Molecular Therapy
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Review

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),[11–13] Noggin, which was originally isolated from the aquatic frog genus *Xenopus*[14] and is encoded by the NOG gene, has received much attention due to its biological functions in cancer. Sharov et al.[15] 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.[16] 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

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Table 1. BMP Components in Various Cancers

Components Involved	Cancer Cell/Model	Related Targets/Pathways	Roles	References
Antagonists				
Noggin	K14-Noggin mice	Wnt, Shh	promotes skin tumorigenesis	15
	tumor cells	–	reduces tumor size and decreases bone loss compared to untreated control animals	19
	blood vessels	BMP4	suppresses BMP4 induction of vascular endothelial growth factor receptor (VEGFR)-2 in embryonic blood vessels	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 *in vivo*	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
			promotes tumor cell proliferation	
	tumor cells	BMP2, p21	promotes proliferation and tumor growth by non-stem glioma cells	17
			induces cell cycle progression via p21	
Drm/Gremlin	chick embryo CAM implants	BMP4	interacts directly with target endothelial cells	91
			acts as a proangiogenic factor to regulate angiogenesis	
DMH1	primary mammary tumor	SMAD1/5/8, inhibitor of DNA-binding (ID)1, Ecad	reduces metastasis in a mouse model of breast cancer	92
			alters tumor-associated fibroblasts	
			suppresses tumor growth	
Receptors				
BMPR2	tumor cells	SMAD1/5/8, pRb, Cyclin B	BMPRII expression is associated with clinicopathological features of chondrosarcomas	93
			BMPRII suppression inhibits chondrosarcoma tumor growth *in vivo*	
	MMTV.PyVmT mice	cytokines, growth factors	disruption of BMPRII is associated with tumor development and metastasis	94
			loss of BMPRII signaling in tumors leads to increased inflammation and myeloid cell infiltrates	
BMPIA and BMPIB	BMPRIA BMPRIB double-mutant mice	SMAD1/5	ovarian tumor development was observed in BMPRIA BMPRIB dknockout (dKO) mice but not in BMPRIA cKO or BMPRIB$^{-/-}$ mice	95
BMPR1A	mice	Muc5ac	BMP signaling via BMPR1A inhibits tumorigenesis at gastric junctional zones	28
BMPR1A	K19-C2mE mice	PGE_2	BMP suppression and prostaglandin E_2 (PGE_2) induction lead to gastric hamartoma development independent of the Wnt/β-catenin pathway	96
BMPR1B	invasive ductal carcinoma (IDC) patients	–	low expression of BMPR1B shows poor prognosis of breast cancer and is sensitive to taxane-anthracycline chemotherapy	97
	breast tissue samples		reduced expression of BMPR1B increases the proliferation of breast cancer cells	98
BMPR1B	estrogen receptor (ER)-stratified breast tumors	miR-125b	BMPR1B transcript is a direct target of miR-125b, which differentially modulates the C/T allelic variants of rs1434536	99
BMPR1A	KO mice	EMT-like changes	BMPR1A acts as a tumor promoter in human breast cancer	27
			BMPR1A deletion in mammary carcinomas inhibits tumor development	

compared to control animals in prostate cancer (PC) cells implanted with tibias.[19] Busch et al.[20] 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.[21] 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

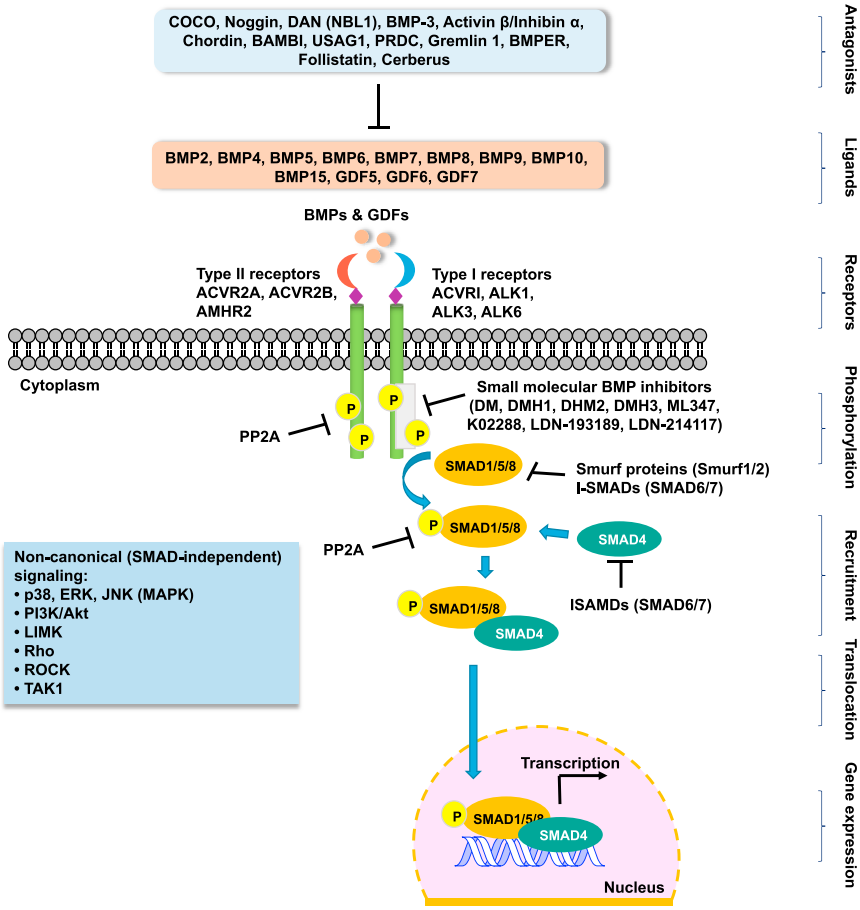

Figure 1. BMP-Mediated Signaling Pathways
The type II receptor *trans*-phosphorylates the type I receptor, which, in turn, stimulates transcriptional regulators called SMADs, which transduce the signal to the nucleus to modify gene expression.

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 squamocolumnar 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-κB (NF-κB) 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 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	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
				stimulates cell proliferation, migration, and invasiveness	
				enhances the growth of metastasis tumors; promotes tumor development	
	human aortic endothelial cells (HAEC)/tumor neovasculature		Noggin, SMAD1/5/8, ERK-1/2	enhances the angiogenic response in developing tumors	102
	150 patients and 69 healthy volunteers		–	a significantly higher level of serum BMP-2 was observed relative to the control group	103
				positively correlates with the stage and metastasis burden	
				identified as a probable predictor of survival in NSCLC patients	
	A549/nude mice	BMP4	p-ERK, VEGF, SMAD1	BMP4-treated cells exhibit significantly smaller xenograft tumors compared to untreated cells	104
	lung tissues		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
				a positive correlation between VEGF and BMP2 gene expression has been indicated	
	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	47
	lung tissues	BMP7	SMAD1	higher BMP7 expression may be an indicator of bone metastasis	108,109
				BMP7 expression is associated with lymph node involvement in patients with lung cancer	
	A549/mouse	Spp24	BMP2	Spp24 reduces tumor growth in both soft tissue and intraosseus environments	110
Breast cancer	MDA-MB-231/nude mice	BMP7	–	stable overexpression of BMP7 suppresses *de novo* formation and progression of osteolytic bone metastases	34
				BMP7 treatment suppresses intrabone tumor growth	
	primary tumor specimens			high expression of BMP7 in breast cancer tissues compared to normal breast tissues	111–113
	breast tumors	BMP4 and BMP7	–	BMP4 and BMP7 are the most frequently expressed and display the highest expression levels	114
	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	115
				suppresses breast tumor growth and decreases leptin expression in pre-adipocytes/adipocytes	
	MDA-MB-231/mouse xenograft model	BMP4	–	causes a trend toward metastasis formation, especially in bone	116
	BALB/c mice		NF-κB	suppresses leukocytosis, splenomegaly, and metastasis	32
				reduces G-CSF secretion by suppressing NF-κB activity	
	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
				BMP2 and BMP5 reduce baseline and IGF-I-induced Akt protein phosphorylation	

(*Continued on next page*)

Table 2. *Continued*

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	BMP4	Atoh1, Shh	BMPs are potent inhibitors of MB	119
				BMP4 inhibits mouse MB proliferation *in vivo*	
	tissue MB	BMP7	Myc	Myc-dependent modulation of BMP7 activation	120
Colorectal cancer	primary tumors	BMP3	–	BMP3 is downregulated in 50 of 56 primary tumors	121
				related to early polyp formation and colorectal tumor growth	
	colorectal tumors	BMP4	PI3K/Akt	recombinant BMP4 induces apoptosis and differentiation of chemoresistant colorectal cancer stem cells (CRC-SCs)	122
				activates the canonical and non-canonical BMP signaling pathways	
	HCT16/xenograft tumor model	BMP2	–	forced expression of BMP2 stimulates a significantly induced level of apoptosis	123
	mouse model of gastric tumorigenesis	BMP signaling	PGE_2	promotes epithelial cell differentiation	124
				BMP suppression appears to contribute to gastric cancer development	
	serum from patients	BMP2	–	the mean serum BMP-2 level from patients with bone metastasis is significantly higher compared to patients without bone metastasis	125
				plays a role in progression to metastatic disease in gastric cancer	
	cancer patients		ERK-1/2, Akt, EMT	BMP2 stimulates the expression of ERK-1/2, Akt, N-cadherin, and MMP2	126
				BMPRII serves as a biomarker to antagonize the progression of gastric cancer	
	mice		DNA damage	BMP-SMAD1 loss-of-function causes tumorigenesis	127
	mice infected with *Helicobacter spp.*		CDX2, SOX2	BMP pathway is associated with *H. pylori* infection in the modulation of intestinal and gastric-specific genes	128
Prostate cancer (PC)	MDA-PCa-118b/tumor	BMP4	cytokines: Interleukin (IL)-8, GRO, C-C motif chemokine ligand (CCL)2	BMP4 mediates osteogenesis in the progression of PC in bone	129
	human PC tissue	BMP7	SMAD1/4/5, E-cadherin, vimentin	acts as a potential inhibitor of PC bone metastasis *in vivo*	130
	PC patients		–	BMP7 induces reversible senescence in PC	
	cancer cases	BMP6	ID-1, MMP activation	associated with increased ID-1 protein level and a more invasive phenotype	36
Pancreatic cancer	epithelial tumor cells	SMAD	–	related to stromal features and shorter postsurgical overall survival in pancreatic ductal adenocarcinomas	131
	PANC-1 cells/ xenograft tumor model	BMP2	Spp24	BMP2 dramatically promotes tumor growth	132
				secreted phosphoprotein (Spp)24 abolishes the effect of BMP-2 and induces tumor shrinkage when used alone	

(*Continued on next page*)

Table 2. *Continued*

Tumor	Cell Type/Model	BMPs and Their Involvement	Related Targets or Pathways	Expression and Functions	References
Ovarian cancer	SK-OV-3/nude mice	–	–	high SMAD5 expression is associated with poor prognosis in serous ovarian cancer patients	133
				stimulates the proliferation of serous ovarian cancer	
	tumor cells	BMP2	–	BMP2 promotes $ALDH^+CD13^+$ cell expansion and inhibits progenitor cell growth	67
				BMP2 suppression or knockdown inhibits tumor growth *in vivo*	
				BMP2 increases chemoresistance	
Bladder cancer	archival tissues of the human bladder	BMP4	–	restoration of BMPRII expression leads to a decreased rate of tumor development	134
	tumor patients	BMP2, BMP4, and BMP7	–	the expression of BMP2 and BMP7 is downregulated in infiltrating urothelial carcinoma and is associated with a shorter time to recurrence	135
				BMP4 is downregulated in non-invasive tumors	
	cancer cases	BMP2	–	BMP2 is significantly higher in cases with bone metastasis and is positively related to cases with muscle invasion	136

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] Krauz 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.[53] 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.[55] 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

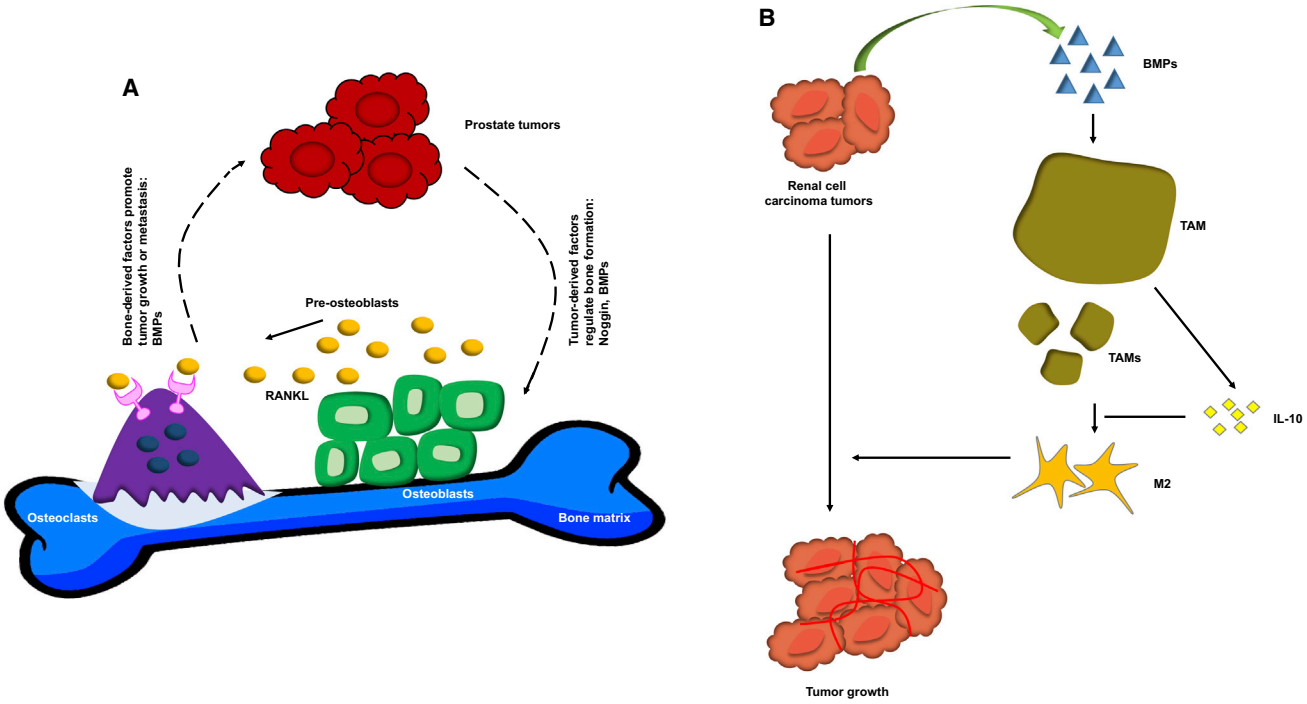

Figure 2. The Role of BMPs in Tumorigenesis

(A) Prostate tumors produce tumor-derived factors, including BMPs, for the regulation of bone formation, which promote the process from osteoblast to osteoclast via RANKL. Subsequently, osteoclasts make bone-derived factors including BMPs, which promote tumorigenesis. (B) BMPs from tumor tissues activate TAMs and stimulate the type II cytokine, IL-10. IL-10 promotes the M2 polarization of TAMs and leads to tumor development by suppressing the local antitumor immune response.

pathway.[56] In primary mouse keratinocytes following BMP4 treatment, Ahmed et al.[57] 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.[57] Consistent with this observation, Qin et al.[58] 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.[7,59,60] Such a phenomenon has been indicated for the superfamily member TGF-β, which is suggested as an emerging player in drug resistance;[61] BMPs and their components have also been implicated to various different drug resistance of cancer. Indeed, Wang et al.[62] 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.[62] Xian et al.[63] 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.[64] reported that knockdown of BMP2 increased chemoresistance of the MCF-7 breast cancer cell line. Similarly, Liu et al.[65] 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 PC cells via tumor-infiltrating macrophages.[66] Choi et al.[67] also demonstrated that treatment with BMP2 *in vivo* leads to increased tumor growth and chemotherapy resistance. Octamer-binding transcription factor (Oct)4 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.[68–70] Langenfeld et al.[71] 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.[72] 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

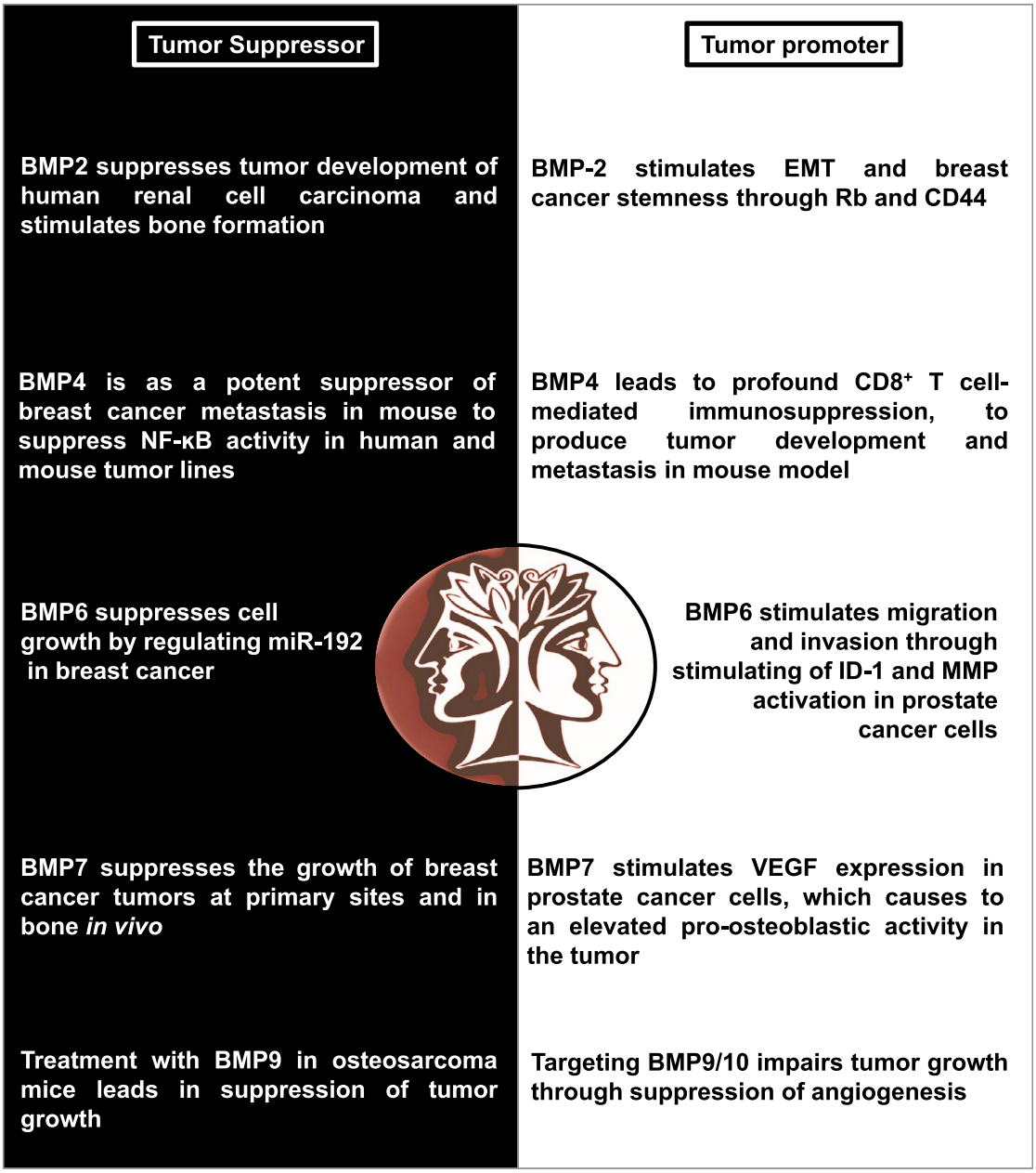

Figure 3. The Dual Function of BMPs in Cancer Cells

BMPs can suppress tumor growth and metastasis, acting as tumor suppressors. Paradoxically, BMPs also accelerate tumorigenesis as tumor promoters through various mechanisms, such as activation of oncogenes, and stimulation metastasis in tumor microenvironment. The bifrontal figure displays the Janus face of BMPs in tumor progression.

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.

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
				the levels of expression of BMP are not indicative of tumor stage	
Prostate cancer	human tissues	BMPR1A, BMPR1B, BMPR2	decreased	BMPRs often lose their expression during the progression of prostate cancer	137
	human tissues	BMP2	decreased	BMP2 is downregulated in prostate cancer compared to benign prostate tissue	40
				loss of BMP2 is associated with increasing Gleason score	
Carcinoma	human tissues	BMP2	increased	tumors with high BMP-2 expression have higher rates of local failure compared to other tumors with low expression	138
	patient tissues	BMP4	increased	associated with tumor invasion and progression in papillary thyroid carcinoma	139
Blood	anemia/patients	BMP6	increased	patients with cancer-associated anemia (CRA) have high expression of BMP6	140
				negatively related to s- Hemojuvelin (HJV)	
Breast cancer	tissues	BMP12	decreased	associated with a poor prognosis	117
Melanoma cancer	tissues	BMP7	increased	the expression of BMP7 in metastatic and primary melanomas is strongly expressed compared to weak expression in normal nevi	141

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[77–80] 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.[81] 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 (ALK)2-SMAD1 endoglin-associated signaling. Hallahan et al.[82] 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.[82] 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.[82] Kodach et al.[83] 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.[84] 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.[85] 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.[86] 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.[84] In conclusion, the identifying bioactive compounds that specifically target BMPs and their involvement 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.

AUTHOR CONTRIBUTIONS

D.-H.B. conducted the literature review and co-wrote the manuscript, H.J.P. discussed the contents of the manuscript, and S.K.L. provided overall supervision and co-wrote the manuscript.

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