment increased the temozolomide response in hypoxic drug-resistant glioblastoma multiforme (GBM)-derived cells. Eramo et al.74 indicated that chemotherapy resistance is one of the leading reasons for poor GBM among the most aggressive tumor types. However, Tate et al.75 found that a BMP7 variant may reduce tumor growth and stem cell marker expression in subcutaneous and orthotopic glioblastoma stem-like xenografts. Lian et al.76 also demonstrated that knockdown of BMP6 in breast cancer cells increased chemoresistance to doxorubicin by upregulating multiple drug resistance (MDR)-1/P-glycoprotein expression and activating the ERK signaling pathway.
Overall, BMPs and their involvements highly related to drug resistance of cancer cells and employing BMP family inhibitors may promisingly enhance efficiency of cancer treatment.

**Bioactive Compounds Targeting the BMP Pathway**

Natural compounds have been employed to cancer treatment for thousands of years and therefore, targeting BMPs with dietary natural-product-derived compounds is considered one of several therapeutic strategies in preventing cancer progression. To illustrate, Craft et al. demonstrated that genistein, a component of soybean, therapeutically induces reversion to a low-motility phenotype in aggressive endoglin-deficient human PC cells by activating anaplastic lymphoma kinase (ALK2)-SMAD1 endoglin-associated signaling. Hallahan et al. indicated that retinoid treatment may abrogate tumor growth in medulloblastoma xenografts. Using specific retinoid receptor agonists and gene expression arrays, they identified BMP2 as a candidate mediator of retinoid activity. Retinoid-stimulated expression of BMP2 is subsequently important and sufficient for apoptosis of retinoid-responsive cells, and the expression level of BMP2 by retinoid-sensitive cells is sufficient to promote apoptosis in surrounding retinoid-resistant cells. Kodach et al. also reported that statins, which induce apoptosis in colorectal cancer (CRC) cells via stimulation of BMP2, may only be effective in SMAD4-expressing CRCs and have adverse effects in SMAD4-negative tumors. Subsequently, based on these possible effects of statins on bone tissue, Chen et al. found that simvastatin induces osteoblast viability and differentiation via the RAS/SMAD/ERK/BMP2 signaling pathway.

Additionally, by employing in silico screening, Ahmed et al. attempted to identify new low-molecular-weight drug-like compounds with high theoretical scores to bind to Noggin to suppress the BMP-Noggin interaction. Sanvitale et al. also identified a new small molecule inhibitor of BMP signaling, K02288, a highly selective 2-aminopyridine-based inhibitor with in vitro activity against ALK2 at lower concentrations, similar to the current lead compound, LDN-193189, by screening a panel of 250 recombinant human kinases. In conclusion, the identifying bioactive compounds that specifically target BMPs and their involvements will provide the promising for high-through screening in a range of in vitro and in vivo models of disease where BMP functions are implicated. The progression of this study will drive toward clinical trials for new potential inhibitors of BMPs and their involvements in cancer treatment.

**Conclusions**

From the data described in the present review, it is necessary to understand the roles of BMPs and their functions in tumor growth so that the pleiotropic effects of BMPs can be manipulated by antagonists, small molecular inhibitors, miRNAs, or bioactive compounds. Altered expression of BMPs has been detected in many types of cancers and can be used as a marker of good prognosis in cancer treatment. However, the specific regulatory factors responsible for the dual behaviors of BMPs in cancer remain unclear. Further studies on a larger number of cancers are needed to investigate the molecular events involved in BMP signaling and their functions in tumorigenesis and metastasis. This review also supports the general conclusion that BMPs are a double-edged sword in cancer biology, as they can serve as tumor suppressors or tumor promoters depending on the type of cell or tissue in the microenvironment, epigenetic background of the patient, or stage of tumor growth.

### Table 3. Expression of BMPs and Their Involvement in Cancer

| Cancer Type       | Cell Type/Model | BMPs and/or Their Related Components | Expression | Functions                                                                                      | References |
|-------------------|-----------------|--------------------------------------|------------|-----------------------------------------------------------------------------------------------|------------|
| Bladder cancer    | patient specimens | BMP2, BMP7                           | decreased  | low expression of BMP2 and BMP7 is highly correlated to a shorter time to recurrence           | 135        |
|                   | human tissues   | BMPR1A, BMPR1B, BMPR2                | decreased  | the levels of expression of BMP are not indicative of tumor stage                              | 137        |
| Prostate cancer   | human tissues   | BMP2                                 | decreased  | BMPs often lose their expression during the progression of prostate cancer                      | 40         |
|                   | human tissues   | BMP2                                 | decreased  | BMP2 is downregulated in prostate cancer compared to benign prostate tissue                    | 40         |
|                   | human tissues   | BMP2                                 | increased  | tumors with high BMP-2 expression have higher rates of local failure compared to other tumors with low expression | 138        |
|                   | human tissues   | BMP2                                 | increased  | associated with tumor invasion and progression in papillary thyroid carcinoma                  | 139        |
|                   | patient tissues | BMP4                                 | increased  | patients with cancer-associated anemia (CRA) have high expression of BMP6                     | 140        |
|                   | anemia/patients | BMP6                                 | increased  | negatively related to s-Hemojuvelin (HJV)                                                    | 141        |
| Blood             | tissues         | BMP12                                | decreased  | associated with a poor prognosis                                                              | 135        |
|                   | tissues         | BMP12                                | decreased  | the expression of BMP7 in metastatic and primary melanomas is strongly expressed compared to weak expression in normal nevi | 141        |
| Melanoma cancer   | tissues         | BMP7                                 | increased  |                                                                                               | 141        |
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