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Review article

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The risk of tumor with the use of recombinant human bone morphogenetic proteins

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Abstract

Introduction Bone morphogenetic proteins (BMPs) are members of a large family of growth factors known as the transforming growth factor-β (TGF-β) superfamily. BMPs are known for their ability to induce bone formation and successfully used in orthopaedic and neurosurgical applications. Various proteins, such as BMP-2, 4, 7, have been reported to have osteoinductive abilities. Recombinant human bone morphogenetic protein-2 (rhBMP-2) and recombinant human bone morphogenetic protein-7 (rhBMP-7) are widely used for surgical correction of bone defects and spinal fusions. In addition to the effect on bone formation, BMPs also play a role in cell lineage determination, differentiation, proliferation and apoptosis, and BMP receptors are present in many cell types including tumor cells. A large number of studies *in vitro* and *in vivo* have examined the role of BMPs as stimulating oncogenesis and metastasis. Therefore, there are some concerns about the use of rhBMPs in clinical practice. **Objective** In the present study, we aimed to investigate the causal relationship between the use of rhBMPs and oncogenesis by presenting the results of some preclinical and clinical studies. **Material and methods** For a comprehensive search, we used the following databases: PubMed, Embase, the Cochrane Database and Google Scholar to identifying studies that described a causal relationship between therapeutic use of rhBMPs and oncogenesis. **Results** The paper represents the findings on the role and identification of molecular mechanisms of BMP involvement in oncogenesis. In addition to that, the studies reporting a risk of oncological diseases with the use of rhBMPs in both preclinical and clinical studies were also analyzed. Conclusion There is a need for further clinical trials in a wide population over a longer timeframe.

Keywords: bone morphogenetic proteins, recombinant human bone morphogenetic proteins, oncogenesis, complication, therapy

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INTRODUCTION

Bone morphogenetic proteins (BMPs) are a diverse class of molecules with more than 20 species that belong to the transforming growth factor-β (TGF-β) family and are closely associated with bone formation and development of diseases [1]. Aberrant expression of various BMPs and their receptors has been reported in various tumor tissues [2, 3]. The role of BMPs is closely related to various aspects of oncogenesis, such as angiogenesis, epithelial-mesenchymal transition (EMT) and tumor stem cells [4]. Many publications report the role of BMPs signaling pathways in tumor cells [4, 5]. The BMPs ligands bind to their receptors including type I and type II to form a heterotetrameric complex that activates phosphorylation, recruitment, translocation, and expression of Smad in cells [1]. These interactions between BMPs and their antagonists or receptors establish the aggressiveness of primary tumors and the mechanism of metastasis [4].

In recent decades, many researchers have undertaken to develop high profile osteogenic hydrogel implants by incorporating bioactive agents, stem cells and osteogenic growth factors, including BMPs [6]. Recombinant human DNA technologies are known to be used for the creation of recombinant human bone morphogenetic proteins (rhBMPs) for clinical use [6]. RhBMP-2 and rhBMP-7 have been approved by the US Food and Drug Administration (FDA) and are clinically recognized for use in open tibial fractures, critical bone defects, spinal fusion of the lumbar spine and osteonecrosis in femoral fractures [7–9]. In addition to the effect on bone formation, BMPs also play a role in cell line determination, differentiation, proliferation and apoptosis [10]. Although the use of rhBMP-2 and rhBMP-7 has steadily increased since their approval, there is controversy regarding their safety. There is a concern that rhBMPs may contribute to tumorigenesis. However, given the influence of BMPs on bone development and their potential role in the associated processes of tumor formation and spread, the role of rhBMPs in promoting primary tumorigenesis and metastasis is still unkbnown.

Objective In the present study, we aimed to investigate the causal relationship between the use of rhBMPs and oncogenesis by presenting the results of some preclinical and clinical studies.

MATERIAL AND METHODS

We conducted a comprehensive literature search demonstrating the role of BMPs as oncogenes and tumor suppressors in the development of tumors, and as a causal relationship between therapeutic use of rhBMPs and tumorigenesis. Databases including PubMed, Embase, the Cochrane Database and Google Scholar were used to retrieve all relevant studies. Keywords: "bone morphogenetic proteins", "recombinant bone morphogenetic proteins", "growth factors", "TGF-β family", "tumor" and "oncogenesis", "oncogene", "tumor suppressor", "complications", "clinical studies", "preclinical studies", "therapy", "regulation", "side effect". In addition to that, references of each relevant study was searched for other relevant papers.

RESULTS AND DISCUSSION

BMPs and oncogenesis

BMPs – oncogene or tumor suppressor

There is evidence that BMPs can be involved in the oncogenesis of various types of tumors [4, 5]. BMP-4 has been reported to stimulate invasion of breast cancer cells (BC) and promote bone remodeling [11]. Paez-Peda et al. reported the role of BMP-4 in prolactinoma oncogenesis through the Smad/estrogen receptor signaling pathway [12]. In contrast, BMPs have been shown to have a tumor suppressive function in more recent studies. Ye L. et al. suggested that BMP-10 inhibits the growth and aggressiveness of prostate cancer (PC) cells by inducing apoptosis through a Smad-independent pathway that correlates with modulation of expression of extracellular signal-regulated kinase (ERK) 1/2 and X-linked inhibitor of apoptosis protein (XIAP) [13]. Cao Y. et al. reported that BMP-4 suppresses breast cancer metastasis by inhibiting the activity of myeloid-derived suppressor cells in mice [14]. They also suggested that BMP-4 reduces the secretion of granulocyte colony-stimulating factor (G-CSF) through suppression of nuclear factor-kappa B (NF-kB) activity. The same BMP ligand within the same tumor type is likely to function differently depending on the type of examination performed. Conclusions based on one cell line only may be too simple, and different tumor cell lines or different types of tumors should be used. An appropriate consensus is that BMPs can be involved as both tumor promoters and oncogenes (Table 1) [15–19]. Although there is no definitive correlation between BMPs and tumorgenesis, a large number of studies indicate a positive effect of BMPs on tumor development. Therefore, a special attention should be paid to the role of BMPs in the treatment of cancer patients, and oncological anamnesis should be taken into account with BMP administered.

Aberrant expression of BMPs and their effect on oncogenesis

The role of BMPs in tumor biology, breast cancer and prostate cancer, in particular, is widely explored. The proteins are known to be widely involved in the regulation of tumor cell functions, which vary from growth, death, migration, and invasion of tumor cells to EMT (Table 2) [14–23]. The role of BMPs signaling has been extensively studied in bone metastasis among various types of tumors with BMPs being involved in the progression. Horvath LG et al. suggested that BMP-2 may act as a marker of poor prognosis due to a significant decrease in its expression in prostate cancer compared with benign prostate tissue [24]. Morrissey C. et al. suggested that BMP-7 is overexpressed in bone and soft tissue metastases compared to primary PCa [25]. They also reported that BMP-7 signaling may be associated with disease progression. Ye L. et al. previously reported that BMP-7 activation in PCa tissues may be associated with hepatocyte growth factor (HGF) *in vivo* [26]. Ma Y. et al. reported that the expression of BMP-2 and bone morphogenetic protein receptors type I B and type II (BMPRIB and BMPRII) is reduced in tissues of epithelial ovarian cancer and suggested that their low expression is associated with a poor prognosis for this cohort of patients [27]. Therefore, aberrant expression of BMPs has been associated with the development of various solid tumors and bone metastases.

Table 1

The dual role of bone morphogenetic proteins (BMPs) in tumors

Oncogenes	Tumor suppressors
BMP-2 stimulates EMT and breast cancer stem cell differentiation through Rb and CD44	BMP-9 activation leads to suppression of osteosarcoma growth *in vivo*
BMP-4 leads to profound immunosuppression mediated by CD8 T cells resulting in tumor and metastasis *in vivo*	BMP-7 activation leads to suppression of breast cancer growth *in vivo*
BMP-6 stimulates migration and invasion of prostate cancer cells by activating ID-1 and MMP	BMP-2 inhibits the growth and development of renal cell carcinoma
BMP-6 stimulates VEGF expression in prostate cancer cells which causes increased pro-osteoblastic activity in the tumor	BMP-2 suppresses breast cancer growth through miR-192 regulation
BMP-9 and BMP-10 stimulate tumor growth by activating angiogenesis	BMP-4 is a potent suppressor of breast cancer metastasis by suppressing NF-kB activity *in vitro* and *in vivo*

Table 2

The role of bone morphogenetic proteins (BMPs) and target genes or signaling pathways involved in tumors

Type of tumor	Type of BMPs	Study model	Expression	Target genes or signaling pathway	Function	Reference
Lung cancer	BMP-7		Increased	Smad1	High expression of BMP-7 may be an indicator of the likelihood of metastasis to bone tissue and damage to regional lymph nodes. экспрессия BMP-7	[1, 2]
Lung cancer	BMP-4	Tumor tissue (*ex vivo*, human), *in vitr*o (A549 cell line) and *in vivo*	Decreased, increased	p-ERK, VEGF, Smad1, miR-200 and JAG2	BMP-4 inhibit tumor growth *in vivo*. High expression of BMP-4 stimulates oncogenesis and metastasis	[3, 4]
PC	BMP-4	*In vivo*	Decreased	Cytokines: IL-8, GRO-α/β and CCL2	High expression of BMP-4 stimulates oncogenesis and metastasis	[5]
PC	BMP-7	Tumor tissue (*ex vivo*, human)	Decreased	Smad1/4/5, E-cadherin and vimentin	Acts as a potential inhibitor of bone metastasis of PC *in vivo*	[6]
PC	BMP-6	Tumor tissue (*ex vivo*, human)	Decreased	ID-1 and MMP	Associated with increased ID-1 protein levels and a more invasive phenotype	[7]
BC	BMP-9	*In vitro* (MDA-MB-231 cell line, preadipocytes and adipocytes) and *in vivo*	Decreased	STAT3, ERK-1 signal transducer and transcription activator, 2/Akt signaling pathway	Suppresses the growth and metastasis of tumor cells. Suppresses tumor growth and reduces leptin expression in preadipocytes/ adipocytes	[8]
BC	BMP-4	*In vivo* (BALB/c)	Decreased	NF-kB	Suppresses leukocytosis, splenomegaly and metastasis. Decreases G-CSF secretion by inhibiting NF-kB activity.	[9]
Colorectal cancer	BMP-4	Tumor tissue (*ex vivo*, human)	Decreased	PI3K/Akt signaling pathway	RhBMP-4 induces apoptosis and differentiation of chemoresistant colorectal cancer stem cells. Activates canonical and non-canonical BMPs signaling pathways.	[10]

Abbreviations: PC, prostate cancer; BC, breast cancer; Smad1/4/5, mothers against homologue of decapentaplegia 1/4/5; p-ERK, p-kinase associated with an extracellular signal; VEGF, vascular endothelial growth factor; miR-200, microRNA-200; JAG2, jagged canonical Notch 2 ligand; IL-8, interleukin 8; GRO-α/β, oncogenic protein associated with the growth of CXC chemokines; CCL2, monocytic chemoattractant protein-1; ID-1, DNA-binding protein inhibitor; MMP, matrix metalloproteinases; STAT3, signal transducer and transcription activator 3; ERK-1, 2 – kinase associated with extracellular signal 1, 2; NF-kB, nuclear factor-kappa B; PI3K, phosphoinositide-3-kinase; rhBMP-4, recombinant human bone morphogenetic protein-4

Regulatory factors for BMPs

The change in expression (increase or decrease) of BMPs and the signaling that occurs in malignant tumors during the development and progression reflects the complexity of both the BMPs regulation mechanism and their interaction with other factors. A number of hormones and other growth factors have been indicated in the regulatory network of BMPs.

Sex hormones

Androgens play an important role in oncogenesis, tumor progression, and metastasis, and control of circulating androgen levels is the only way to control the effectiveness of therapy in PC. Androgens can induce the expression of some BMPs, BMP receptors, and intracellular signaling [28]. As for receptors, androgens induce BMPRIB mRNA expression, but not BMPRIA and BMPRII mRNA expression in the androgen-sensitive human PCa cell line LNCaP [30]. RhBMP-4 has been found to induce a biphasic effect on LNCaP proliferation [29]. There is a decrease in cell proliferation in response to the application of rhBMP-4 in the presence of androgen. This is believed to be the result of high expression of BMPRIB. Therefore, androgen induction of BMPRIB expression appears to inhibit cell proliferation in response to BMPs activation [30]. As for the BMPs, orchidectomy leads to decreased expression of BMP-7 *in vivo*, and the administration of testosterone or dihydrotestosterone can cause a greater expression level of BMP-7 [30]. However, androgen deprivation does not appear to affect BMP-6 production in normal rat prostate tissue suggesting an alternative and androgen-independent gene regulation of BMP-6 [31].

Epigenetic regulation of BMPs and their receptors in breast cancer is associated with the estrogen receptor (ER). Estrogen can suppress the expression of some BMP receptors, such as BMPRIA, BMPRIB, activin receptor type 2A and type 2B (ACVR2A and ACVR2B), but does not affect the expression of activin A receptor type I (ACVR1) and BMPRII [32]. BMP-7 expression has been found to correlate with the level of expression

of both the ER and the progesterone receptor [33]. The antiestrogen reagent raloxifene can increase BMP-4 activity in osteoblast-like U-2 OS cell lines [34]. It is believed that ER-α, but not ER-β, is required for BMP-4 activation. However, ER-β can synergistically enhance BMP-4 activation by raloxifene [34]. The role of ER-β in the regulation of BMPs and estrogen signaling of BMPs in breast cancer cells remains poorly understood. Estrogen and BMP may influence each other's function through interactions between their receptors and downstream signaling pathways such as ER and Smads. However, the interaction between estrogen and rhBMPs-activated signaling pathways and their role in the development and progression of breast cancer still needs further study.

Growth factors

Several other growth factors and signaling pathways have been identified in the regulation of expression and function of BMPs. Nacamuli R.P. et al. reported that BMP-3 expression can be controlled by recombinant human fibroblast growth factor (rhFGF) in calvarium-derived osteoblasts *in vivo* [35]. The expression of BMP-6 was shown to be reduced in breast cancer tissues, which was accompanied by a simultaneous decrease in the expression of the EGF receptor. The relationship between BMP-6 and EGF was further confirmed by the activation of BMP-6 in the breast cancer cell line MCF-7 via activation of the EGF receptor [36]. There is evidence that retinoid induces BMP-2 expression in retinoid-sensitive cell lines, and rapamycin induces BMP-4 expression and reduces follistatin expression in PC3 cell line, which ultimately contributes to its antitumor effect [37]. Recent studies have shown that hepatocyte growth factor (HGF), a key regulator of metastasis and angiogenesis, can enhance the expression of BMP-7 and its receptors in PCa cells [14]. This effect can be blocked by NK4, an HGF antagonist and an angiogenesis inhibitor. This suggests that HGF is involved in changing the BMP expression profile during tumor progression and metastasis. These studies indicate that BMPs, together with other growth factors, may play a potential role during tumor development and progression, in bone metastases, in particular.

Angiogenesis

Angiogenesis is an important component for the development and progression of primary and secondary tumors. In order for tumors to grow, they must induce the formation of new blood vessels, a process known as neovascularization. The process of angiogenesis has an early activation phase, when endothelial cells (ECs) proliferate and migrate, and a late phase, when ECs stop migrating and stabilization and formation of a mature blood vessel occurs [38, 39]. It has been proposed that Transforming Growth Factor Beta 1 (TGF-β1) signaling via activin receptor-like kinase 1 (ALK1)/Smad1/Smad5 induces an early activation phase of angiogenesis, whereas TGFβ-1 via activin receptor-like kinase 5 (ALK5)/Smad2/Smad3, is responsible for the promotion of the late phase [40]. Cultivation on type I collagen can promote the spontaneous formation of tubular EC structures by increasing the expression level of BMPRIB and BMPRII [41]. Smads are transcriptional regulators of BMPS target genes, including vascular endothelial growth factor (VEGF) [42]

In gastric cancer cells, Smad3 leads to the suppression of VEGF expression and a decrease in the size of tumor nodes with decreased formation of blood vessels [42]. Unlike Smad2 and Smad3, overexpression of Smad4 in pancreatic cancer cells can lead to both a decrease in VEGF expression and an increase in the level of thrombospondin-1, which leads to inhibition of angiogenesis [43]. Unlike TGF-β1 and most BMPs, BMP-9 has been shown to inhibit EC proliferation and block VEGF-mediated angiogenesis via ALK-1 and BMPRII and downstream Smad1/5 signaling [44] showing the dual role of BMPs in oncogenesis.

Clinical trials

Given the high morbidity and mortality in some types of tumors, the risk of potential postoperative tumor formation following the use of rhBMPs is critical to study. Establishing cases of tumor formation through clinical trials is limited by issues of power and sample size, and the relatively short duration of follow-up period. RhBMP-2, introduced in 2002, has become one of the most commonly used bone graft substitutes [46]. Although rhBMP-2 is approved for use in anterior lumbar fusion, its use has expanded and misused, both in terms of location and dosage. In 2012, DeVine JG et al. conducted an independent review of the risk of oncology with rhBMP-2 in spinal fusion based on published literature to date and FDA public data summaries and concluded that tumor risk may be dose dependent. This conclusion was based on data from off-label use of rhBMP-2 for posterolateral fusion in three randomized controlled trials and one retrospective cohort study [46].

Attempts have been made to retrospectively explore larger patient populations with longer follow-up periods. Although there are several limitations to a retrospective study, the ability to study larger patient populations with longer follow-up and off-label use of rhBMPs, both in application (anterior and posterior cervical, posterior lumbar fusion) and dosage, may provide some benefit in understanding of the potential risk of tumor formation. The FDA approval document reported one case of pancreatic cancer during a 12-month follow-up [47]. However, this case appears to be coincidental as a large retrospective cohort study conducted in elderly patients did not reveal any increased risk of pancreatic

cancer associated with exposure to rhBMP-2. Carragee E.J. et al. reported 239 rhBMP-2 spinal fusion patients and 224 controls (no rhBMP-2) [48]. At 24 month follow-up, the risk of cancer increased in rhBMP-2 patients (hazard ratio 3.45; 95 % confidence interval (CI): 1.98–6.00), but the event rate was low and the tumors were heterogeneous, and 37 % of patients were lost after five years of follow-up, significantly reducing the power of the statistical analysis. Recently, Kelly M.P. et al. reported a retrospective study analyzing the incidence of cancer in 467,916 Medicare patients who underwent spinal fusion surgery between 2005 and 2010 [49]. The relative risk of developing a tumor after exposure to rhBMPs was 0.938 (95 % CI: 0.913–0.964), which is a low value. The incidence of tumor development was similar in the rhBMP group and the control group (5.9 % vs. 6.5 %). It was concluded that the use of rhBMP was not associated with an increased risk of tumor development during the median follow-up period of 2.9 years. Table 3 presents clinical studies that explored possible risk of oncology after the use of rhBMPs [47–52].

Table 3

Clinical trials exploring the risk of tumors after the use of recombinant human bone morphogenetic proteins (rhBMPs)

Authors	Type of study	BMP/ trademark	Procedure	Suspected tumor	Number of patients, n	BMP dose	Risk of oncology, n (%)	Follow-up period
Sayama et al. [49]	RCT	rhBMP-2/ Infuse™	Posterior fusion of the occipito-cervical, cervical, thoracic, lumbar or lumbosacral spine	–	57	2.8, 5.6 and 8.0	0 (0)	48.4 months (range, 24–70 months)
Dettori et al. [51]	Database	rhBMP-2 and rhBMP-7	Fusion of the cervical and lumbar spine	The most commonly reported were PC, BC, lung cancer, melanoma, and colon cancer.	4246	–	117 (2.76)	8 years
Carragee et al. [48]	MPRT	rhBMP-2/ Amplify™	Fusion of lumbar spine	The most commonly reported were PC, squamous cell carcinoma, melanoma, and thyroid cancer	239	40	15 (6.3)	60 months
Cooper et al. [50, 52]	Database	rhBMP-2 and rhBMP-7		The most commonly reported were PC, BC, melanoma, and non-Hodgkin's lymphomas.	2345	–	49 (2)	4.87 years
Mines et al. [47]	RCT			Pancreas cancer	15453	–	8 (0.05)	1.4 years

Abbreviations: RCT, retrospective cohort study; MPRT, multicentre prospective randomized trial; PC, prostate cancer; BC, breast cancer; rhBMP-2, recombinant human bone morphogenetic protein-4; rhBMP-7, recombinant human bone morphogenetic protein-7

CONCLUSION

BMPs are known to have a dual function in the development and progression of tumors. They can serve as tumor suppressors or promoters depending on the type of cell or tissue in the microenvironment and the patient's epigenetic background. Further studies are needed to assess the possible relationship between tumorigenesis and the use of rhBMPs. The alleged carcinogenicity of rhBMP-2, which was suspected as early as 2011, is not conclusively confirmed by the largest retrospective study published by Kelly M.P. et al. and performed on nearly half a million patients treated for lumbar fusion with and without rhBMP-2.

Although some clinical studies suggest that there are a number of complications after the use of rhBMPs in spinal surgery and adverse events like inflammation or heterotopic ossification, there is an FDA document confirming the safety of the use of rhBMP-2 or rhBMP-7 (indications, surgical method and implant, BMPs dose). The following postulate can be found in the relevant FDA document: "The safety and efficacy of the BMP component when used with other spinal implants implanted at sites other than the lower lumbar spine or used in surgical techniques other than anterior open or anterior laparoscopic approaches have not been established." The results of clinical studies have shown that the use of rhBMPs for therapeutic purposes does not increase the risk of subsequent occurrence of malignant neoplasms. However, further clinical studies are required with larger patient populations and longer follow-up.

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